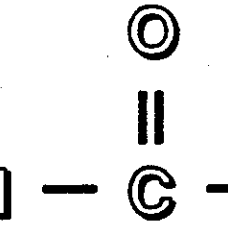
California Environmental Protection Agency

Air Resources Board

TECHNICAL SUPPORT DOCUMENT

Final Report on the Identification of FORMALDEHYDE



as a Toxic Air Contaminant

PART C
Public Comments and ARB/OEHHA Staff Responses

STATIONARY SOURCE DIVISION

JULY 1992

PART C - PUBLIC COMMENTS AND RESPONSES TO THE PRELIMINARY DRAFT PART A AND B FORMALDEHYDE

Prepared by the staffs of the Air Resources Board
and the Office of Environmental Health Hazard Assessment

September 1991

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I.

Comment Letters Recieved on the Preliminary Draft Version of the Formaldehyde Identification Report, Parts A and B

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March 26, 1991

Comments on the Proposed Listing
of Formaldehyde as a California
Toxic Air Contaminant

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Formaldehyde
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Dear Ms. Shiroma:

We have the following comments on the preliminary draft report, "Proposed Identification of Formaldehyde as a Toxic Air Contaminant". As requested, we have tried to limit our discussion to the portions of the report that discuss the toxicity of formaldehyde and whether or not there is a threshold concentration below which no significant adverse health impacts are anticipated.

1) The Air Resources Board (ARB) should consider extending the comment period on future drafts of this document.

It is unfortunate that only 30 days are allowed for outside reviewers to comment on this formidable document. Because formaldehyde has been the focus of intense research and debate in the field of risk assessment, there is voluminous literature to be reviewed and assimilated.

2) ARB should ask DHS to update their cancer risk assessment to compare the most recent EPA analysis (1990) with their own.

The Health Assessment section of the document was written by the Department of Health Services (DHS) primarily to estimate the unit risk associated with exposure to airborne formaldehyde. ARB should be aware that the Environmental Protection Agency (EPA) is currently revising their estimate of unit risk for formaldehyde's carcinogenic potency. The EPA's "best estimate" is approximately two orders of magnitude lower than DHS's "best estimate". This appears to be because the EPA used dosimetry data developed in the monkey while DHS used dosimetry data developed in the rat. Since DHS often referred to the 1987 EPA Risk Assessment of Formaldehyde as a reference point for their assessment, an analysis of the two draft risk assessments would be extremely informative. Why do the experts disagree?

3) ARB should have DHS update their analysis of the relationship between predicted and observed human cancer rates (pages 2-19 to 2-22).

The Health Assessment section utilizes epidemiology data to evaluate the unit risk estimates developed from data in rats. The assessment relies on the lung cancer incidence observed in industrial formaldehyde workers in one study (Blair et al. 1986). Since DHS wrote their draft report, Blair has published a meta-analysis of over 30 epidemiology studies (Blair et al., Scand J Work Environ Health (1990) 16:381-393). Blair et al. (1990) concluded that, "Inconsistencies among and within studies impede assigning formaldehyde a convincing causal role for the excesses of lung cancer found among industrial workers." In addition, "The excess risk was small among industrial workers (CRR 1.1) and was not seen consistently in all the plants studied. In some plants there were deficits. No such excess for lung cancer occurred among the embalmers."

4) The review of Toxicity and Carcinogenicity of Formaldehyde (page 2-2 through 2-5) should be revised to reflect the weak epidemiology link between formaldehyde exposure and human cancer.

In addition to the lung, other potential sites of formaldehyde-induced cancer were reviewed by Blair et al. (1990). The authors state that, "... a causal association between formaldehyde exposure and cancer of the nasopharynx seems credible and likely. As with nasal cancer, small numbers, inconsistency among studies, and a possible independent role for particulates preclude definitively labeling formaldehyde as a nasopharyngeal carcinogen." Blair et al. (1990) also noted that, "The excesses of leukemia and brain and colon cancer found among professionals may not be related to formaldehyde exposure, since similar excesses were not observed among industrial workers."

5) ARB should ask DHS to reconsider their decision that no threshold exits for the carcinogenic risk of airborne formaldehyde.

As an endogenous and essential metabolite, formaldehyde is constantly being formed within most tissues. There are homeostatic mechanisms to control free formaldehyde concentrations within each cell. There must be a concentration of airborne formaldehyde that would not overwhelm the homeostatic controls and change the intracellular concentration. This implies that there is a "practical" threshold for the carcinogenic effects of airborne formaldehyde.

We hope these comments will help ARB improve the formaldehyde risk assessment before it is finalized. We realize that most of our recommendations are very general but the 30 day comment period provides little opportunity to develop alternative proposals in any detail. If ARB staff would like to discuss these comments, I can be reached at (415) 231-6027.

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March 26, 1991

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SUBJECT: Comments On Proposed Identification Of Formaldehyde As A Toxic Air Contaminant Part A - Exposure Assessment and Executive Summary

Dear Ms. Shiroma:

We have reviewed the February 1991 preliminary draft of the Part A - Exposure Assessment report on formaldehyde prepared by the California Air Resources Board (CARB). These comments should be considered preliminary with primary focus on the general approach used by CARB in developing the formaldehyde exposure assessment. A thorough analysis of the report would require obtaining references not immediately available to us and reviewing these references in context with the CARB report. Moreover, indoor formaldehyde exposures involve a number of complexities including the relationship of outside ambient levels and indoor home background levels, source strengths and changes in source strengths, the ability of home age analysis to appropriately portray decay rates from products, and the effects of infiltration rates on home levels. The time for response to the report has not allowed us to undertake this type of thorough analysis. Nevertheless, we have several major concerns with the exposure assessment draft report.

I. In-Home Exposures Are Likely Overstated Relative to Outdoor Exposures

The "out-of-home" exposures displayed in the Executive Summary (Page 8) of the CARB report are based on relatively new information, whereas the data for the "in-home" exposures are from older data. The result is that exposures for the in-home 62% time segment (14.9 hours) are overstated relative to the out-of-home (outdoor) 38% time segment (9.1 hours) of the 24-hour day.

A. Out-of-Home Exposure Concentrations

The out-of-home average statewide formaldehyde exposure of 4.4 ppbv, weighted by population, are derived from a summary of data collected during September 1988 - August 1989 as summarized on Table IV-4 (pages A-34 and A-35) of the CARB draft Exposure Assessment report. These data are significantly lower than that reported by various other investigators for urban areas.

Data shown on Table IV-3 of the CARB report and data referenced in reports prepared during the 1970s and early 1980s for various agencies are summarized below.

- Part A - Exposure Assessment draft report

  Table IV-3 (Page A-32) of the CARB report lists California ambient air values from 0.5 ppbv to 70 ppbv with the average point value or mid-range value at 32 ppbv (19 data sets). Dates of the measurements cited in this table were from 1980 to 1986 with most in 1980.

- Investigation of Selected Potential Environmental Contaminants: Formaldehyde (1976). One section of this report, prepared for EPA in August 1976, reviews atmosphere monitoring studies (See Appendix A for copies of appropriate sections of this report). The report references a study by Altshullen and McPherson (1963) that states that formaldehyde concentrations of the Los Angeles atmosphere averaged approximately 0.04 ppm (40 ppbv).

- Formaldehyde and Other Aldehydes (1981). This review report prepared by the National Research Council summarizes data from urban areas including Huntington Park, CA; El Monte, CA; Riverside, CA;and Newark, NJ (see Appendix B for copies of the section on urban atmospheres). In this report, the NRC concludes:

  > "From these data and the more extensive data from urban centers in 26 states and Washington, D.C., it appears that the 24-h average concentration of total aldehydes is frequently above 0.1 ppm (12 ug/m^3) in many urban areas, but with wide variations; hourly daytime averages may be near 0.05 ppm (60 ug/m^3 and infrequently above 0.1 ppm (120 ug/m^3)."

- Formaldehyde: A Survey of Airborne Concentrations and Sources by Science Applications, Inc. (SAI) was prepared for the California Air Resources Board in 1984. Ambient and commuter exposures values are summarized as follows:

"Hourly average formaldehyde concentrations at the Lennox and Pico-Rivera monitoring stations ranged from 7.3 to 18.2 ppb and 4.3 to 33.3 ppb, respectively, during the January 1983 sampling. Commuter exposures during this time varied from 10.7 to 91.5 ppb.

"In the May-June 1983 sampling, concentrations at Pico-Rivera and Azusa were 2.0 to 17.0 ppb and 5.6 to 23.3 ppb, respectively. Commuter exposures in the summer sampling ranged from 11.3 to 22.5 ppb."

While the state of California relied heavily on the Science Applications, Inc. 1984 study for conventional home exposures, there was little or no consideration by CARB of outdoor levels of formaldehyde reported by SAI as being particularly relevant in the 1991 exposures assessment document.

The outside concentrations for urban atmospheres listed in the four reports cited above differ significantly (by a factor of about 2 to 12) from outdoor formaldehyde concentrations actually used in the draft 1991 CARB exposure assessment. It is not likely that the large magnitude difference can be explained only by differences in sampling times, the time of day that samples are taken, and changes having occurred in recent years to reduce outside levels of formaldehyde. Other factors of importance could include differences due to different methods of analysis of air samples, and the weighting and extension procedures used by CARB in 1991 in making exposure assessments.

B. In-Home Exposure Concentrations

In contrast with the out-of-home CARB exposure estimates, which relied on 1988 - 1989 data, the in-home exposure assessment relied almost entirely on older data. If there have

been significant reductions in out-of-home formaldehyde exposures during the past 5 to 7 years, it is likely that there also has been significant reductions for in-home formaldehyde exposures. There has been a great deal of emphasis in reducing building product formaldehyde emissions from federal agencies such as HUD, CPSC and EPA, and states such as Minnesota in recent years. Voluntary product standards were established during 1986 and 1987 for the three most important urea-formaldehyde (UF) bonded wood products (particleboard, hardwood plywood and medium density fiberboard) used in the interior of buildings. Records of the Hardwood Plywood Manufacturers Association and the National Particleboard Association indicate that emissions from these wood products have declined 75 to 90% since the 1979-1981 period.

1) Pickrell Emission Rate Table

In respect to older data, the publication by CARB of the 1983 table from Pickrell (Page A-40, Table IV-5 - Typical Emission Rates of Continuous Indoor Sources of Formaldehyde) is misleading, vastly out-of-date, and irrelevant in respect to current pressed wood products. Particleboard and hardwood plywood complying with product emission standards established by the U.S. Department of Housing and Urban Development represent products with much lower emission rates than were available in the early 1980s as shown in CARB Table IV-5. Formaldehyde emission rates have also decreased for other listed products such as textiles and paper products. Urea formaldehyde foam insulation (UFFI) has virtually disappeared as a product although some older homes still contain UFFI. UFFI has no real relevance for new manufactured or conventional home construction.

2) Manufactured (mobile) Homes

The California Department of Health Sciences work

reported by Sexton et al. (Page A-45) is the primary basis for the exposures of 1,000,000 manufactured (mobile homes) occupants in California. The field data for this study was collected in the summer of 1984 and in February of 1985 and included a total population of mobile homes (manufactured homes) built prior to the February 1985 effective date of the U.S. Department of Housing and Urban Development for formaldehyde emission requirements for particleboard and plywood used in manufactured homes.

3) Conventional Homes

The 1984 Science Applications, Inc. (SAI) report by Rogozen et al. (Pages A-45 and A-48), describing formaldehyde concentrations in 64 conventional (non-mobile) homes, was apparently used by CARB as the primary basis for determining the 50 ppbv average exposure of 29,000,000 (~97% of population) Californians in conventional homes for 14.9 hours a day. The field data for this study is older than the manufactured (mobile) home data reported by Sexton et al.

The SAI study in conventional homes showed that new homes (0 to 4 years old) had significantly higher formaldehyde concentrations than homes in other age groups. Homes where cigarettes were smoked, and homes with both gas cooking and cigarette smoking also had higher formaldehyde levels. Group means for different levels of smoking, however, were not significantly different. Some unusual findings from the SAI study are described below:

- Mean formaldehyde concentration values summarized on pages 5-22 through 5-24 of the SAI study show concentrations higher in electric fuel homes at

65.1 ppb (11 homes) than in gas fuel homes at 47.4 ppb (50 homes). Everything else being equal (air exchange rates, nature of formaldehyde emission sources), it would be expected that gas (a combustion source) fuel homes would have higher formaldehyde levels than electric fuel homes.

- Homes with UF foam would be expected to have higher formaldehyde concentrations than homes without UF foam. Four UF foam homes had an average formaldehyde concentration of 49.3 ppb while 60 homes without UFFI had an average concentration of 49.9 ppb.

- Thirteen energy efficient homes (usually such homes have significantly lower ventilation rates) had a mean concentration of 50.7 ppb, only about 1 ppb higher than formaldehyde levels in 51 homes not characterized as energy efficient.

- Perhaps most unusual is that the 35 homes where windows were open had a mean formaldehyde concentration of 50.9 ppb, as compared with 29 homes with closed windows with a mean concentration of 48.6 ppb. The similarity of data between the 35 homes with open windows as compared with the 29 homes with unopened windows indicates, for the homes in this data set, that outdoor concentrations may not have differed greatly from indoor concentrations.

No doubt some of the data anomalies in this report are due to the

small number of homes in some of the comparison categories. The introductory paragraph of the Statistical Evaluation of Results (Page 1-14) section of the SAI report is as follows:

> "Before discussing our findings, two limitations on the results must be mentioned. First, project resources were insufficient to permit a sample size large enough to detect small differences among subgroups of the residential sample. In addition, infiltration rates, which can be critical in determining indoor air pollutant concentrations, were not measured."

It is unlikely that Rogozen and co-authors (SAI) would be comfortable with the exposure assessment of 29,000,000 Californians being based on a 64 home study in view of the first recommendation appearing in the report (Page 1-19).

> "Since indoor exposure comprises most of the total exposure of the general public to formaldehyde, and since exposures at the upper end of predicted ranges can produce deleterious health effects, we recommend a comprehensive field measurement program by the appropriate agency to determine the causes of high (e.g. greater than 100 ppb) indoor concentrations. Our preliminary estimates indicate the need to sample a minimum of 500 homes, using a stratified sampling design."

II. Flawed 24-hour Exposure Patterns for California Citizens

While there is good basis for separating an average person's 24-hour time into home (62%) and out-of-home (38%), exposures have been overstated for the in-home segment and understated for the out-of-home segment. Moreover, the assumption that out-of-home exposures are the same as outdoor exposures is incorrect. Most out-of-home exposures would be in office buildings, factories, schools, etc. and not outdoors. The fact that there is limited formaldehyde concentration information and limited

information on the number and exposure patterns of people in such buildings is no reason to oversimplify and use outdoor exposures for 38% of the 24-hour period. It is very unlikely that . . .

> "average exposure in environments other than residences is about the same as the outdoor population-weighted exposure" (Executive Summary, Page 7).

Even assuming that outdoor formaldehyde exposures can be used as an adequate surrogate for out-of-home exposures there is significant data which indicates that the 9.1 hours (38% of time) that people spend out of the home would roughly coincide with the highest outdoor formaldehyde levels. This would be the daylight hours, the peak periods for photochemical oxidation formed formaldehyde, and formaldehyde from motor vehicles. These are the two most important sources of atmospheric formaldehyde. The following figures in Appendix A and Appendix B show patterns of higher levels of formaldehyde and aldehydes in the daylight hours.

1) Appendix A
   - Figure 11 (Page 97) - Formaldehyde concentrations in urban atmosphere in Huntington Park, California on October 22 and October 23, 1968.

2) Appendix B
   - Figure 5-2 (Page 39) - Hourly aldehyde concentrations at Huntington Park and El Monte, California in October 1968.
   - Figure 5-3 (Page 40)- Concentrations of formaldehyde and formic acid measured in Riverside,

California at various times on October 14, 1977.

- Figure 5-4 (Page 41) Diurnal variation of formaldehyde concentrations measured at Newark, New Jersey in the summer of 1972, 1973 and 1974.

The absolute magnitude of atmospheric formaldehyde may have decreased in recent years. It is unlikely, however, that the pattern of higher relative formaldehyde atmospheric levels in the daylight hours has changed.

Formaldehyde emissions from building products and various other indoor sources are highly dependent on temperature. In general, temperatures in homes are higher in the late morning and afternoon hours than at night. Thus, the daylight hours from ~9 A.M. to ~6 P.M. (9 hour period) would include the times of higher anticipated formaldehyde levels in homes. During these hours, fewer people would be home; most would be at work, at school, shopping or engaging in other activities.

Diurnal variations in formaldehyde formation and formaldehyde release must be appropriately overlayed on movement patterns of people over the 24-hour period. Since this was not apparently done in the CARB exposure assessment, formaldehyde exposures have been overstated for the 62% of the time people spent in the home and understated for the 38% of the time people spend outside the home.

III. <u>Importance of UF-bonded Wood Products as a Formaldehyde Emission Source is Overstated</u>

In the Introduction of Part A - Exposure Assessment

(page A-1), the following statement appears in the last paragraph:

> "By far the largest source of formaldehyde indoors is pressed wood products made with urea-formaldehyde resins"

In the first paragraph under section E. Indoor Exposure To Formaldehyde (Page A-38) is the statement:

> "Formaldehyde concentrations are generally much higher indoors than outdoors due to the abundance of building materials and consumer products in buildings that emit formaldehyde."

On page A-38, in the last paragraph:

> "Building materials (especially pressed wood products and urea-formaldehyde foam insulation), because they emit relatively large amounts of formaldehyde and are present in large quantities, make the most significant contribution to indoor formaldehyde concentrations."

> "In general, building materials tend to be the highest emitters, followed by combustion sources, paper products, new clothes, draperies and other fabrics."

The primary studies used by CARB in making their exposure assessment (Sexton et al. for manufactured homes and Rogozen et al. for conventional homes) contain little or no specific information about formaldehyde emissions from UF-bonded building materials. These two studies neither attempted to quantify the amount of these building materials in California homes nor provided emission characteristics for such products.

The CARB investigation of source strengths and in-home exposures rely on out-dated information from the early 1980s. The primary basis for statements regarding wood building products appears to be the 1983 Pickrell paper (CARB Table IV-5). There have been significant reductions in emissions from particleboard and hardwood plywood since 1985 when the United States Department of Housing and Urban Development and the state of Minnesota moved forward with product emission requirements for these products. Moreover, since 1985 UF-bonded pressed wood products are used to a lesser extent as building materials. This is particularly true of manufactured (mobile) homes. "Particleboard," "interior plywood" and "paneling" are the only products on the Pickrell list for which there are mandatory emission standards. Thus, UF-bonded wood products have likely become relatively less important than those other products on this list and other indoor formaldehyde sources not identified by Pickrell.

Another distortion created by the use of outdated data is that the emission rates listed are essentially initial emissions and do not account for "emission decay" (the change in emission rate over time) from UF-bonded wood panels. For example, data from four laboratories have been combined in a study that indicate that initial emission levels from particleboard decrease by half in one year or less (see Attachment C: Zinn, Cline, and Lehmann, "Long-Term Study of Formaldehyde Emission Decay from Particleboard," Forest Products Journal, June 1990). After about a year, emission decay from a product continues at a more moderate rate until the product reaches equilibrium with the indoor ambient concentration of formaldehyde.

Because of emission decay, UF-bonded wood building products probably contribute little to formaldehyde levels in homes built

before March, 1980. California's housing stock built before March, 1980 is reported as 8.9 million or 80% of the total stock (as of September, 1990) of about 11.1 million. This would also represent about 80% of the household population of California.

IV. Conclusions

1) The in-home levels of formaldehyde are very likely overstated by CARB because the data (early and mid 1980s) used in making these assessment predates the effective date of HUD and Minnesota standards for formaldehyde emissions from urea-formaldehyde bonded wood products. Reduction in emissions have occurred from these building products and from many other potential indoor emitters, such as textiles, over the past 5 to 7 years.

2) Outdoor formaldehyde concentrations are not an adequate surrogate for out-of-home concentrations. Most people spend most of the time out of the home in commercial, institutional, or workplace buildings. Many of the same inside sources of formaldehyde in homes (inside cooking and heating; cigarette smoking; emissions from building materials, furnishings, and other indoor emitters) are also present in these buildings.

3) While atmospheric (outdoor) concentrations of formaldehyde have likely decreased during the past 5 to 20 years, it is unclear that such reductions as suggested by CARB (2 to 12 fold reductions) can be fully explained by the 24-hour sampling period used by CARB as compared with earlier sampling practices, reduction in the number of point sources, and decreased formaldehyde

emissions from outside sources. Moreover, the daylight hours, when most people are out of homes, coincide with both outdoor and indoor peak exposures. Thus exposures are overstated for the 14.9 hours (62%) that people are in their homes and are understated for the 9.1 hours (38%) that people are generally out of the home.

4) The importance of UF-bonded wood building materials is over emphasized as a source of formaldehyde, particularly in the older housing stock in California. In older housing, continual and episodic sources such as gas cooking, unvented heating devices, cigarette smoking and outside ambient air; and new furnishings and other items later brought into the home are much more important than the building materials originally used in constructing the home.

Sincerely,

William J. Groah
Technical Director
Hardwood Plywood Manufacturers Association

William H. McCredie
Executive Vice President
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Attachments (3)

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SM-2063
March 27, 1991

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Air Resources Board
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Dear Ms. Shiroma:

Please find attached General Motors comments on the California Air Resources Board preliminary draft report titled Proposed Identification of Formaldehyde as a Toxic Air Contaminant, dated February 1991. General Motors comments focus on the following points:

- The report significantly overstates the risk from outdoor formaldehyde exposure due to motor vehicles, and does not properly inform the reader that the risk from motor vehicle formaldehyde emissions has been reduced dramatically over the past 20 years and will continue to decrease substantially due to CARB's regulatory program for controlling criteria pollutants;

- The report fails to recognize the high level of uncertainty introduced by extrapolating the effect of excessive formaldehyde concentrations to low ambient levels; and

- The report disregards the potential existence of no-effect threshold levels indicated by laboratory investigations.

If you have any questions concerning these comments, please contact either J. M. Heuss or J. J. Vostal of my staff at 313-947-1787 or 313-947-1637, respectively.

Sincerely,

Leam A Drake/for

S. A. Leonard, Director
Automotive Emission Control

GENERAL MOTORS COMMENTS ON PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT BY THE STATE OF CALIFORNIA

General Motors (GM) has reviewed the preliminary draft prepared by the Staffs of the Air Resources Board and the Department of Health Services and offers the following comments. While the document indicates that formaldehyde may cause or contribute to an increase in mortality and illness, thereby posing a potential hazard to human health, GM is concerned that the risk from present and future ambient concentrations of formaldehyde is not put into the proper perspective in the preliminary draft. In particular, the preliminary draft fails to inform the reader that the risk from outdoor exposures attributed to formaldehyde emissions from mobile sources, while only a small portion of the total risk in California, is significantly overstated in the preliminary draft. In addition, the risk from both direct formaldehyde emissions and indirect formaldehyde formation in the atmosphere as a result of the use of motor vehicles has been reduced dramatically over the past 20 years and will continue to decrease substantially due to CARB's regulatory program for controlling criteria pollutants. Finally, part B, Health Assessment of Formaldehyde, while introducing pharmacokinetic principles into the risk assessment methodology, fails to recognize the high level of uncertainty caused by extrapolating the effect of excessive formaldehyde concentrations to low ambient levels and disregards the potential existence of no-effect threshold levels described by recent laboratory investigations.

Comments on Executive Summary

The discussion of the direct emission of formaldehyde and the formation of formaldehyde from photochemical oxidation of hydrocarbons includes estimates in "tons per year" but the estimates are not referenced to a given year. The impression given the reader is that these estimates have not varied in the past and will not vary in the future. In contrast, the CARB regulatory program for hydrocarbons has been reducing the emissions of both direct formaldehyde emissions and formaldehyde precursors for many years. The document should clearly indicate this very important fact.

For example, the emission estimates for passenger cars in Appendix I-B of Part A Exposure Assessment, when combined with the vehicle miles traveled (VMT) estimates (February 1991 1,3-butadiene Exposure Assessment by CARB[1]), demonstrate that the formaldehyde emissions from catalyst equipped vehicles have been reduced 88 or 89 percent compared to non-catalyst vehicles. The average emission

rate of non-catalyst vehicles is estimated at 120 mg/mi, while that of catalyst cars is about 14 mg/mi. Based on the inventory in Appendix I-B, non-catalyst passenger vehicles contribute 12 percent of the VMT but emit 52 percent of the direct formaldehyde emissions and 38 percent of the Total Organic Gases (TOG) from passenger cars.

Another way to calculate the overall statewide average emission rate of formaldehyde from the on-road vehicle fleet can be based on the total VMT estimate in California (Reference 1: 6.1×10^8 VMT/day) and the total emissions estimate in Appendix I-B (9386 tons/year). The average fleet-wide emission rate is 38.2 mg/mi. This compares favorably with the average formaldehyde emission rate in the 1987 SCAQS tunnel study of 42.1 mg/mi.[2]

Not only is the favorable comparison between emission estimates and on-road measurements reassuring, but it gives us assurance that the continued attrition of older, high-emitting non-catalyst vehicles together with the addition of low-emitting catalyst vehicles will continue to reduce ambient formaldehyde concentrations and any associated risk. For example, CARB should use the significant data from the Auto/Oil Air Quality Improvement Research Program to estimate future TOG and formaldehyde emissions from motor vehicles.

GM is also concerned that the Table of "Excess Potential Cancer Cases For California Exposure" on page 8 of the Executive Summary overstates the risk from outdoor exposure to formaldehyde. The use of the "out of home" category together with the assumption that the out of home exposure is about the same as outdoor exposure will leave the misleading implication that the "out of home" cancer risk is associated with outdoor sources of formaldehyde. GM recommends that the out of home category be broken down into three separate sub-categories: offices and public buildings; outdoor exposures in urban areas; and outdoor exposures in rural and remote areas. These sub-categories have distinctly different exposures and risks associated with them. Introducing additional exposure categories will permit a better comparison of the specific risk contributions from these exposures and can be helpful in defining the most effective risk reduction strategies. Table 1 illustrates that when the outdoor and indoor fractions of the "out-of-home" exposures are separated, the overall contribution of motor vehicle emissions represents a minimal fraction of the total exposure and public health risk. This is important information since it shows that the sources of personal exposures are producing a completely different result than would be expected from the inventories of outdoor formaldehyde emissions in California (Figures III-1 and III-2, page A-13-14: 78% of the inventory is from mobile source vs. 1.4% contribution of mobile sources to personal exposures. This corresponds to an estimated excess of six cancer cases per year.)

Table 1. Exposure Contributions to Estimated Excess Cancer Cases from California Exposure

	Persons (million)	Conc. (ug/m3)	Air Vol. (m3/day)	Dose Rate (ug/day)	Cancers (thousands)	Overall Risk Contribution (%)
In home						
Conventional homes	29	61 (50 ppbv)	9.3	570	19.8	67.0
Mobile homes	1	92 (75 ppbv)	9.3	860	1.0	3.3
Out of home - indoors						
Office & public bldg.	30	31 (25 ppbv)	7.43	230	8.3	28.1
Out of home - outdoors						
Urban areas	20	5.4 (4.4 ppbv)	3.27	17.7	0.4	1.4
Rural areas	10	1.5 (1.2 ppbv)*	3.27	4.9	0.06	0.2
Total	30				29.6	100.0

* Rural concentration used in U.S.EPA/OMS assessment (Adler and Carey, 1989)

Part A: Exposure Assessment of Formaldehyde

Part A of the draft (Exposure Assessment) indicates that the average formaldehyde inside offices and public buildings ranges between 20 and 60 ppbv (page A-47), significantly higher than the 4.4 ppbv assumed in the Executive Summary. GM is particularly concerned that the risk from smoking in offices and public buildings - although briefly mentioned in the document - may be a much more important source of exposure than the outdoor environment. Lofroth et al. (1989)[3] measured formaldehyde in environmental tobacco smoke not only in experimental chambers but also analyzed the air in a tavern during normal smoking conditions. The formaldehyde concentrations were as high as 104 and 89 ug/m3 in two separate studies. Because people spend a significant fraction of their "out-of-home" time in these microenvironments, this exposure and risk should not be ignored. Since the time spent in public places represents a non-voluntary exposure, this microenvironment may be particularly amenable to cost-effective risk reduction strategies.

Concerning the outdoor exposures, the population in urban areas (noted on page 3 as 20 million) should be used in assessing the risk of urban environment. The fraction of time spent outdoors and the volume of air inhaled per day should be adjusted taking into account new literature data on human activity and behavioral patterns (Ott, 1988)[4]. For example, people routinely spend about 15 percent of their time outdoors. Similarly, the balance of the California population should be used, together with appropriate concentrations and fractions of time spent outdoors, also for outdoor exposures in rural and remote areas (Table 1). The U.S.EPA Office of Mobile Sources estimated an average formaldehyde concentration of 1.5 ug/m3 (1.2 ppbv) as the representative level for the ambient concentrations in these areas[5].

Part B: Health Assessment of Formaldehyde

The DHS Staff's update of the health effects of formaldehyde is a significant step forward in the evaluation of public health impacts of air pollutants because it recognizes the importance of pharmacokinetic principles in risk assessment methodology and introduces a new concept of the tissue dose rate instead of the administered dose into the risk estimation process.

In general, GM scientists agree with the document's conclusion that there is <u>sufficient</u> evidence that high concentrations of

formaldehyde produce tumors in experimental animals. There is, however, a considerable uncertainty whether or not the documentation is sufficient to show that formaldehyde "should not be considered to have a carcinogenic threshold" (Summary, page 1-5).

The document acknowledges that "the mechanisms by which formaldehyde causes cancer in experimental animals have not been fully elucidated". (page 2-5). The text also recognizes that the main evidence of formaldehyde genotoxicity comes from in vitro tests whose predictive significance has been questioned by many scientists. There are many unresolved issues in the assumed chemical carcinogenicity of formaldehyde, such as the need for unwinding of the double helix molecule (cell replication) before the interaction with formaldehyde can occur (Singer and Kusmierek, 1982)[6] and the apparent cell-cycle specificity of the chemical (Swenberg et al., 1983)[7]. The exact mechanism responsible for formaldehyde carcinogenicity is obviously complex and the uncertainty of purely genotoxic action of formaldehyde is indicated by the fact that neither the animal studies nor the experience in humans have demonstrated any teratogenic or reproductive outcomes of formaldehyde exposures.

Using a correct explanation of the carcinogenic action of formaldehyde is important in the assessment of its public health risks because of the uncertainties in extrapolating the effects of high doses to low ambient concentrations. Considering existing scientific views on the role of non-genotoxic factors in animal testing (see Ames and Gold, 1990 et al.)[8], the automotive industry believes that the DHS Staff's conclusion that formaldehyde "is genotoxic and should not be considered to have a carcinogenic threshold." (page 1-5) is an overly conservative conclusion because the possibility of non-genotoxic mechanisms in formaldehyde tumorigenesis has never been adequately excluded. Butterworth and Slaga (1991)[9] and Cohen and Ellwein, (1990)[10] have demonstrated the potential for chemically induced cell proliferation in animal tumors, and the National Academy of Sciences is reviewing the existing guidelines for chemical carcinogenicity testing under similar concerns. Moreover, the scientific community at large points out that under the current methodology, society can spend "hundred of billions of dollars on programs that will have little impact on human health" (Abelson, 1990)[11].

The solely genotoxic character of formaldehyde is questionable because of many experimental observations. First, the non-linearity of formaldehyde response is well known and the formaldehyde-induced tumors exhibit an extremely sharp dose/response curve and prominent species differences (Swenberg, 1983)[7]. It is particularly important to note that all animal experiments producing

formaldehyde-induced tumors used levels that are orders of magnitude higher than any monitored formaldehyde concentration in ambient air. Second, data used in the document to estimate the tissue dose reassure that "multiple naturally-occurring defense mechanisms limit the amount of inhaled formaldehyde reaching the DNA" (page 1-2, 2-7, 2-9). This suggest that the tissue dose must exceed a discrete level "needed to exert an effect."

Third, inhalation of formaldehyde has been shown to form DNA-protein crosslinks in nasal respiratory mucosa only when concentrations were equal to or higher than 2 ppm and the formation of crosslinks is interpreted in terms of a "provisional" pharmacokinetic model incorporating oxidation of inhaled formaldehyde as a primary defense mechanism (Casanova et al., 1989)[12]. While the crosslinks document an interaction of formaldehyde with DNA and offer a good index of tissue dose, the authors explicitly warn that "since such a calculation involves an extrapolation beyond the observable range, the results should be regarded with caution. The data do not exclude the possibility that at sufficiently low concentrations (<0.1 ppm), all of the inhaled formaldehyde is trapped in the mucous layer, and none is absorbed into the cell" (Casanova et al., 1989)[12]. The DHS document confirms on page 2-9 that"at low concentrations of formaldehyde a detoxification takes place more efficiently than at higher concentrations" and that only "at sufficiently high exposure concentrations the detoxification mechanisms become overwhelmed."

These findings show more than anything else a well-established no-effect level in the action of formaldehyde because not every inhaled molecule of formaldehyde would reach the target tissue and result in tumors. The observation of measurable crosslinks after 0.3 ppm exposures (Casanova et al., 1989)[12] does not exclude the presence of a threshold since this exposure level still exceeds the ambient exposures by more than two orders of magnitude and the threshold may be below this level.

In fact, all of these data question preceeding statements in the DHS document (page 1-3) that "using molecular dosimetry to calculate the quantity of formaldehyde reaching the site of action provides a non-threshold explanation ... ...describing the cancer bioassay in rats." If the DHS Staff accepts the molecular dosimetry data as an index of "a more accurate dose.. ... providing a more accurate risk assessment", it should also pragmatically recognize the possibility of a discrete threshold for the tumor producing action of formaldehyde exposures. Or at least, the high level of uncertainty in our understanding of the tumorigenic response and in the extrapolation of high doses to low ambient concentrations should be explicitly discussed in the document.

General Motors believes strongly, that by referring to the Casanova-Heck studies and accepting the molecular dosimetry approach, DHS staff should no longer insist on "having not found evidence of a carcinogenic threshold of formaldehyde (page 1-3). Because of the presence of defense systems and the non-linear response, the DHS assumption of DNA-crosslinking mechanisms as an index of the tissue dose requires that the statement in the Summary be changed and the "provisional" risk extrapolation models modified so that the possibility of a no-effect level is recognized.

In addition, General Motors feels that the risk assessment should include discussion on the alternative possibility that the tumors may be product of epigenetic mechanisms (such as an increased cell proliferation) because of the following observations:

(1) No respiratory tumor was reported in CIIT studies when exposures were lower than or equal to 2 ppm and the response was minimal (1/119) even at concentrations as high as 5.6 ppm, indicating a non-linear carcinogenic effect with a documented no-effect level in rats (Kerns 1983)[13]. It should be noted that these concentrations still exceed average ambient exposures by three orders of magnitude;

(2) An 18-fold increase in epithelial cell proliferation occurs in nasal passages of rhesus monkeys after exposure to formaldehyde (6 ppm - Monticello et al., 1989)[14], documenting the non-specific irritating action of high formaldehyde concentrations as a plausible explanation of animal tumors;

(3) Much higher levels of DNA crosslinking occur in rats compared with rhesus monkeys when exposed to high concentrations of formaldehyde. This is explained by accelerated elimination of the inhaled chemical or by a more effective DNA repair in subhuman primates (Heck, 1989)[15]. Again, saturation kinetics of the defense mechanisms that must be overwhelmed by excessive exposures corroborates the non-genotoxic character of tumors and reaffirms the existence of an observable threshold at low exposures.

(4) The high tolerance of rats to perorally administered doses of formaldehyde (25 mg/kg/day) without carcinogenic effects contradicts the systemic action of formaldehyde as a genotoxic agent and confirms the predominantly local action of inhaled high concentrations on the sensitive nasal epithelial cells (Til et al., 1989)[16];

(5) Numerous epidemiological studies on occupationally exposed workers have failed to produce convincing evidence of a higher cancer incidence in these populations in spite of elevated formaldehyde exposures documented by metaplastic alterations on nasal epithelium (Holstrom, 1989[17], Boysen, 1990[18])

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TIMBER ASSOCIATION
OF CALIFORNIA

April 4, 1991
File No. 8115 (form.)

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Branch
Stationary Source Division
P.O. Box 2815
Sacramento, CA 95814

RE: Proposed Listing of Formaldehyde as a TAC

Dear Ms. Shiroma:

The Timber Association of California would like to offer some comments on the draft staff report for the proposed listing of formaldehyde as a toxic air contaminant. We were observers during the April 3 workshop, but these comments did not seem appropriate within the context of the more technical discussions that occurred there.

We fully support the comments of the representatives from the Formaldehyde Institute, so did not provide technical comments of our own. However, we also have some concerns with the treatment of "wood processing facilities" in the report.

Both in the staff report and during the workshop, it was suggested that there are expected to be "hot spots" near "wood processing facilities". We are unclear exactly what a "wood processing facility" is, but in the context of this report it appears that what is meant are facilities producing reconstituted wood products (SIC 2493) and plywood (SICs 2435 and 2436). The term "wood processing facilities", however, gives the impression that all facilities handling wood, such as sawmills, remanufacturing mills, etc., are potential "hot spot" sources. We request that this be clarified in the report and that appropriate terminology be adopted.

Besides this general point, we are also concerned about the basis for such statements. The ARB air toxics monitoring network is entirely oriented to urban exposure monitoring. Consequently, only two of the sites (Stockton and Fresno) are even in the same city or town as a wood products facility, and none are near a reconstituted wood products facility. Thus, statements about potential wood products "hot spots" are entirely conjectural and have no supporting basis.

Further, the one piece of data cited, the 1987 SARA Title III reports, is clearly erroneous. We believe that we know which two facilities are being referred to and know that the data reported as 1987 emissions are incorrect. The emissions testing at one of these facilities was riddled with errors and recent testing has shown actual

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emissions to be some 10 times lower. This correction changed the estimated emissions from 111 TPY (almost all of the amount reported in the staff report) to 12 TPY. The facility in question proposed to report these changes to the EPA database, but were told that it wouldn't be changed, so why bother! At any rate, it appears that actual emissions from the two facilities are in the range of 10-15 TPY each. One other facility that we recently acquired data on has emissions of only 1.5 TPY.

Of course, ARB staff could not be aware of these problems, so cannot be blamed for such errors. However, we think that it is in the best interest of public policy to ensure that accurate data is used. We are currently collecting information on the formaldehyde emissions from the reconstituted wood products facilities that we know of. We are only aware of 6 or 7 in the state (and 3 plywood plants), so should be able to collect this data very quickly. We will then provide this information to staff for incorporation into the report.

We hope that these comments will help to ensure a clearer and more accurate final document. Please contact our office if you should have any questions or wish to discuss the data collection project.

Sincerely,

STEVEN PETRIN
Director
Environmental Affairs

BEFORE THE STATE OF CALIFORNIA
AIR RESOURCES BOARD

COMMENTS REGARDING DRAFT DOCUMENT ON PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT

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March 26, 1991

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15. Marsh, et al., "A Reanalysis of the National Cancer Institute Study on Mortality Among Industrial Workers Exposed to Formaldehyde" (Mar. 1990)

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17. CPSC, Status Report on the Formaldehyde in Textiles Portion of Dyes and Finishes Project (excerpts)

18. Letter from Dr. John Clary to Dr. Bruce Ames Regarding Classification in Ingestion Studies (Oct. 28, 1987)

19. Comments on the Soffritti Study by Dr. James Swenberg (Mar. 14, 1990)

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COMMENTS REGARDING DRAFT DOCUMENT ON PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT

The Formaldehyde Institute, Inc. (the "Institute") appreciates the opportunity to comment on the Preliminary Draft Document of the California Air Resources Board on the "Proposed Identification of Formaldehyde as a Toxic Air Contaminant" (Feb. 1991) (hereinafter referred to as "Draft Document").

The Institute is a not-for-profit corporation whose membership consists of firms and trade associations representing all phases of the formaldehyde industry, including formaldehyde manufacturers, resin and adhesive producers, textile and apparel producers, plastics manufacturers, and wood product producers.

The Institute has among its charter purposes sponsorship of research on safe use of formaldehyde and presentation to government agencies of information relating to formaldehyde so as to encourage responsible regulation of formaldehyde and formaldehyde products. The Institute has sponsored over $2 million in research on formaldehyde toxicology and epidemiology, and significant further research has been sponsored by member companies. The Institute has made extensive prior submissions to California on formaldehyde issues.

I. EXECUTIVE SUMMARY

The governing statute requires careful evaluation of all data to support identification of a substance as a toxic air contaminant. The governing statute defines "toxic air contaminant" as:

> an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Cal. Health & Safety Code § 39655. In making a listing determination, the agency is required to conduct a careful review of all available data:

> In conducting this evaluation, the State Department of Health Services shall consider all available scientific data . . . .
>
> The evaluation shall assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substances.

Cal. Health & Safety Code § 39660(b), (c).

As currently formulated, the Draft Document does not reflect such review:

(1) Although the Draft Document has the worthy goal of seeking to update EPA's 1987 risk assessment, it does not properly incorporate all of the relevant mechanistic information regarding formaldehyde. EPA recently has issued a revision to its risk assessment yielding a prediction of risk much lower -- by a factor of 10 to 100 -- than that provided in the Draft Document. Further, cell proliferation data are available; incorporation of that data would further reduce the prediction of risk by over one order of magnitude. The Draft Document should be revised to reflect EPA's updated analysis and the other available data.

(2) The risk assessment uses an interspecies scaling factor which significantly overestimates the true risk of

formaldehyde exposure.

(3) The Draft Document does not provide a balanced discussion of the formaldehyde epidemiology data. In particular, the epidemiology data regarding lung cancer do not show excess risk attributable to formaldehyde.

(4) The Draft Document improperly concludes that formaldehyde is genotoxic in vivo.

(5) The Draft Document relies upon poorly-conducted studies in deriving a conclusion that formaldehyde is likely to be carcinogenic by the oral route.

(6) The Draft Document incorrectly suggests that benign tumors are meaningful in assessing cancer risk of formaldehyde.

(7) The Draft Document gives undue weight to a few poorly-controlled studies finding hyperplasia in exposed workers.

(8) The Draft Document's exposure analysis is flawed.

Revision of the Draft Document would provide a sound scientific basis for a determination whether listing formaldehyde as a toxic air contaminant is appropriate.

It is especially significant that EPA has issued a draft revised risk assessment and currently is in the final stages of its process to issue its revised formaldehyde risk assessment in final form. EPA expects to have the revised risk assessment undergo final peer review in the next few months. A brief delay in finalizing the Draft Document would enable California's risk assessment to reflect the expert analysis by EPA and its outside reviewers and would avoid the confusion and uncertainty that would result from inconsistent approaches.

II. THE DRAFT DOCUMENT DRASTICALLY OVERESTIMATES THE TRUE CANCER RISK FOR FORMALDEHYDE

A. The Evidence Shows that Formaldehyde Is Not Genotoxic In Vivo

The Draft Document's discussion of genotoxicity is one-sided, ignoring relevant evidence that formaldehyde is not genotoxic in vivo. While formaldehyde has been shown to be weakly genotoxic in vitro, it does not have the same effect in the intact, healthy, live animal. The Brusick study[1] showed formaldehyde is not mutagenic at levels up to 25 ppm in live animals repeatedly exposed through inhalation. In live animals, the presence of various defense mechanisms (such as metabolic deactivation of inhaled formaldehyde, cellular repair processes, and the protective action of mucus) affect the action of formaldehyde.

A panel of scientists which reviewed the literature on genotoxicity in a report for the Canadian government concluded:

> The genetic toxicity of formaldehyde has been studies extensively in both in vitro and in vivo test systems. . . .
>
> The results of in vivo studies of genetic toxicity are equivocal and postive results, when obtained, were generally marginal and occurred only at very high exposure rates (25 ppm) No consistent positive results have been reported in dominant lethal studies in rats and formaldehyde failed to induce micronuclei or chromosome abberations in vivo.
>
> While formaldehyde has been shown to be weakly genotoxic in several test systems in vitro, there is no substantial evidence that it is mutagenic in mammalian systems in vivo. The nasal mucosal epithelium has not

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[1]Brusick, et al., "Genetic and Transforming Activity of Formaldehyde," (April 1980).

> been studied in this regard. This lack of clear evidence of genotoxicity in vivo may be explained by the rapid metabolism of formaldehyde in intact animals.

I. Munro, E. Farber & L. Golberg, "Review of the Available Information on the Health Effects of Formaldehyde on Behalf of the Ontario Ministry of Labour" (Mar. 1985) (attached hereto as Ex. 1). Genotoxicity studies are, of course, of less relevance given the extensive data base on animal carcinogenicity and mechanism research.

B. The Draft Document's Risk Assessment Overestimates Risk

The Draft Document recognizes the importance of taking into account the extensive mechanistic data regarding formaldehyde, and it attempts to incorporate some of that data into its risk assessment. However, the Draft Document does not properly incorporate all of the relevant and well-recognized mechanistic data. The Draft Document compounds its error by applying a scaling factor for interspecies extrapolation from rats to humans based on theoretical projections concluding that humans are five times more sensitive than rats to formaldehyde exposure. In fact, the rhesus monkey experiments recently conducted by CIIT provide a basis for a risk assessment that does not rely on a theoretical and overly-conservative scaling factor.

The Draft Document relies extensively on the 1987 formaldehyde risk assessment document prepared by the U.S. Environmental Protection Agency. However, the Draft Document fails to recognize that, in September 1990, EPA issued a draft revision to its risk assessment document that properly

incorporated the mechanistic data for formaldehyde -- DNA cross-linking data in the rat and monkey -- that had become available during the intervening three years.[2] The difference between the Draft Document's approach and EPA's approach is stark. When both the mechanistic data and the scaling factor are taken into account, EPA's 1990 unit estimate of incremental risk is 10 to 100 times less than that presented in the Draft Document.

EPA's revised risk assessment was unanimously endorsed upon peer review by the expert Science Advisory Board at its meeting on October 25, 1990.[3] EPA is expected to issue the risk assessment in final form in the next few months.

The Draft Document relies upon EPA's 1987 analysis as the starting point for its risk assessment. The 1987 EPA analysis is now out of date, and EPA is in the process of revising its risk assessment. Instead of the 1987 analysis, the Draft Document should be revised to rely upon the EPA revision which has been publicly issued, endorsed by the experts, and is soon to be finalized.

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[2]EPA Office of Toxic Substances, "Formaldehyde Risk Assessment Update - External Review Draft" (Sept. 24, 1990), Ex. 2.

[3]See "EPA Science Advisers Approve Use of New Dosimeter, Use of Biological Data," BNA Chemical Regulation Reporter 1125-26 (Nov. 2, 1990); "Formaldehyde Seen as 25-Fold Less Risky in New Assessment," Pesticide & Toxic Chemical News 20-21 (Oct. 31, 1990) (provided in Ex. 3). The members of the Science Advisory Board's Environmental Health Committee, which peer-reviewed EPA's revised risk assessment, included Warner North of Decision Focus, Mel Anderson of CIIT, Bernard Weiss of the University of Rochester School of Medicine, Richard Monson of the Harvard School of Public Health, Ronald Wyzga of the Electric Power Research Institute, and Fred Miller of Duke University Medical Center.

1. Background Regarding the Mechanistic Data

As the Draft Document notes, there is strong evidence that the cancer observed in rats at high doses is related to the "cytotoxic" effects of those high doses, thus indicating that cancer will not occur at low doses. CIIT research showed that a 10 to 20-fold increase in cell replication occurs when rats are exposed to 6 or 15 ppm. In addition, at doses that do not increase cell proliferation, biological protective mechanisms (e.g., cell repair, detoxification, mucus secretion and mucus reactions with formaldehyde, and immunologic, tumor-associated rejection mechanisms) prevent or mitigate carcinogenic effects of formaldehyde.[4] As Dr. Swenberg concluded:

> The overloading of protective mechanisms such as mucociliary clearance, metabolic detoxification and DNA repair, and the stimulation of the proliferative response by tissue injury are likely to be responsible for the observed non-linearity in tumor response versus administered dose. It thus appears that the ratio of delivered to administered formaldehyde dose may be much larger at high ambient air concentrations than it is at

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[4]For example, the nasal mucus acts as a protective barrier against low concentrations of formaldehyde, but it becomes saturated and permits formaldehyde to reach the epithelial cells at high concentrations. The Carcinogenicity Panel at the workshop on formaldehyde sponsored by the National Center for Toxicological Reseach ("NCTR") stated:

> [I]ncreasing the exposure concentration of formaldehyde from 6 to 14 ppm, less than a three-fold increase, resulted in a 50-fold increase in squamous cell carcinomas in rats. Possible mechanisms for this include impairment of mucociliary clearance, detoxification, and DNA repair leading to greater effective target site doses.

Report of the NCTR Consensus Workshop on Formaldehyde, 58 Envt'l Health Persp. 323, 341 (1984).

low concentrations.[5]

However, the Draft Document does not adequately account for all of the recent mechanistic data. In 1990, Drs. Heck, Casanova-Schmitz and Starr of CIIT published a comprehensive article[6] based on ongoing primate studies following on their previous experiments with rodents. The new research confirms earlier CIIT findings that formaldehyde dose response is highly non-linear; cell-proliferation caused by exposure to high cytotoxic doses appears to represent the mechanism of formaldehyde carcinogenicity. CIIT concludes that the new data demonstrates that the toxic effects induced by formaldehyde depend non-linearly on concentration and are highly tissue-and species-specific. The "Conclusions" section of CIIT's article summarizes the major advances that have been made in recent years on the implications of mechanistic data:

> (1) Concentrations that are demonstrably carcinogenic are also cytotoxic and increase cell proliferation in the nose. Increased cell turnover is an extremely important, and possibly essential, component of the carcinogenic mechanism of formaldehyde. The rate of cell proliferation in the nasal mucosa of rats exposed to a constant total dose of formaldehyde increased with increasing concentrations.
>
> (2) Increased turnover resulting from a single

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[5]Swenberg, et al., "Non-Linear Biological Responses to Formaldehyde and Their Implications for Carcinogenic Risk Assessment," Carcinogenesis 4:945, 950 (1983) (emphasis in original). On the significance of non-linearity generally, see Hoel, et al., "Implication of Nonlinear Kinetics on Risk Estimation in Carcinogenesis," 219 Science 1032 (Mar. 4, 1983).

[6]Heck, Casanova-Schmitz & Starr, "Formaldehyde Toxicity -- New Understanding," Crit. Rev. Toxicol. 20:397-426 (1990).

infliction of severe tissue damage was insufficient by itself or when coupled with exposure to a low concentration of formaldehyde (≤ 1.0 ppm) to induce nasal cancer in rats. A statistically significant tumor incidence was observed only when tissue damage took place in conjunction with exposure to a very high concentration (e.g., 10, 15, or 20 ppm). The concentration of formaldehyde delivered to cells of the nasal mucosa increases nonlinearly with the airborne concentration, with rapid increases occurring at concentrations above 2 to 3 ppm. . . .

* * * *

(4) The nonlinear concentration dependence of DNA-protein cross-link formation and the predominant role of concentration in determining cell turnover and mutagenic efficiency strongly suggest that the intracellular concentration of formaldehyde is modulated by saturable defense mechanisms. . . .

(5) Lesions induced in the rate nose (squamous metaplasia and epithelial hyperplasia) by a subchronic exposure to 10 ppm of formaldehyde were reversible if exposure was discontinued before 8 weeks. Irreversible lesions were induced by exposures for longer times or to higher concentrations.

(6) Formaldehyde-induced lesions in the respiratory tract of monkeys exposed to 6 ppm for 6 weeks were similar in nature to those observed in rats. However, the lesions were more widespread in monkeys than in rats exposed under the same conditions, while the concentration of DNA-protein cross-links in the turbinates and anterior nose following a single exposure to [^{14}C] formaldehyde was significantly lower in monkeys than in rats. Cross-links were also detected in more distal regions of the respiratory tract of some monkeys exposed to 2 or 6 ppm, but not to 0.7 ppm.

(7) Formaldehyde failed to induce hepatotoxicity, immunotoxicity, or DNA-protein cross-linking at sites remote from the site of deposition following inhalation exposures, it failed to induce hepatotoxicity following oral exposures, and it failed to induce tumors in rats when administered at high concentrations in the drinking water. Formaldehyde concentrations in the blood of rats, monkeys, and humans were not significantly increased by inhalation exposure.

(8) Inhaled formaldehyde does not impair pulmonary function and does not induce airway hyperreactivity in humans at airborne concentrations as high as 3 ppm. In Rhesus monkeys, absorption occurs primarily in the nasal cavity, and very little penetrates to the lung, especially at low concentrations. The concentration of DNA-protein cross-links in nasal cavity tissues of Rhesus monkeys was about an order-of-magnitude lower than in the nasal mucosa of rats.

CIIT concluded that the primate data should result in a reduction in the cancer risk estimates for formaldehyde:

> By utilizing DNA-protein cross-links as an internal dosimeter, the Rhesus monkey is predicted to be at much lower risk of nasal cancer than the rat. [Citations omitted] Thus, assuming that the monkey is susceptible to formaldehyde-induced carcinogenesis, the upper bound estimate of risk to the nasal turbinates and anterior nasal mucosa is 13 to 20 times smaller between 1.0 and 0.1 ppm than that predicted for the rat based on the administered concentration (column 5; "DPC/Monkey"). The maximum-likelihood estimate of risk for the monkey is between four and five orders-of- magnitude lower than that predicted for the rat over the same concentration range.
>
> In Rhesus monkeys, absorption occurs primarily in the nasal cavity, and very little penetrates to the lung, especially at low concentrations. The concentration of DNA-protein cross-links in nasal cavity tissues of Rhesus monkeys was about an order-of-magnitude lower than in the nasal mucosa of rats.

Id. at 41, 43.[7]

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[7]Similarly, a recent summary of the data by Dr. Starr, formerly of CIIT, concluded:

> An impressive array of data points to significantly nonlinear relationships between rodent tumor incidence and administered dose, and between target tissue dose and administered dose (the latter for both rodents and Rhesus monkeys) following exposure to formaldehyde by inhalation. Disproportionately less formaldehyde binds covalently to the DNA of nasal respiratory epithelium at low than at high airborne concentrations. Use of this internal measure of delivered dose in analyses of rodent bioassay nasal tumor response yields multistage model

A report by V. Feron and R. Woutersen, "Role of Tissue Damage in Nasal Carcinogenesis" (TNO-CIVO) (presented to Toxicology and Nutrition Institute, Zeist, The Netherlands) (Sept. 1988) (the "Feron Report"), concluded from the CIIT data that human exposure to non-cytotoxic levels of formaldehyde represents a negligible cancer risk. Feron found that malignant tumors occurred in rats exposed to 10 ppm, concentrations that were observed to cause severe tissue damage. The Feron Report provided examples of human cancers which develop in chronically injured tissue, such as skin cancer and colon cancer, and noted that "[c]ytotoxic effects and epithelial hyperproliferation appear to play an almost essential role in the development of nasal tumors in rats exposed to formaldehyde."

With respect to the Feron study and a more recent study by Woutersen,[8] CIIT recently stated:

> These results demonstrate that irreparable tissue damage and cancer can occur in rats exposed subchronically to formaldehyde, but that the induction of cancer appears to require very high concentrations of formaldehyde. . . .
>
> The important studies of Woutersen et al. indicate

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estimates of low-dose risk, both point and upper bound, that are lower than equivalent estimates based upon airborne formaldehyde concentration. In addition, risk estimates obtained for Rhesus monkeys appear at least 10-fold lower than corresponding estimates for identically exposed Fischer-344 rats.

Starr, "Quantitative Cancer Risk Estimation for Formaldehyde," 10 Risk Analysis 85 (1990).

[8]Woutersen, et al., "Nasal Tumors in Rats After Severe Injury to the Nasal Mucosa and Prolonged Exposure to 10 ppm Formaldehyde," J. Appl. Toxicol. 9:39 (1989).

> that increased cytotoxicity and cell turnover play a significant, and perhaps an essential role in the induction of nasal cancer by formaldehyde. Two major effects of an increased rate of cell turnover are an increase in the number of cells that are at potential risk of suffering a heritable mutation, and an increase in the probability that a mutated cell may redivide and perhaps experience further DNA damage, ultimately generating a transformed cell population. The experiments of Woutersen, et al., [footnote omitted] suggest that increased cell replication due to a single tissue injury is probably insufficient in itself or when coupled with a chronic exposure to a low concentration (≤ 1.0 ppm) of formaldehyde to generate a population of fully transformed cells. A significant increase in the incidence of nasal cancer was only observed when the increase in cell turnover took place in conjunction with a chronic or a subchronic exposure to a very high concentration of formaldehyde, i.e., 10, 15, or 20 ppm. [footnotes omitted]

CIIT, supra at 15-16.

CanTox, Inc. has conducted a comprehensive literature review of all formaldehyde health effects studies, including laboratory animal and human epidemiology studies. CanTox prepared a biological risk assessment utilizing data on respiration rate, respiratory tract physiology, mucociliary clearance mechanisms, cytotoxicity, and DNA repair. CanTox, Inc., "Biological Risk Assessment of the Potential Carcinogenesis from Exposure to Airborne Formaldehyde," (Oct. 27, 1988), Ex. 4. CanTox reached the following conclusion:

> the data demonstrate that the no effect level for carcinogenicity of formaldehyde is 1 ppm and an assessment of biological relevance of available formaldehyde data indicates that an exposure level of 1 ppm or less would eliminate the risk of developing cancer in humans.

Id. at viii.

CanTox reached the following findings with respect to

specific aspects of the biological data:

Protective Mechanisms. The average human adult produces about 51 grams per day of formaldehyde as a metabolite for use in building essential body chemicals and in breaking down other chemicals. In contrast, a person continuously exposed to 1 ppm of formaldehyde for 24 hours would take in 24.6 milligrams, over 2,000 times less than that produced in the body. CanTox concluded that "[t]he addition of such a tiny fraction to the body pool would not be expected to add significantly to the risk of developing formaldehyde-induced systemic effects" and that "[a]t diminished delivered doses [less than 2 ppm], it is reasonable to expect that normal cellular metabolism and DNA repair would adequately protect cellular systems from adverse effects of formaldehyde. These mechanisms exist to protect against adverse effects from normal endogenous formaldehyde. . . ."[9]

Cell Proliferation and DNA repair. CanTox reached the following conclusions regarding the biological data that indicate a non-linear response to formaldehyde -- in other words, that the cancer observed in laboratory rats at 14.3 ppm results from

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[9]CanTox referred to studies by CIIT using rhesus monkeys that showed no significant increase in blood formaldehyde concentration following exposure to 6 ppm for four weeks and finding that, at an exposure of 6 ppm for one and six weeks, only effects on the nasal cavity, larynx, trachea and upper bronchi, and not in the lung or other organs, were observed. Id. at 31-32, 74 (citing Casanova-Schmitz, et al., "Formaldehyde (HCHO) Concentrations in the Blood of Rhesus Monkeys Exposed to HCHO by Inhalation" (1989); Monticello, et al., "Effects of Formaldehyde Gas on the Respiratory Tract of Rhesus Monkeys" (1988)).

persistent cytotoxicity at high doses and would not be expected to occur at lower levels:

> [A]bove 2 ppm . . .[n]ormal metabolism and repair functions would begin to become saturated and there would be a greater chance of formation of DNA-protein cross-links from formaldehyde. Increased cellular injury would produce a hyperproliferative response and the resulting increased cellular turnover would further increase the DNA-protein cross-linking with formaldehyde.[10]

Id. at vii.

Interspecies variation. CanTox noted that "[t]he occurrence of high local concentrations of formaldehyde in the rodent, as influenced by the unique geometry of the rat nasal cavity, leads to hyperproliferative responses that are critical to the development of cancer in that species." Applying the recent CIIT data, CanTox also concluded that there are substantial species differences which make humans less susceptible to the effects of formaldehyde than rats:

> The respiratory tract of humans more closely resembles that of the monkey than the rat. Therefore, based on species differences in breathing patterns, respiratory tract physiology and doses of formaldehyde delivered to nasal tissues, the linear extrapolation of formaldehyde data from rodents to humans would result in an overestimation of expected cancer incidence.

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[10]CanTox also described the recent results of an improved analytical method developed by CIIT to determine the extent of binding of formaldehyde to mucosal DNA. The data based on rats exposed to 0.3, 0.7, 2, 6 and 10 ppm formaldehyde confirmed the non-linearity of covalent binding: "(1) at the limit of inhaled formaldehyde concentration approximately 12% of absorbed formaldehyde is bound to DNA (88% is detoxified; (2) the detoxification pathway is half-saturated at an airborne concentration of 2.6 ppm; and (3) the limiting slope of the concentration-response curve for DNA-protein cross-linking at high concentrations." Id. at 86 (citing Casanova-Schmitz, et al., supra).

Id. at vii-viii.

> Based on review of these data, CanTox concluded:
>
> Assessment of the factors that affect tumor development, respiratory patterns, respiratory tract physiology, mucociliary clearance, rate of cell turnover, detoxification metabolism, DNA-binding and DNA repair, and lower delivered doses of formaldehyde to nasal tissues of primates compared with rats leads to the conclusion that at 1 ppm the operation of protective mechanisms would eliminate the risk of developing formaldehyde-induced cancer of the upper respiratory system.

Id. at 195.

2. The Revised EPA Risk Assessment Properly Reflects the Currently-Available Mechanistic Data

Although the Draft Document recognizes that use of mechanistic data can improve formaldehyde risk assessment, it does not reflect all of the available information including EPA's recent revision to its risk assessment and further data regarding cell proliferation. In addition to the discussion below, these issues are addressed in detail in the attached comments of Dr. James A. Swenberg (Attachment A) and of Dr. Thomas B. Starr (Attachment B).

EPA has revised its 1987 risk assessment to incorporate much of the currently-available mechanistic data -- the DNA cross-linking data in rats and rhesus monkeys developed by CIIT. EPA carefully considered the appropriate uses of the DNA cross-linking data. EPA specifically determined that the DNA cross-linking data was a proximate measure of dose more representative of exposure than airborne levels and that analytical improvements since 1987 supported the use of the cross-linking data as the

measure of dose. See EPA 1990 Risk Assessment, Ex. 2, at 10-19.

Although the Draft Document recognizes the utility of the DNA cross-linking data, it does not fully reflect the available data in its risk assessment.

EPA constructed a linear interpolation model for the data and was able to use a "two stage" multistage model fit. See EPA 1990 Risk Assessment at 56-58, 65-70.

EPA considered in detail whether the monkey DNA cross-linking data or the rat DNA cross-linking data is the best measure of internal dose. Although EPA stated that the rat data are more conservative, EPA noted that the monkey data are significant in view of the similarity of the species and breathing patterns and the comparable toxic response between rats and monkeys. EPA 1990 Risk Assessment, Ex. 2, at 5, 61. EPA noted that the Heck (1990) study had found more widespread DNA cross-linking in the respiratory tract of monkeys than in rats. However, EPA concluded that this effect occurred only at high exposures where biological protective mechanisms would be overwhelmed, and therefore would not be expected to occur at the low levels to which humans are exposed. At such levels, the effects in monkeys were confined to anterior portions of the upper respiratory tract. See EPA 1990 Risk Assessment at 58-60.

Use of the DNA cross-linking data significantly lowers the risk estimate compared to EPA's 1987 risk assessment. EPA's 1990 prediction of incremental unit risk at exposure levels less than 0.3 ppm is 3×10^{-3}/ppm for continuous daily exposures using

the rat DNA cross-linking data[11] and 3 x 10^{-4}/ppm for continuous daily exposures using the monkey DNA cross-linking data. These are factors of two and 20 less than the Draft Document's unit risk of 6 x 10^{-3}/ppm, prior to application of the scaling factor used in the Draft Document, and are factors of 10 and 100 less than the Draft Document's final prediction of risk using the scaling factor.

As EPA stated, the predicted risk level using the rat DNA cross-linking data is believed to overestimate true risk, for three reasons. First, EPA reiterated that the data showing lower DNA cross-linking in monkeys are more significant to the likely effects in humans:

> As stated before, nonlinear dose responses for nasal tumors in rats and [DNA cross link] formation as well as mucociliary clearance, cell proliferation, cytotoxicity, and nonneoplastic pathology in rats and monkeys argue for the true risk being well below that predicted by the upper bound. . . .
>
> Rat-based estimates may be too high at a given exposure concentration, due to differences in breathing patterns.

EPA 1990 Risk Assessment, Ex. 2, at 4, 70. Second, EPA noted that airborne concentration is a more important exposure parameter than total dose:

> The combined results of several toxicologic studies further support the importance of airborne formaldehyde concentration in the induction of toxic effects. Inhalation exposure to a low level of formaldehyde for a long duration of daily exposure (1 ppm for 22 hours) over the course of 6 months does not cause lesions in

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[11]For six-hour exposures using the rat data, the risk prediction was 7 x 10^{-4}/ppm.

> the rat nose. In contrast, subchronic or chronic inhalation exposure to higher formaldehyde concentrations (2-4 ppm) but with a shorter duration of daily exposure (6 hours) produces varying degree of nasal damage in rats. . . .
>
> All these findings demonstrate that airborne formaldehyde concentration is an important exposure parameter and imply that the utilization of lifetime average daily concentrations for risk quantification purposes may overestimate risk potential by arbitrarily lowering the dose at which adverse effects are observed.

EPA Formaldehyde Risk Assessment Update -- Preliminary Analysis Discussion of Evidence, Sept. 28, 1990, Ex. 5, at 4; see Comments of Dr. James A. Swenberg, Mar. 25, 1991, at 4; Comments of Dr. Thomas B. Starr, Mar. 26, 1991, Attachment B, at 6. Third, recent data also show the importance of cytotoxicity and cell proliferation in carcinogenesis. Further data regarding cell proliferation currently is being developed, and EPA deferred consideration of that data pending further work. Further data is now available, and incorporation of that data would further reduce the prediction of risk by over an order of magnitude. See Comments of Dr. James A. Swenberg, Mar. 25, 1991, Attachment A; Comments of Dr. Thomas B. Starr, Mar. 26, 1991, Attachment B, at 2, 6-7; Comments of CIIT to EPA, Oct. 25, 1990, Ex. 6; Comments of Dr. James A. Swenberg to EPA, Oct. 19, 1990, Ex. 7.

The Draft Document has relied upon and endorsed EPA's 1987 risk assessment analysis. That analysis has now been recognized by EPA to be out-of-date. The Draft Document should be revised to reflect EPA's most current analysis.

3. The Risk Assessment Uses an Improper Scaling Factor

There is no basis for the Draft Document's use of a theoretical scaling factor adopting the position that humans are more susceptible to formaldehyde than the rat. In the case of formaldehyde, extensive available data show that humans are less susceptible to the effects of formaldehyde. These data include the fact that humans, unlike the rat, are not obligatory nose breathers and the recent data showing that monkeys had lower levels of DNA cross-linking than did rats.[12]

As discussed in detail in the Comments of Dr. Thomas B. Starr, Mar. 26, 1991, Attachment B at 3-6, the availability of the monkey DNA cross-linking data, which is uniquely available in the case of formaldehyde, confirms the inappropriateness of the scaling factor. EPA conducted the following analysis:

> In the absence of detailed pharmacokinetic or mechanistic data, one of EPA's default positions with respect to equivalence of dose across species has been that inhalation exposures expressed as continuous lifetime average concentrations are assumed to pose equivalent carcinogenic risks across species. This follows from a consideration of the allometry of inhaled doses. A larger animal has a lower surface-to-volume ratio, so that there is less surface to react with inhaled formaldehyde per unit volume of air. A larger animal would be expected to have a higher concentration of DPX, all else being equal. Since some formaldehyde is known to be breathed back out and some is absorbed into the systemic circulation, the critical issue in determining relative rates of DPX formation is in understanding the rates of the various other processes removing formaldehyde from the lumen of the nasal passages. There is no particular reason to

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[12]EPA 1990 Risk Assessment, Ex. 2, at 14, 16, 64; CanTox Report, discussed at pages 13-14, supra; Discussion of DNA cross-linkg data at pages 16-17, supra.

> expect differences across species in the ratios of these rates, so the amount of DPX per mg of DNA would be expected to be about equal.
>
> . . . The EPA assumed that carcinogenic risk is proportional to the DPX level. The assumption implicit in this approach is that humans would experience the same risk as monkeys at a give ambient formaldehyde concentration, because their covalently bound DNA concentrations, and their breathing and deposition patterns, would be similar. This approach acknowledges the differences between rodent and primate respiratory anatomy and dynamics.

EPA 1990 Risk Assessment, Ex. 2, at 61.

Based on the extensive available data, EPA specifically rejected use of a scaling factor that would increase the predicted risk to humans. EPA stated:

> Since the DPX were lower in the monkey nasal mucosa, use of the rat-based estimates, without adjustment for monkey DPX formation, possible overestimates the probability of nasal tumors in primates. On the other hand, the monkey-based estimates may be too low, because the DPX levels measured in the nasopharynx of monkeys, corresponding to a site having strong association of tumor incidence in humans, are not considered in the derivation of risk estimates. . . . The lifetime risks to humans could be expected to be somewhere between the monkey- and rat-based risk estimates.

EPA 1990 Risk Assessment, Ex. 2, at 70-72.

Accordingly, the presence of mechanistic data in the rat and monkey render inappropriate the use of a theoretical interspecies scaling factor in the case of formaldehyde. The data demonstrate that the rat-based estimates overestimate risk. At a minimum, the Draft Document should be revised to use the highly-conservative approach adopted by EPA -- use of the DNA cross-linking data without further application of a scaling factor.

C. The Discussion of the Epidemiology Data is One-Sided and Does Not Appropriately Reference the Findings of the Authors of the Studies

The Draft Document's discussion of the human cancer data is one-sided and does not provide an overview of the extensive epidemiology data base. The Draft Document -- implying that many sites are in excess (ignoring that sporadic excess may be due to chance and other factors), asserting that formaldehyde may cause cancer at remote sites, and contending that very low formaldehyde levels elevate cancer risk -- differs from the positions taken by consensus panels and from a review of the epidemiology data taken as a whole. In the discussion of lung and pharyngeal cancer, the Draft Document cites Blair, Vaughan and Acheson without giving full weight to the published conclusions of each of these well-credentialed investigators.[13]

1. Overview of the Formaldehyde Epidemiology Data Base

Although formaldehyde has been widely used in the workplace for more than ninety years, at levels substantially higher than current occupational exposures or levels attributable to formaldehyde products, epidemiologic studies covering thousands of workers show no overall excess cancer risk among formaldehyde workers. The numerous epidemiology studies reported to date when viewed collectively do not demonstrate that formaldehyde enhances or increases background incidence of

[13]In addition to the discussion below, an overview of the epidemiology data is provided in the Comments to EPA by Dr. John Higginson of Georgetown University Medical Center, Oct. 22, 1990, Ex. 8.

cancer. Individual studies may cover too small a sample to be dispositive, but it is important to note the aggregate size of the various individual study cohorts is substantial. The epidemiologic evidence is especially significant because past workplace exposures were much higher than those observed today, and yet no association has been shown. While sporadic excesses may have occurred and would have been expected, there is a lack of a consistent pattern of excesses at specific sites.[14]

The Draft Document differs from NCTR, OSHA and EPA in finding remote sites (beyond the upper respiratory tract) in excess. There are, however, recognized tests for evaluating an epidemiologic study to provide evidence that a suspected factor is a cause of a disease: strength of the association, consistency between studies, dose-response relationships,

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[14]A 1985 Canadian government panel concluded with respect to the epidemiologic evidence:

> Certain patterns appear to be evident to date. One obvious pattern is the absence of any indication that individuals exposed to formaldehyde (as well as other chemicals simultaneously) have shown an increased risk of developing any neoplasms of the upper or lower respiratory tract including the nasal mucosa and bronchi. This pattern was seen in all studies reported. This negative trend seems also to be present for chronic respiratory disease, especially emphysema.
>
> Another pattern that emerges is the absence of a reproducible increase in incidence of any single type of cancer in all the groups exposed to formaldehyde occupationally. Although some individual studies do show increased standardized mortality ratios for one or more types of cancers or other chronic diseases, the patterns are not reproducible from study to study.

Munro, et al., Ex. 1, at 8.

specificity, biological plausibility, and coherence. Absent assessing the epidemiology evidence against these criteria, chance and confounding factors cannot be eliminated.

Recently a distinguished panel of scientists headed by Dr. John Higginson, the former chairman of the International Agency for Research on Cancer (IARC), issued a report based on review of all of the human epidemiologic studies, including the recent NCI data. The Ad Hoc Panel on Health Aspects of Formaldehyde, convened under the auspices of Universities Associated for Research and Education in Pathology ("UAREP"), concluded that there is no convincing evidence of human cancer risk:

> Two conclusions from this review that would have widespread agreement among epidemiologists are: (1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure; and (2) furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small.

UAREP, "Epidemiology of Chronic Occupational Exposure to Formaldehyde," Tox. Ind. Health 4:77 (1988).[15]

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[15]Respecting specific sites for cancer, UAREP found:

- "[N]either the presence nor the absence of an association between formaldehyde exposure and sinonasal cancer can be said to be firmly established. It should be noted that even a doubling of this rare form of cancer represents a very small absolute risk."

- Regarding nasopharyngeal cancer, "These shortcomings and inconsistencies [of the epidemiologic studies] indicate that the association of nasopharyngeal cancer with formaldehyde exposure must be regarded as weak. However, it is to be noted that despite extensive studies no definite evidence exists in humans that nasopharyngeal cancer can be produced by

The epidemiologic studies are discussed below, looking at particular cancer sites: upper respiratory (nasal and pharyngeal and buccal cavity), lung, and remote sites such as the brain.

2. Upper Respiratory Cancer

If formaldehyde were to pose a cancer risk to man, it is likely that it would be a risk of upper respiratory cancer (i.e., nasal or nasopharyngeal/buccal cavity), for two reasons. First, for known carcinogens, cancer in humans usually occurs at the same site where it is observed in the experimental animals; only nasal cancer was observed in the CIIT tests. Second, formaldehyde is rapidly metabolized by the human body. It is highly unlikely that it would travel to points in the body beyond the site of contact. As the NCTR Consensus Panel stated, "[t]he data now available lead the Risk Estimation Panel to believe that the target sites of formaldehyde are not primarily distant from the site of exposure."[16] Based on knowledge of the mechanisms of toxicity, metabolism, detoxification, repair and carcinogenicity of formaldehyde in animals, it is unlikely that formaldehyde

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inhaled carcinogens."

- "More data are available about lung cancer and formaldehyde than for any other topical site . . . . Overall, the evidence is not indicative of an association between formaldehyde exposure and lung cancer risk."

Id. at 81-83.

[16]NCTR Report at 355.

would have an effect other than at its point of contact.[17]

The epidemiologic studies are examined below with respect to upper respiratory cancer, first for nasal cancer, then for nasopharyngeal/buccal cavity cancer.

a. Nasal Cancer

Given the likelihood that nasal cancer would be the observed effect if formaldehyde were carcinogenic to humans, it is reassuring to note that nasal cancer is extremely rare, despite the ubiquity of formaldehyde exposure in daily life. Moreover, in two dozen retrospective cohort mortality studies to date, there has been no excess nasal cancer.

The National Cancer Institute ("NCI") study by Blair, et al., observed no excess nasal cancer overall among 26,511 workers employed in various plants from 1938-1968 with a total follow-up of 600,000 person-years. (Two nasal cancers were observed; 2.2 would be expected).[18]

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[17]NIOSH cited formaldehyde's rapid metabolism in concluding that excesses of various cancers detected in its study of garment workers were probably not attributable to formaldehyde. See Stayner, et al. (1985). Experimental data show that inhaled formaldehyde does not increase the level of formaldehyde in the blood stream. This evidence, along with data on covalent binding of formaldehyde with DNA, "strongly suggest[s]," according to CIIT scientists, "that the toxicity induced by inhalation of HCHO gas is confined to tissues at the initial site of contact." Starr, et al., "Estimating Human Cancer Risk," at 28. See also the CPSC briefing package on formaldehyde in textiles, in which CPSC examined the question whether formaldehyde, applied dermally, penetrates the skin and can cause carcinogenesis at a site remote from the site of contact. CPSC found that it would not. Cohn, "Dermal Application of Formaldehyde and Carcinogenesis" (Nov. 10, 1983).

[18]"Mortality Among Industrial Workers Exposed to Formaldehyde," J. Nat'l Cancer Inst. 76:1071 (June 1986).

The NIOSH study by Stayner, observed no excess nasal cancer (and no excess cancer overall) in a cohort of 11,030 female garment workers. (0 nasal cancers observed; 0.6 nasal cancers expected).[19]

A study of 2,490 formaldehyde workers by Dr. Gary Marsh of the University of Pittsburgh found no nasal cancer and no dose-response relationship between formaldehyde exposure and respiratory or other cancer.[20] Similarly, a study of 2,026 formaldehyde workers by Dr. Wong found no nasal cancer mortality, no excess upper respiratory cancer mortality, and no excess lung mortality.[21] Two studies of morticians by Doctors Walrath and Fraumeni of the National Cancer Institute (1,132 from New York state[22] and 1,109 from California[23]) also disclosed no nasal

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[19]Stayner, et al., "Retrospective Cohort Mortality Study of Workers Exposed to Formaldehyde in the Garment Industry," Am. J. Ind. Med. 13:667-81 (1988). The study follows a prior proportionate mortality study by Stayner, et al., Am. J. Ind. Med. 7:229-40 (1985).

[20]Marsh, G., "Proportional Mortality Among Chemical Workers Exposed to Formaldehyde," Brit. J. Ind. Med. 39:313 (1983). A follow-up study examined the same cohort for one overlapping year (1976) and four years forward. Liebling, T., et al., Amer. J. Ind. Med. 5:485 (1984).

[21]Wong, O., "An Epidemiologic Mortality Study of a Cohort of Chemical Workers Potentially Exposed to Formaldehyde, with a Discussion on SMR and PMR," reprinted in Formaldehyde Toxicity (Gibson, ed.) at 256-72. A follow-up study of the Wong cohort was conducted with 58 additional cohort members. See Tabershaw Associates, "Historical Prospective Mortality Study" (1982).

[22]Walrath, et al., "Mortality Patterns Among Embalmers," Int'l J. Cancer 31: 407 (1983).

[23]Levine, et al., "Mortality of Ontario Undertakers," J. Occup. Med. 26:740 (1980).

cancer mortality or unusual level of respiratory cancer mortality. Dr. Levine's study of 1,477 morticians licensed over a 20-year period showed no deaths from nasal cancer, and upper respiratory cancer was less than expected.

Professor Acheson reported on a large-scale study of formaldehyde workers conducted by the British Medical Research Council's Environmental Epidemiology Unit.[24] Records on 7,716 workers who entered the workforce before 1965 were traced through 1981. Exposure levels in the early years were high. Yet, there were fewer cancers than expected. There were no nasal cancer deaths, although one such death would have been expected. Acheson concluded that "[t]he findings of this study do not support the hypothesis that formaldehyde is a human carcinogen."

The case-control studies also show a generally negative pattern with respect to formaldehyde and upper respiratory cancer. Case-control studies by Fayerweather,[25] Hernberg,[26] and

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[24]Acheson, "Formaldehyde in the British Chemical Industry," Lancet 611-16 (Mar. 17, 1984). The workforce experience did not show a significant increase in mortality from lung cancer at any of these factories when compared with the local male population. (There was an increase at one of the six factories studied when compared to the male population of England and Wales as a whole.) No excesses for other cancer sites (e.g., skin, kidney, pancreas, brain) were found.

[25]Fayerweather, et al.,"Case-Control Study of Cancer Deaths in Du Pont Workers with Potential Exposure to Formaldehyde", reprinted in Formaldehyde: Toxicology, Epidemiology, Mechanisms (Clary, et al., eds.) at 47-125. Fayerweather examined exposure to formaldehyde for 481 cancer deaths and an equal number of controls. There was no excess mortality among exposed workers and no excess nasal cancer.

Partanen[27] show no association between nasal cancer and formaldehyde. Olsen's study shows an elevated risk from formaldehyde exposure in the European furniture industry,[28] and one of the two exposure assessments in Hayes' study of sinonasal cases in the Netherlands[29] shows a statistically significant association between sinonasal cancer and formaldehyde exposure. However, the accuracy of the exposure assessments in the Olsen and Hayes studies is questionable, a problem characteristic of case-control studies, and wood dust may be a confounding exposure.

A recent article has compared the results of EPA's 1987

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[26]Hernberg, "Nasal Cancer and Occupational Exposures," Scand. J. Work Envt'l Health 9:208 (1983). Hernberg examined nasal and sinonasal cancer using Finnish and Swedish national cancer registries and Danish hospital data. Occupations where formaldehyde exposure may have occurred showed no association with nasal cancer. There were significant associations between nasal and sinonasal cancer and exposure to softwood dusts. Welding, flame-cutting, soldering and chromium exposure were significantly associated with nasal cancer.

[27]Partanen, et al., "Formaldehyde Exposure and Respiratory and Related Cancers: A Case Referent Study Among Finnish Woodworkers," Scand. J. Work. Envt'l Health, 11:409-415 (1985). Partanen and conducted a case-referent study among Finnish woodworkers to investigate the associations between formaldehyde exposure and respiratory and related cancers. There were no statistically significant excesses. No exposure-response relation was observed for the level, duration, or dose (ppm-years) of formaldehyde exposure.

[28]Olsen, et al., "Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities," Brit. J. Ind. Med. 43:769 (1986); "Occupational Formaldehyde Exposure and Increased Nasal Cancer Risk in Man," Int'l J. Cancer 34:639 (1984). A critique of the Olsen study is provided as Ex. 9.

[29]Hayes, et al., Cancer of the Nasal Cavity and Paranasal Sinuses, and Formaldehyde Exposure," Int'l J. Cancer 37:487-94 (1986).

risk assessment using the animal data to actual levels of nasal cancer observed in human populations.[30] That report concludes:

> It is EPA policy for quantitative risk assessment of formaldehyde to use the data on rat nasal squamous cell carcinomas and linearized multistage extrapolation modeling for calculating low dose cancer risk. When this is taken a step further to predict across species to man, it happens that quite ludicrous estimates result. . . . Squamous cell carcinomas are very rare in humans, the rate for Europe and the United States being 5 in a million populous for females, and 10 in a million populous for males. . . . [Based on EPA's risk assessment], one could expect the background incidence of nasal tumors to be 500 in a million for females and 10,000 in a million for males. These rates would certainly have been detected in epidemiology studies, if such a formaldehyde-induced carcinogenic response occurred in man.

Id. at 199.[31]

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[30]Brown, "Do Rats Comply with EPA Policy on Cancer Risk Assessment for Formaldehyde?," 10 Reg. Toxicol. Pharmacol. 196 (1989).

[31]In addition to the above-described studies, Brinton, et al., conducted two case-control studies relating to cancer of the nasal cavities and sinuses. Brinton, et al., Am. J. Epid. 119:896-906 (1984); Brit. J. Ind. Med. 42:469-474 (1985). In the first study, with respect to occupational formaldehyde exposure the odds ratio was below 1.0. A follow-up study reported that formaldehyde exposure in the textile industry not only did not elevate the risk of nasal cancer but "was actually associated with a non-significant decrease in risk."

Tola conducted a case-control study for cancer of the nose and nasal sinuses. Occupational risk was not elevated but leisure time knitting and sewing and chronic nasal disease was more common among female cases than among controls. No association with formaldehyde exposure was reported. Int'l Arch. Occup. Envt'l Health, 46:79 (1980).

A review conducted at New York University surveyed nasal and oral cancer rates in Los Angeles, San Francisco, and the United States as a whole. Los Angeles, with its severe smog, actually had lower nasal and oral cancer rates than San Francisco and the same nasal and oral cancer rates as the United States overall. Demopoulos, et al., "An Academic Review of the Possible Adverse Health Effects of Formaldehyde" (1981).

b. Pharyngeal and buccal cancer

No overall excess in the category "pharynx and buccal cavity cancers"[32] emerges from the retrospective cohort mortality studies of industrial workers. In three 1986 studies -- Stayner, et al. at NIOSH, the National Cancer Institute (NCI) Study (Blair), and Vaughan[33] -- excesses were seen in certain anatomical sites (nasopharyngeal in the NCI and Vaughan studies, buccal cavity in the Stayner study), based on small numbers of cases. Careful review demonstrates that claims of an association between formaldehyde exposure and nasopharyngeal cancer based on the NCI and Stayner cohort mortality studies and the Vaughan case control study are unsupported.

NCI Study

The National Cancer Institute study is the largest study ever done on persons exposed to formaldehyde. This study concluded that "these data provide little evidence that mortality from cancer is associated with formaldehyde exposure at levels experienced by workers in this study."

The NCI study shows a statistically significant increase in nasopharyngeal cancer ("NPC") based on a small number of cases (seven). Four of the cases were clustered at a single plant. NPC levels for the other nine plants in the study are

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[32]In view of diagnostic difficulties, it is appropriate to combine the nasopharynx and buccal cavity subsites in the epidemiology analysis. See Letter from Bernard Wagner, M.D. to OSHA, June 30, 1986, Ex. 10.

[33]Vaughan, et al., "Formaldehyde and Cancers of the Pharynx, Sinus and Nasal Cavity, Int'l J. Cancer 38:677-88 (1986).

about as expected. Absent the "cluster effect" at the American Cyanamid plant, there would have been no excess of nasopharyngeal deaths in the NCI study. No nasopharyngeal cancer deaths were observed in the large cohort mortality studies by Acheson and Stayner.

There are a number of reasons why, on the basis of current evidence, the excess observed in the NCI study should not be attributed to formaldehyde exposure:

> (1) According to American Cyanamid, two of the four nasopharyngeal cases at the cluster plant (and three of the seven total cases) were in workers who had been employed only for a few months. It is most unlikely that the two short-term cases could be due to formaldehyde. American Cyanamid notes that "[w]ere short term workers not included in the study, NPC levels are not significantly elevated."
>
> (2) Three of the four cases had worked in metal plants in the area. Increased risks have been associated with exposure to metal manufacturing fumes, chemicals, and a variety of dusts.
>
> (3) The local cancer rate for New Haven County, Connecticut -- where the "cluster" plant is located -- shows an excess over the national rate, indicating that other local causes may account for the cluster cases.

American Cyanamid has recently completed a study to reexamine the NCI data and to supplement these data with additional data from its Wallingford, Connecticut plant.[34] The NCI data as reanalyzed by American Cyanamid do not support the hypothesis of an association between nasopharyngeal cancer and <u>combined</u> exposure to formaldehyde and particulates:

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[34]American Cyanamid's analysis and subsequent review have been published. <u>J. Nat'l Cancer Inst.</u> 78:192 (Jan. 1987); Collins, <u>et al.</u>, "Formaldehyde Exposure and Nasopharyngeal Cancer: Reexamination of the NCI Study and an Update of One Plant" <u>J. Nat'l Cancer Inst.</u> 80:376-77 (Jan. 1988).

- If NPC were associated with combined exposure formaldehyde and particulates, one would expect to find a consistent pattern of NPC excesses in other plants having similar exposures. Only a single plant of the ten plants in the study had an excess of NPC, although a number of other plants had particulate exposure.

- The four NPC cases in the American Cyanamid plant did not occur among persons known to have had the highest exposure to formaldehyde and particulates.

- The NCI analysis ignores entirely duration of exposure to formaldehyde and particulates. If a person were exposed to formaldehyde and particulates for a single day, the person's lifetime cumulative exposure to formaldehyde would be included in the analysis as if that person were exposed to particulates and formaldehyde for an entire career.

- Absent the cluster plant, there is no observed formaldehyde/particulate and NPC association.

American Cyanamid's analysis concludes that "[i]n the absence of more definitive data at this time, it is highly speculative to infer any association between NPC and formaldehyde/particulate exposure. . . . [F]ormaldehyde is an unlikely cause because of the clustering of the deaths."

Stayner Study

The Stayner study of apparel workers reported "a statistically significant excess in mortality from cancers of the buccal cavity (SMR=343)." An excess of buccal cavity cancer was found based in 6 cases (2 parotid gland, 1 oral mucosa, 1 floor of mouth, and 2 tonsils). The study cautions that "these findings are based on relatively small numbers and that confounding factors may still exist."

Moreover, the buccal cavity excess found in the Stayner study results from use of unconventional statistical analysis.

The excess disappears if conventional probability analysis is utilized. Stayner found a slight excess of buccal cavity cancer based on an unconventional "one-sided" statistical analysis which was predisposed to yield a positive result.[35] As Professor Philip Cole of the University of Alabama testified at the May 1986 OSHA hearings, the excess found by Stayner disappears if conventional statistical analysis (two-sided, p value = .05) is used.

Dr. Sidney Shindell of the Medical College of Wisconsin has also evaluated Stayner's study.[36] Dr. Shindell evaluated the study against the seven recognized tests for evaluating an epidemiologic study to provide evidence that a suspected factor is a cause of a disease: strength of the association, consistency, dose-response relationship, chronological relationship, specificity, biological plausibility, and coherence.[37] Dr. Shindell concludes that the Stayner study fails to meet any criteria for evaluating epidemiologic evidence.

Vaughan Study

The Vaughan case-control study of 13 counties in the State of Washington included both residential and occupational exposures; it is essentially negative, and the so-called positive

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[35]Use of unconventional statistical analyses are designed to increase the likelihood of finding statistically significant excess. See Dr. Cole's letter to OSHA, Ex. 11.

[36]Dr. Shindell's critique is provided as Ex. 12.

[37]See National Research Council, National Academy of Sciences, Epidemiology and Air Pollution (1986).

findings are subject to serious questions.

Vaughan examined whether occupational formaldehyde exposure was related to cancer of the oro- and hypopharynx (OHPC), nasopharynx (NPC), or sinonasal (SNC) cavities. The study concludes that "no significant associations were found between occupational formaldehyde exposure and any of the cancer sites under study." Relative risks were elevated for OHPC and NPC accounting for an induction period.

The authors acknowledge limitations inherent in the case-control study methodology, including incomplete information on exposures and the small number of cases. A large number of cases are from workers in the shipbuilding industry with exposure to metal fumes, known to be associated with the types of cancer involved in this study. The categorization of jobs is very general. There is no estimate of exposure levels to formaldehyde, or estimates of exposures to other chemicals or materials.

The Vaughan residential study examined 9 scenarios: 3 cancer sites and 3 residential exposures -- conventional homes with particleboard/plywood, UFFI homes, and "mobile homes." Vaughan found "no association" with respect to conventional homes or UFFI homes and any of the three cancer sites. For mobile homes, there was no association with OHPC. There was a significant decrease for SNC and mobile homes, and there was a significant increase for NPC and mobile homes. This study should not be characterized as a "positive" formaldehyde study.

The Vaughan study showed a single statistically significant increase in the exposure scenarios studied, related to residence in mobile homes for more than ten years and NPC. The authors cited "a strong association between a history of having lived in a manufactured home and NPC." However, there is the significant caveat that "[t]he association found with living in a mobile home must be interpreted with caution since it is based on a small number of cases and may be due to factors other than formaldehyde." The authors recommend additional studies of indoor air pollutants.

There are a number of additional question marks concerning an association between mobile home residence and nasopharyngeal cancer:

- The claimed association between living in a mobile home and increased risk of NPC is based on only 4 cases. Chance cannot be excluded. If one case is misclassified, the excess is no longer significant.
- It is hard to distinguish diagnostically between pharyngeal cancers. If NPC and OHPC are combined, there is virtually no difference in the number of cases in mobile homes and in controls.
- The 4 cases involving more than 10 years exposure were all pre-1965 mobile homes where formaldehyde exposure is not likely to be different than controls. Indeed, in 2 of the 4 homes, which were pre-1950 homes, formaldehyde may not have been the resin used in the products in the home.
- The method of selecting controls may understate mobile homes residences among controls, thus biasing the outcome to more mobile home residents among NPC cases.
- Socioeconomic factors, such as drinking, smoking and respiratory disease, may account for observed excesses of NPC among residents of mobile homes if there is a

real excess.[38] The study controlled for these factors for other sites, but not for NPC.

- There is also no correction for age or sex in the Vaughan studies for NPC -- a potentially serious source of error.

See Comments on the Vaughan study provided in Ex. 13.

In conclusion, the spot excesses which Vaughan finds are in no way inconsistent with chance. Vaughan studied at least nine scenarios of residential exposure; it would not be unusual for one of nine truly null relationships to appear to be statistically significant by chance alone. Indeed, there was one statistically significant decrease (association with SNC and residence in a mobile home). As the authors themselves caution that "the association found with living in a mobile home may not be due to formaldehyde."

3. Lung Cancer

The Draft Document improperly attempts to compare the results of animal-based risk assessment to claimed excesses of lung cancer in the epidemiology studies. In fact, there is no overall excess of lung cancer in the epidemiologic studies that can properly be attributed to formaldehyde. The Draft Document's discussion on this issue has no validity and should be deleted.

Overall lung cancer was not elevated in the NCI study.

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[38]NPC has been related to respiratory infections and smoking. E.g., U. Prasard, "Nasopharyngeal Carcinoma in Man," Nasal Tumors in Animals and Man I:158-164 (Reznik & Stinson eds.) Socioeconomic bias has been related to NPC. Occupational Mortality (Registrar General's Decennial Supplement for England and Wales) at 46-48. Occupational factors also need to be considered in cases based on residential exposure.

However, significant elevation was observed in the NCI study among a subgroup of workers (white male 20-29 year latency) when compared to national rates. There was no excess when compared to local rates. NCI found no evidence of a dose-response relationship and no increased incidence of lung cancer with duration of employment, despite special efforts to analyze the data using different, more sensitive techniques.[39] Significantly, Blair and the co-authors of the study concluded that "[t]he data provide little evidence that mortality from cancer is associated with formaldehyde exposure at levels experienced by workers in this study." Lung cancer is not elevated across the collective cohort; given that lung cancer is not a rare cancer, the power of the collective epidemiology data base is considerable.

The Draft Document improperly references the now-discredited Sterling and Weinkam analysis. Dr. Theodore Sterling, who has previously "reanalyzed" smoking data to raise questions about whether smoking causes lung cancer,[40] has attempted to reanalyze the NCI Study results to attribute lung

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[39]A slight excess in lung cancer was observed in the Stayner study but there was no dose response relationship and the authors did not attribute the excess to formaldehyde.

[40]Dr. Sterling has inferred that working is a more significant cause of lung cancer than smoking. See Sterling, "Does Smoking Kill Workers or Working Kill Smokers," 8 Int'l J. Health Serv. 437-52 (1978).

cancer to formaldehyde.[41] Expert epidemiologists have critiqued Dr. Sterling's analysis, and identified such gaping holes that Sterling's study must be entirely disregarded. A few of the key points are as follows:

- Sterling's reanalysis ignores the increased rate of lung cancer in the general population since World War II principally as a result of smoking. Sterling's failure to make this correction for time trends in respiratory cancer casts doubt on the validity of his observations of increased risk, given that lung cancer has doubled in the U.S. over the past 40 years. NCI took into account changes in lung cancer over time, as must be done in any well-conducted lung cancer study analysis.

- Sterling's insistence on a healthy worker effect for cancer does not comport with the published literature.

- Sterling does not adequately support his two methods of analysis -- a categorical log-linear analysis and a Mantel-Haenzel analysis. The categorical log-linear model does not adequately fit the data, and there is no comment on whether the Mantel-Haenzel model fits the data. It appears that Sterling did not control for sex or race in the Mantel-Haenzel analysis. In both cases, Sterling failed to perform a trend test to show whether there was a significant trend.

- Sterling's analysis inexplicably concludes that the shorter the duration of exposure, the greater the likelihood of cancer risk. This suggests that the observed cancers likely are due to a cause other than formaldehyde.

- Sterling arbitrarily selected his exposure categories to maximize support for his theories.

- Sterling mischaracterizes the results of essentially

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[41]After several rejections, the fourth version of the paper has been published. Sterling and Weinkam, "Reanalysis of Lung Cancer Mortality in a National Cancer Institute Study," 30 J. Occup. Med. 895 (Nov. 1988). The same authors subsequently published corrections which significantly changed the results but not the authors' conclusions. Sterling and Weinkam, "Reanalysis of Lung Cancer Mortality in a National Cancer Institute Study: Additional Discussion," 31 J. Occup. Med. 881 (1989).

negative epidemiology studies as providing evidence of carcinogenicity, and he improperly tries to explain away negative studies.

- Sterling's classification of hourly and salaried employees is simplistic, incomplete and selective.

- Sterling uses confusing terminology and does not adequately explain the methods used or the raw data, which appears to differ significantly from the NCI data.

Several comments on Dr. Sterling's analysis are included in Exhibit 14. The authors of the NCI study also published a rebuttal to Sterling's work.[42]

Sterling's report has led to further evaluation of the NCI data. Those evaluations have confirmed NCI's initial findings of no association between formaldehyde and lung cancer.

First, Blair, et al. -- the original authors of the NCI study -- have performed further analysis to determine whether any association between lung cancer and formaldehyde occurred in a subgroup of the cohort and to identify other occupational risk factors that may have been involved.[43] The further analysis confirms Blair's earlier conclusion that there is no

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[42]Blair, et al., "Formaldehyde Revisited - Comments on the Reanalysis of the National Cancer Institute Study of Workers Exposed to Formaldehyde," 31 J. Occup. Med. 881 (1989) (reaffirming the conclusion that "it was unlikely that the excess was due to formaldehyde because, in our analysis, mortality from lung cancer did not rise significantly with increasing intensity, cumulative, average, peak, or duration of exposure to formaldehyde, and because of the lack of consistency among the ten plants").

[43]Blair, et al., "Mortality from Lung Cancer Among Workers Employed in Formaldehyde Industries," 17 Am. J. Ind. Med. 683-90 (1990). The further analysis included use of various estimates of exposure, including duration, intensity, peak, cumulative, and average, and consideration of exposures lagged by 5, 10, 20 and 30 years.

exposure-response relationship and therefore no evidence of a causal association between lung cancer and formaldehyde:

> The relative risk for lung cancer (whether estimated by SMRs or SRRs) 20 or more years after first exposure did not generally rise with increasing exposure to formaldehyde. Various estimates of exposure were investigated including duration, intensity, peak, cumulative, and average, and by exposures lagged by 5, 10, 20 and 30 years. The excess did not appear to arise gradually, but emerged suddenly among workers whose total cumulative exposure was less than 0.1 ppm-years. Slightly positive, but nonsignificant, exposure-response associations between lung cancer and level of formaldehyde occurred in only a few out of a large number of comparisons (e.g., for persons hired before the start dates for the study and for workers also exposed to particulates). There was a lack of consistency among the various plants for risk of lung cancer, with six plants having elevated SMRs and four plants having deficits. Mortality from lung cancer was more strongly associated with exposure to other substances including phenol, melamine, urea, and wood dust than with exposure to formaldehyde. Workers exposed to formaldehyde without exposure to these substances did not experience an elevated mortality from lung cancer. The risk did not increase with cumulative levels of formaldehyde among those exposed to other substances and there was a slightly negative trend for those exposed to formaldehyde alone. Although some role for formaldehyde, particularly in association with other substances, in the excess of lung cancer seen among these workers cannot be ruled out, these findings suggest that exposure to phenol, melamine, urea, wood dust or other exposures also occurring in the area where these substances were used (i.e., production of resins and molding compounds) may play a more primary role.

Id. at 683. Specific findings of the study include the following:[44]

> Among the exposed, neither SMRs nor SRRs rose consistently with formaldehyde level for any measure of exposure and there were no statistically significant trends (id. at 687).

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[44]Emphasis is added in the following quotations.

No significant exposure-response pattern was uncovered in analyses which included only jobs in which the industrial hygienists were more confident of exposure estimates, which included workers employed after the initial start date of person-year accumulation at each plant (new hires), which included persons also exposed to formaldehyde in solution, or which lagged exposures by 5, 10, 20, or 30 years (id.).

The risk of lung cancer did not increase with duration of exposure to particulates alone for any latency category, nor in combination with different levels of exposure to formaldehyde. . . . None of these analyses revealed an exposure-response gradient (id.).

Because cumulative exposure combines persons with heavy exposure for short durations with those having lower exposure for longer durations, we evaluated the independent effects of intensity and duration of exposure to formaldehyde on lung cancer mortality. No significant trends occurred either by intensity within duration categories, or by duration within intensity categories (id.).

A strength of multi-plant studies is the opportunity to evaluate the consistency of effects among different plants. . . . Six plants had SMRs greater than 1.0 and four plants had SMRs of 1.0 or less. . . . [T]he overall risk of lung cancer by plant did not appear to be correlated with the average formaldehyde level in the plant (id. at 688).

Evaluation of lung cancer mortality among further subdivisions of the highest latency and cumulative exposure categories showed no consistently increasing exposure-response pattern (id. at 689).

Short-term and long-term workers may encounter different exposures in the workplace, may have different sensitivities to exposure, or may have different lifestyle factors which could influence their risk of cancer. To address this issue, we evaluated the risk of lung cancer by cumulative exposure, latency, and number of years employed in the plants (Table VI). . . . Among wage workers the lung cancer excess was greater among those employed <1 year (SMR = 1.3) than among those employed for more than 1 year (SMR = 1.1) for the total cohort, but the two groups were similar 20 or more years after first exposure (SMRs = 1.4 and 1.3, respectively). . . . The excess

> among those employed for <1 year may have occurred because they represent a more transient group of workers with lifestyle factors that increase cancer risks. Excess mortality form arteriosclerotic heart disease, emphysema, and diseases of the digestive system was also noted among short-term workers. Excesses for such diverse diseases suggest that lifestyle factors are a more likely explanation than formaldehyde (id. at 689, 695).
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> Excesses are particularly striking among workers from areas producing formaldehyde resin and molding compounds where, in addition to formaldehyde, exposure to phenol, urea, melamine, wood dust, and other substances may have occurred. . . . The association between lung cancer and exposure to phenol, melamine, urea, and wood dust and other substances suggests that these substances might account for some, or all of the excess observed . . . (id. at 697).

Blair evaluated the possibility that worker misclassification could explain the finding of no lung-cancer dose response. The report determined that six characteristics of the formaldehyde data argue against that possibility:

(1) analysis by different exposure measures provided the same result;

(2) the greater lung cancer risks occurred in persons entering the cohort or dying in recent years, even after controlling for latency, even though exposure levels have been lower in recent years;

(3) there is no pattern between lung cancer risk and duration of exposure, although such pattern often is found for actual carcinogens;

(4) lung cancer risk did not decline with increased latency, as would be expected if formaldehyde acted at a late stage in the carcinogenic process;

(5) there was no exposure-response relationship where the analyses included only the exposure data in which industrial hygienists had the most confidence; and

(6) there was "a sharp, but non-significant, exposure-response gradient between cancer of the nasopharynx and

> cumulative exposure to formaldehyde among persons also exposed to particulates," so one would expect to see a similar result of formaldehyde actually were associated with lung cancer.

Id. at 695-96.

Accordingly, Blair concluded that "[f]urther analyses in the present report did not uncover any clear exposure-response gradients between lung cancer mortality and various estimates of exposure to formaldehyde." Id. at 693.

Second, Dr. Gary Marsh of the University of Pittsburgh has performed a reanalysis of the NCI cohort data.[45] The reanalysis corrected several flaws in the Sterling work, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to the different measures of exposure.

Marsh first compared its data set, which was in "excellent agreement" with the Blair data, and the data set used by Sterling and Weinkam. Marsh found that Sterling and Weinkam apparently made several cohort data management decisions which were not typical of current epidemiological practice, including (1) exclusion of deaths with no death certificates, (2) exclusion of deaths with unknown vital statistics, (3) inclusion of unknown job types with hourly workers, and (4) for purposes of the

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[45]Marsh, et al., "A Reanalysis of the National Cancer Institute Study on Mortality Among Industrial Workers Exposed to Formaldehyde" (Mar. 1990), Ex. 15.

observed death data, inclusion of unknown race with the non-white cohort. However, even after taking these data management decisions into account, Marsh found that Sterling and Weinkam apparently made a significant counting error in computing person years at risk. Marsh Report at pages 8-9.

Marsh then reanalyzed the data to correct several flaws in Sterling and Weinkam's analysis, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to different measures of exposure. Marsh stated:

> We did not confirm Sterling and Weinkam's finding of an increased risk for lung cancer mortality as a function of cumulative formaldehyde exposure, adjusting for length of exposure. Lack of adjustment for length of exposure did not mask a positive association . . . . We found no evidence of a positive trend with cumulative exposure in the models we considered . . . . There was no evidence of confounding by calendar time. . . . Latency was the only statistically significant exposure measure among those we considered (cumulative exposure, average exposure, length of exposure, exposure with particulates, exposure without particulates, and latency).

Id. at 21. Marsh concluded that "[u]nlike Sterling and Weinkam, none of our estimates [relating to cumulative formaldehyde exposure] were statistically significantly elevated and the trend with cumulative exposure was not statistically significant." Id. at 22.

The Acheson study found no significant increase in mortality from lung cancer at any of six factories studied when each was compared with the local lung cancer rate. One plant

showed an excess when compared to the national rate, but not when compared with the local rate. Moreover, Acheson further analyzed lung cancer mortality for the workers at that plant by examining the levels and duration of exposure to formaldehyde, but found no relationship between cumulative dose of formaldehyde and lung cancer.

Accordingly, there is no basis to predict a cancer risk to humans based on the epidemiology studies. EPA concluded that "apparent elevations in lung cancer risk were not statistically significant" and that "[n]o statistically significant exposure-response trends were observed." EPA 1990 Risk Assessment, Ex. 2, at 46. The Draft Document's discussion of a risk estimate derived from the lung studies should be deleted.

4. Remote Site Cancers

Contrary to the Draft Document, there is no evidence that distant site tumors are related to formaldehyde. Although individual epidemiology studies indicate sporadic excesses of cancer in organs other than the respiratory system, no consistent excesses have been observed and such random excesses would be expected by chance alone.[46] There were no remote site tumors in the CIIT inhalation study. See CIIT Activities (April 1989). Because formaldehyde is rapidly metabolized, formaldehyde could not plausibly have an effect other than at its point of initial

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[46]Even if a substance had no effect, by chance alone 50 percent of sites would show an excess and five percent of sites would show a statistically significant excess.

contact.[47] OSHA concluded that "the failure to find distant-site tumors in the CIIT animals . . . suggests there is no such effect." 52 Fed. Reg. at 46222. OSHA further stated:

> Some scientists have viewed the brain as a biologically implausible site of action for formaldehyde. The basis for this point of view is threefold. First, formaldehyde is an extremely active chemical that causes cancer in animals at its immediate site of tissue contact. Second, metabolism studies show that free formaldehyde, once taken into the bloodstream, reacts virtually immediately with endogenous substances. Third, metabolites, once formed, that become part of the normal 1-carbon pool are nontoxic.

52 Fed. Reg. at 46198. OSHA cited the expert review by the NCTR Consensus Workshop, which concluded:

> In individual studies, attention has been drawn to small excesses of death from cancer of the prostate, skin (including melanoma), kidney, bladder, and of the digestive system. . . . In none of these sites, with the possible exception of prostate cancer, do the figures approach statistical significance in either professionals or industrial workers. There is at present scant evidence of an association between exposure and cancer of any of these sites.

NCTR Report at 339.

a. Brain Cancer and Leukemia

The NCTR Workshop Panel noted that studies of professional groups who preserve human tissues with solutions containing various chemicals, including formaldehyde, have shown very slight increased risk of brain cancers and leukemia. As the NCTR Workshop concluded, however, due to its rapid metabolism, it

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[47] See, e.g., NCTR Report at 347, Heck, et al., Starr, et al. at 28 (the data "strongly suggest that the toxicity induced by inhalation of HCHO gas is confined to tissues at the initial site of contact").

is biologically implausible that formaldehyde causes remote site cancer.[48] The 1990 EPA Risk Assessment stated that "[t]he excesses in leukemia and brain cancer observed in those studies of populations occupationally exposed to formalin are most likely related to exposures other than formaldehyde." Ex. 2 at 53.

There is a "substantial deficit" of brain cancer among industrial workers exposed to formaldehyde, according to the NCTR Epidemiology Panel, and the deficit "provides evidence against a close association" with formaldehyde. A significant excess (1.77) observed among professional groups may result from diagnostic bias or other social class factors.[49] Socio-economic status or close association with the medical profession may account for the more frequent diagnosis of brain cancer and leukemia among the pathologists, anatomists and embalmers.

Since these sporadic excesses have only been observed in professionals who handle human tissue, they also may be related to a number of other causal factors, such as contact with other chemicals, excreta, human tissue, bacteria, or viruses. Dr. Mortimer, a member of the NCTR Epidemiology Panel, has told EPA that, "it may turn out that this tumor excess represents an ascertainment artifact, or, if real, may be a consequence of

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[48]NCTR Report at 347.

[49]See R. Levine, Letter to the Editor, Envt'l Health Persp. 62:465 (1985), Ex. 16..

exposure to certain slow viruses."[50]

There are no experimental data linking formaldehyde to brain cancer or leukemia in animals. The NCI and Stayner epidemiologic studies are reassuring with respect to lack of brain cancer risk. The NCI study has an observed-to-expected ratio of 0.81, and the Stayner study has an observed-to-expected ratio of 0.71.

b. Skin Cancer

Walrath reported an elevation of skin cancer among embalmers but did not attribute it to formaldehyde. The elevation was statistically significant only if two different kinds of cancer were combined. Such combination is improper because the two have different histopathologic origins. Walrath pointed out that embalmers are exposed to many other chemicals. Other studies of formaldehyde workers -- including the subsequent Ontario morticians study by Levine -- found no excess of skin cancer.

CPSC notes that, although Walrath observed an increase in skin cancer incidence:

> This finding, however, must be tempered by the facts that an increase in skin cancer incidence has not been observed in any other such study, that the study used proportionate mortality ratio and not standardized mortality ratio (which can lead to greater uncertainty), that the significance of the result with respect to a specific type and location of skin cancer cannot be determined from the data provided, and that

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[50]Letter from Edward A. Mortimer, Jr., M.D., to TSCA Public Information Office, EPA (Dec. 14, 1983).

> embalming fluids contain a mixture of other chemicals which makes it difficult to determine the causative agent.[51]

D. Benign Tumors Are Not a Meaningful Response

The Draft Document suggests that the benign tumors found in the CIIT study are a meaningful response. Extensive evidence shows that benign tumors are not indicators of risk for formaldehyde because: (1) the benign tumors observed -- polyploid adenomas -- were of an entirely different cell type than squamous cell carcinomas whose benign counterpart is papillomas; (2) such tumors did not progress to squamous cell carcinomas, which are the cancers observed in rats after exposure to extremely high levels of formaldehyde; and (3) the incidence of benign tumors is not statistically significant and lacks any dose-response relationship. The NCTR Report stated:

> The panel recommends that this group of lesions not be combined with squamous cell carcinomas for risk estimation because of the differences in cell type of origin.

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[51]Cohn, "Dermal Application of Formaldehyde and Carcinogenesis," Tab A in CPSC, Status Report on the Formaldehyde in Textiles Portion of Dyes and Finishes Project, Ex. 17, at 5, 7-8.

Animal data also indicate a lack of cancer risk from dermal exposure. Mouse studies applying formaldehyde solutions to the skin show neither initiation nor promotion of cancer. See Spangler, et al.; Krivanek, et al., in Formaldehyde Toxicology, Epidemiology, Mechanisms. A joint study commissioned by CPSC and the Department of Agriculture finds that where formaldehyde is exposed to the skin of rabbits (whose skin is more permeable than human skin), formaldehyde will be retained in the skin with little distribution to other tissues, organs, or excreta. Robbins & Norred, "Bioavailability in Rabbits of Formaldehyde from Durable Press Textiles," in CPSC, supra, in Ex. 17.

NCTR Report at 342. OSHA similarly chose not to rely on benign tumor data in its risk assessment because there does not appear to be any biological justification for combining data representing these benign tumors of two distinct cell types. 52 Fed. Reg. at 46219.

E. Well-Conducted Studies Do Not Show Evidence of Carcinogenicity Via the Oral Route

Contrary to the discussion in the Draft Document, the well-conducted studies regarding the effects of ingested formaldehyde indicates that there are no such effects, even at high exposure levels.

A 1968 study by Della Porta administered hexamethylenetetramine ("HMT"), which decomposes to release formaldehyde in acidic conditions, to rats and mice in drinking water.[52] No carcinogenic activity was observed.

A recent, state-of-the-art formaldehyde ingestion study by Til, et al., observed nontumorigenic effects (cellular irritation).[53] However, under the study conditions formaldehyde was not tumorigenic, even at the maximum tolerated dose.

The Til study ran for 104 weeks, and included interim sacrifices and extensive histopathology. Exposures were 5 mg/kg, 25 mg/kg, and 125 mg/kg. Seventy animals of each sex were

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[52]HMT is commonly prescribed as a prescription drug for bladder infections, at a dose of approximately 4 grams per day.

[53]Til, et al., "Two-Year Drinking Water Study of Formaldehyde in Rats," 27 Food Chem. Tox. (1989); Feron, et al., abstract published at Toxicologist 8:1 (Feb. 1988).

included in each group. Based on the formaldehyde content and water consumption, which was measured, the highest dose was equivalent to approximately 2000 ppm formaldehyde.

No tumors were observed, even at the highest dose level. Kidney necrosis was observed only at the high dose and was thought to be related to a 40 percent decrease in water consumption. Also at the higher doses, some necrosis and hyperplasia was observed at the site of direct contact, the fore and the glandular stomach. The 25 mg/kg dose was a no observed effects level for any toxic response. The overall conclusion of the study was that, even at the maximum tolerated dose, formaldehyde is non-carcinogenic via the oral route.

These results are of particular significance because they do not confirm the tumorigenic response noted in an earlier Japanese report by Takahashi, et al.[54] The Takahashi study exposed rats to formaldehyde by way of drinking water containing 0.5% formalin. The authors are unsure what percentage of formaldehyde was present in the formalin, but believe that it contained 37% formaldehyde and 15% methanol. The water thus contained roughly 1850 ppm formaldehyde and 750 ppm methanol. The authors did not measure how much water was consumed by the animals, and it is therefore impossible to provide dosage data in

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[54]"Effects of Ethanol, Potassium Metabisulfite, Formaldehyde and Hydrogen Peroxide on Gastric Carcinogenesis in Rats After Initiation with N-Methyl-N'-Nitro-N-Nitrosoguanidine," Japan J. Cancer Res. (Gann) 77: 118-24 (1986).

the form of mg/kg body weight. The study used a small number of animals per group (from 10 to 30, depending on the group). The study ran for only 32 weeks. Animals exposed to formalin alone developed only benign tumors (forestomach papillomas). The formalin did not initiate any malignant tumors. Moreover, the classification of the benign tumors was based on a very rigid system; the study's authors have subsequently questioned whether the "forestomach papillomas" were true tumors or ridges of hyperplasia arising from irritation. See Letter from Dr. John Clary to Dr. Bruce Ames, Ex. 18. In the promotion experiment, adenocarcinomas were observed when formaldehyde was used as a promoter following initiation by MNNG. However, some adenocarcinomas were also observed in the initiated-only group.

Another recent ingestion study, which exposed rats to 10, 50, 100, 500, 1,000 and 1,500 mg/l formaldehyde by ingestion, reported increased leukemia at all doses above 10 mg/l and increased gastrointestinal cancer at all test levels.[55] However, this study has several weaknesses which lend uncertainty to its conclusions:

- The study does not indicate the substance being ingested. Because the report mentions impurity by methanol, it is possible that the study used formalin rather than formaldehyde as the test material.
- Incidence of stomach tumors -- the observation on which the authors rely for their conclusions -- did not differ significantly from the background rate observed

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[55]Soffritti, et al., "Formaldehyde: An Experimental Multipotential Carcinogen," 5 Tox. Ind. Health 699-730 (1989).

in historical controls. An increase in the embryo group appeared only by combining different stomach tumor types with various gastrointestinal tumors. The tumors did not exhibit a clear dose-response relationship.

- The report does not present statistical evaluation of the data or time-to-tumor information.

- The test animals were not sacrificed at designated intervals, but rather were allowed to live until spontaneous death, which would be expected to result in a higher cancer incidence rate.

- There was no analysis of clinical chemistry, urinalysis, hematology, or non-cancer pathological response. These gaps make interpretation of the study results difficult.

Detailed comments on the Soffritti study are provided in Exhibit 19.

In contrast to the Soffritti and Takahashi studies, the Til study was a state of the art study, more extensive, more fully analyzed, more carefully monitored, and more definitive.

F. The Reports of Hyperplasia Are Not Indicative of a Formaldehyde-Related Response

The Draft Document improperly relies upon recent Scandinavian reports[56] showing squamous metaplasia and in a few cases mild dysplasia in the nasal mucosa, in small samplings of formaldehyde-exposed workers. For example, the most recent report, a Norwegian case-control study, described on the findings of biopsies of the nasal mucosa of 37 chemical workers

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[56]Holstrom, et al., "Histological Changes in the Nasal Mucosa in Persons Occupationally Exposed to Formaldehyde Alone and in Combination with Wood Dust," 107 Acta Otolaryngol. (Stockh.) 120 (1989); Boysen, et al., "Nasal Mucosa in Workers Exposed to Formaldehyde: A Pilot Study," 47 Brit. J. Ind. Med. 116 (1990).

occupationally exposed to formaldehyde for more than five years.[57] The study found a higher degree of metaplastic alterations of the nasal mucosa and three cases of epithelial dysplasia in the exposed group. Based on these findings, the study concluded:

> These results indicate that formaldehyde may be potentially carcinogenic to man. Combination of this finding with the inconclusive epidemiological studies suggests that formaldehyde is a weak carcinogen and that occupational exposure to formaldehyde alone is insufficient to induce nasal cancer.

However, a review of the study, as well as the earlier study by Holstrom, indicates that there is little support even for this carefully-conditioned conclusion:

- There is no statistically significant correlation between the observations and degree and duration of formaldehyde exposure.
- Alterations of the nasal mucosa have many possible causes, including smoking and passive smoking. There was insufficient examination of the confounders.
- The control group was too small to be representative of the population as a whole.
- There is insufficient characterization of the formaldehyde exposure levels.
- These results are inconsistent with other studies of the nasal mucosa of formaldehyde-exposed workers. Berke, et al., 29 J. Occup. Med. 681 (1987) (finding no associated of abnormal cytology and formaldehyde exposure when controlling for age).

See Comments by Dr. Petri, Ex. 20.

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[57]Boysen, et al.

III. THE DRAFT DOCUMENT PROPERLY RECOGNIZES THAT FORMALDEHYDE DOES NOT CAUSE ADVERSE REPRODUCTIVE EFFECTS

The Institute supports the Draft Document's statements that formaldehyde does not appear to be a reproductive hazard. The Consensus Workshop concluded that the evidence does not implicate formaldehyde as a reproductive hazard:

> In summary, the panel could find no evidence clearly demonstrating that formaldehyde caused adverse reproductive outcomes. What it found was a paucity of information from which to make inferences and data that suggested hypotheses to be tested in future studies. This panel feels that formaldehyde poses little, if any, risk as a potential human teratogen. This judgment is based on the irritation potential of formaldehyde at extremely low ambient concentrations (0.05 ppm), existing data from in vivo mammalian studies, and toxicokinetic and metabolism data indicating an extremely short half-life (not detected to 1.5 min) of the parent compound, and relatively short half-life (80-90 min) of the only known metabolite (formate) in the blood, regardless of the route of exposure.

NCTR Report at 349. See also Enders, "Analyzing Formaldehyde's Effect on Reproduction," Contemporary Ob/Gyn, Feb. 1987. EPA states flatly that "[n]o data have been found linking HCHO to teratogenic effects in humans.[58] Having reviewed studies by

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[58]EPA 1987 Risk Assessment at 5-26. Another review of the literature on teratogenicity by CPSC's Andrew Ulsamer similarly states:

> The currently available data do not show that the embryo is unusually sensitive to formaldehyde nor is there any information to show that formaldehyde is teratogenic in rodents when administered orally or applied dermally in nontoxic amounts to the dams. Also, the in vitro data do not provide any evidence to support the conclusion that formaldehyde causes terata at exposure concentrations that are not toxic to the adult.

Ulsamer, et al., "Overview of Health Effects of Formaldehyde," in Hazard Assessment of Chemicals and Current Developments (Saxsena,

Marks, et al., Martin, and others, OSHA concluded that "there is no evidence at this time that formaldehyde demonstrates teratogenic effects at exposure concentrations which comply with the revised standard." 52 Fed. Reg. at 46183. Having reviewed studies by Olsen and Dosing, Shumiling and Hemminki, OSHA found no evidence that formaldehyde caused an increase in spontaneous abortions, menstrual disorders, or other reproductive hazards. Id.

A classic animal teratology study has been performed by the Formaldehyde Council of Canada. Pregnant rats received whole-body exposure to formaldehyde of 2.5 to 10 ppm, 6 hours per day, from days 6 through 15 of gestation. No adverse treatment-related effects (embryotoxicity, fetotoxicity, or teratogenicity) were seen in the fetuses, though the dams in the high-dose group showed evidence of significant maternal toxicity.[59]

IV. THE DRAFT DOCUMENT'S ANALYSIS OF EXPOSURE TO FORMALDEHYDE REQUIRES REEVALUATION

As discussed in the comments of the Hardwood Plywood Manufacturers Association and National Particleboard Association, there are several important deficiencies in the Draft Document's exposure analysis relating to current outdoor and indoor formaldehyde levels and to time of exposure at various locations.

First, the Draft Document relies on out-of-date

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ed., 1984) at 337-40.

[59]Martin, "A Teratology Study of Inhaled Formaldehyde in the Rat," Reproductive Toxicology 4:237 (1990).

residential exposure data from the early 1980s. Since then, voluntary efforts by manufacturers and promulgation of formaldehyde emissions requirements for particleboard and hardwood plywood by the Department of Housing and Urban Development (in 1985) and several states have resulted in substantial reductions in formaldehyde emissions from various products. For example, emission from the three most important urea-formaldehyde (UF) bonded pressed wood products (particleboard, hardwood plywood and medium density fiberboard) used in the interior of buildings have been reduced 75 to 90 percent since the early 1980s. Emission levels from textile and fabrics have also been substantially reduced. Many furniture and cabinet manufacturers have switched to finishes that do not emit formaldehyde or have sharply reduced formaldehyde emissions.

Second, in-home exposures are overstated relative to outdoor exposures. The Draft Document relies on relatively new atmospheric data (1988-1989), while the indoor exposure estimates are based on early-1980s data. Both atmospheric (outdoor) formaldehyde levels and in-home levels have likely declined since the early 1980s. Moreover, outdoor levels are high when most people are out of the home during the daylight hours. Neither the Sexton, et al. study nor the Rogozen, et al. study relied on in the Draft Document describes homes with products with low formaldehyde-emitting characteristics.

Third, formaldehyde emissions from wood products in the

home decay significantly over time. Recent data indicates that the initial emission level from particleboard decreases by half in one year or less. Zinn, et al., "Long-Term Study of Formaldehyde Emission Decay from Particleboard," Forest Products J. (June 1990). After one year, wood product emissions further decrease, but at a more moderate rate. Thus, UF-bonded pressed wood building materials make little or no contribution to formaldehyde levels in the older California housing stock (10 years or older).

For these reasons and those presented in the comments of HPMA and NPA, the Draft Document's exposure assessment should be reevaluated.

CONCLUSION

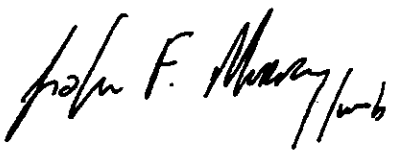
The Draft Document has properly recognized that recent mechanistic data can usefully be incorporated into risk assessment. However, the Draft Document does not reflect EPA's recently-revised risk assessment, which has been endorsed in peer review by EPA's expert Science Advisory Board. That reanalysis yielded a prediction of risk 10 to 100 times lower than that presented in the Draft Document. Further, incorporation of other recent data regarding cell proliferation would reduce the prediction of risk by over one additional order of magnitude.

EPA is in the final stages of its process to issue the revised risk assessment in final form. A brief delay would enable California to reflect the expert analysis by EPA and its

outside reviewers and would avoid the uncertainty that would be raised by inconsistent approaches to risk assessment.

In several other respects, the text of the Draft Document does not reflect a balanced appraisal of the health effects evidence regarding formaldehyde. Revision of the risk assessment and of the text would provide a sound scientific basis for a decision whether to list formaldehyde as a toxic air contaminant.

Respectfully submitted,



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March 26, 1991

COMMENTS ON THE CALIFORNIA AIR RESOURCES BOARD PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT

Prepared for

The Formaldehyde Institute
Washington, DC

Prepared by

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March 26, 1991

COMMENTS ON THE CALIFORNIA AIR RESOURCES BOARD PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT

1. Introduction

In its preliminary draft report dated February 1991, the California Air Resources Board (CARB) has proposed that formaldehyde be identified as a *toxic air contaminant*. CARB based this proposal in part on the California Department of Health Services' (DHS) "best value of potency for unit risk" associated with airborne formaldehyde exposure, namely, 29×10^{-6} $ppbv^{-1}$ (i.e., 0.029, or nearly 3%, per ppm). Employing a population-weighted outdoor exposure estimate of 4.4 ppbv (0.0044 ppm), the DHS staff has estimated that 70-year lifetime exposure to this ambient outdoor level would produce approximately 2,100 excess cancer cases in the states' 30 million people. In-home exposure in conventional housing, where the average formaldehyde concentration was estimated to be 50 ppbv (0.05 ppm), is projected to cause another 19,800 cancer cases. Similar exposure in mobile homes, where the average formaldehyde concentration was estimated to be 75 ppbv (0.075 ppm), is estimated to produce still another 1,000 cancer cases. Thus, excluding occupational exposure, CARB and DHS have determined that 22,900 extra cases of cancer in the state of California's population of 30 million people will arise if their current exposures to formaldehyde in outdoor and in-home air were to continue for an average lifetime of 70 years. If it were an accurate estimate, this number of extra cancer cases, nearly one case per thousand individuals, would, be alarmingly large.

However, the best presently available scientific evidence provides a compelling basis for concluding that CARB and DHS have overstated the potential human cancer risks from formaldehyde exposure by a very substantial margin. Indeed, if only one component of this evidence, namely, the extent of formaldehyde-induced DNA-protein crosslinking, is *fully and properly* taken into account, then CARB's upper bound estimate of human cancer potency should be reduced by a factor of approximately 54-fold.

CARB's exaggeration of formaldehyde's cancer potency arises from the demonstrably invalid procedure they employed in extrapolating cancer risk between species.

CARB also assumed that different temporal exposure patterns corresponding to a given continuous lifetime exposure all yield the same cancer risk. Because this assumption stands in direct contradiction to the acknowledged amplifying effects of increased cell replication on the carcinogenic process at high, but not low, formaldehyde concentrations, it introduces additional conservative bias into CARB's upper bound estimates of human cancer risk, further exaggerating their risk estimates at low exposure levels by a factor of approximately 20-fold. Taken together, CARB's failure to fully and properly account for the DNA protein crosslink and cell proliferation data that is currently available imply an overestimation of human cancer risk from formaldehyde exposure by as much as 1,000-fold! These and other flaws in the CARB and DHS formaldehyde health assessment are discussed below in greater detail.

2. DNA-Protein Crosslinking

The DHS cancer potency factor of 29×10^{-6} $ppbv^{-1}$ was derived from an analysis of nasal cancer incidence among rats exposed for up to two years to 0, 2, 5.6, or 14.3 ppm formaldehyde vapor for six hours per day, five days per week (Kerns et al., 1983). CARB and DHS employed a pharmacokinetic model of DNA-protein crosslink (DPX) formation nearly identical to one originally developed by Casanova et al. (1989) to describe the nonlinear dependence of DPX formation in the rat nasal mucosa upon airborne formaldehyde concentration. The predicted levels of DPX were then multiplied by two scaling factors, 1.2 ppm/(pmol/mg-hr) and 30 hr/wk/(168 hr/wk) to express the DPX levels in ppm units of "lifetime equivalent metabolic exposure." For example, 15.0 pmol/mg is the DPX level predicted to result from exposure of rats for 6 hours to 2 ppm formaldehyde, and also from 24 hour (i.e., continuous) exposure to 0.54 ppm. CARB then used the GLOBAL86 computer program to fit the multistage model to the rat bioassay data with this scaled DPX level as the independent variable. In other words, as CARB has stated, the predicted DPX level "is used as a measure of dose rate of formaldehyde at the target tissue."

The DHS model provides a reasonably accurate description of the relationship

between DPX and airborne formaldehyde concentration, but it also consistently overpredicts the DPX levels observed in rats exposed to low concentrations. For example, after 6 hours exposure to 0.3 ppm, while 1.4 pmol/mg DNA was actually measured by Casanova et al. (1989), CARB's equation (1), with the parameter values given in Table 1, predicts a DPX value of 1.59 pmol/mg DNA, about 14% higher than the observed value. Such overpredictions are expected to occur at all of the comparatively low airborne concentrations of concern to CARB and DHS, namely, 0.075 ppm and lower. This convervative bias in DPX prediction at low airborne formaldehyde concentrations should be corrected, even though it is quite small when compared to the overpredictions resulting from CARB's flawed interspecies extrapolation procedures and its failure to adequately account for formaldehyde's effects on cell replication in target tissues.

3. Interspecies Extrapolation

Appendix A of the draft health assessment document describes the approaches CARB employed in extrapolating to human cancer risks from the corresponding predicted rat risks. The first, denoted as the default approach, has apparently been employed in other cases "in the absence of decisive empirical evidence" for some other scaling procedure. It is predicated on the assumption that "equal rates of intake of carcinogen per species body-surface area imply equal risks" in different species. After adjusting for the less efficient absorption of the human respiratory tract (CARB asserts human absorption to be about 76% that of rats, but the supporting citations, Raabe (1988) and Dallas (1985), do not appear in the references), and accounting for respiratory minute volume and body-surface area differences between these species, CARB concluded that rats and humans would receive the same formaldehyde dose (intake rate per body-surface area) and hence experience the same cancer risk if the rats were exposed to airborne concentrations 1.2 times higher than humans. This default scaling approach further implies that for a given airborne concentration, humans would experience about a 20% greater formaldehyde intake rate per body-surface area than rats and hence a 20% greater lifetime cancer risk.

CARB's second approach, termed the contact approach, purports to take into

account "the contact mechanism of carcinogenesis, in which the average concentration in the respiratory surface layer provides the measure of dose to characterize risk." The resulting calculations lead to a scaling factor of 5.0. In other words, with this contact scaling assumption, CARB has concluded that rats and humans would receive the same formaldehyde dose at the target tissues in the respiratory tract if the rats were exposed to airborne concentrations five times higher than humans. This contact scaling approach thus also implies that for a given airborne concentration, humans would experience about a 5-fold greater formaldehyde dose at the target tissues and hence 5-fold greater lifetime cancer risk.

It is readily demonstrated that both of these scaling assumptions are totally at variance with what is known regarding the molecular dosimetry of airborne formaldehyde in rodents and primates. CARB's health assessment document notes the fact that Heck et al. (1989) have measured formaldehyde-induced DPX in the nasal mucosa of Rhesus monkeys (*Macaca mulatta*). These observations are ideally suited for direct interspecies comparison with previously reported measurements of DPX in the nasal mucosa of rats (Casanova et al. 1989). Indeed, it is possible to check whether the measured DPX levels in monkeys are consistent with what would be predicted by either of the two interspecies scaling assumptions considered by CARB.

The Rhesus monkeys employed by Heck et al. (1989) weighed approximately 7 kg, i.e., 1/10 the 70 kg human body weight employed by CARB. Assuming that the monkey respiratory tract absorption efficiency is comparable to that of the human (namely, 76% that of the rat), the default scaling factor for monkeys is readily calculated:

$$(a_m/a_r)(W_m/W_r)^{0.08} = (0.76)(7.0/0.25)^{0.08} = (0.76)(1.31) = 0.99.$$

Thus, the default scaling procedure predicts that monkeys and rats should receive practically identical target site doses when both are exposed to the same airborne formaldehyde concentration.

The contact scaling factor that CARB would employ for the Rhesus monkey is also readily calculated:

$$(a_m/a_r)(W_m/W_r)^{0.33} = (0.76)(7.0/0.25)^{0.33} = (0.76)(3.04) = 2.31.$$

Thus, the contact scaling procedure predicts that rats and monkeys would receive the same formaldehyde dose at the target tissues in the respiratory tract if the rats were

exposed to airborne concentrations 2.31 times higher than monkeys. This approach thus also predicts that at a given airborne concentration, monkeys would experience about a 2.3-fold greater formaldehyde dose at the target tissues and hence a 2.3-fold greater lifetime cancer risk than rats.

The measured values of DPX in monkey respiratory mucosa reported by Heck et al. (1989) are totally inconsistent with these predictions. Indeed, at the lowest airborne formaldehyde concentration (0.7 ppm) for which DPX measurements were made in both rats and monkeys, the rat DPX value following 6 hours of exposure was 3.9 pmol/mg DNA, while the corresponding monkey DPX value was 0.36 pmol/mg DNA, i.e., 10.8-fold lower. Thus, when CARB's default scaling procedure is applied where DPX measurements exist for comparison, it overpredicts the observed DPX in monkeys by about a 10.7-fold factor. It should be noted that this default scaling procedure also predicts that DPX in humans under these conditions should be (1.2)(3.9 pmol/mg DNA) = 4.7 pmol/mg DNA, i.e., approximately 13-fold greater than was observed in the monkeys.

CARB's contact scaling procedure also overpredicts DPX in monkeys, but the extent of overprediction is even greater, namely, by (3.9)(2.3)/0.36 = 24.9-fold. DPX in humans under these conditions are predicted to be (5.0)(3.9 pmol/mg DNA) = 19.5 pmol/mg DNA, i.e., approximately 54-fold greater than was observed in monkeys. The associated human cancer risks that CARB has estimated are thus clearly overstated by these very same substantial factors.

The findings of Heck et al. (1989) are described in considerable detail on pp. 2-8 and 2-9 of the CARB draft document. In particular, CARB noted that the "monkeys had much lower (up to 10-fold) concentrations of crosslinks in the nasal turbinates and anterior nose than did rats at a given formaldehyde concentration." However, the utility of these data was characterized as limited "because it is not known how susceptible monkeys are to formaldehyde-induced carcinogenesis." Despite this objection, the monkey DPX data can and should be used to estimate human cancer risk, as has been demonstrated and recommended by Starr (1990) and, subsequently, by EPA in the recent draft revision (EPA, 1990) of its 1987 formaldehyde health assessment document. It should also be noted that in October 1990, EPA's Science Advisory Board concurred

with this recommendation.

At the present time, the Rhesus monkey provides the best available animal model for DPX formation in humans exposed to formaldehyde. Heck et al. (1989), Starr (1989, 1990), EPA (1[illegible]), and CARB have all noted that the monkey is far closer to the human than the rat in terms of its respiratory anatomy, physiology, and breathing patterns. Until direct measurements of DPX in humans are available, the most plausible and scientifically defensible assumption is that humans develop DPX following formaldehyde exposure to the same extent as do monkeys. CARB must not casually dismiss these data, as they provide the best available scientific information relevant to estimating a human cancer potency factor for formaldehyde.

4. Exposure Patterns, Cell Replication, and Other Concerns

As noted in the introduction, in making its extrapolations to lifetime continuous exposure conditions, CARB has assumed that 24 hr/day, i.e., continuous, exposure to a given formaldehyde concentration pose the same cancer risk as 6 hr/day exposure to a four times higher concentration. This assumption has been made in the past by other regulatory agencies, including CPSC, OSHA, and EPA. However, in EPA's most recent draft formaldehyde assessment update (EPA 1990), the Agency noted that such an assumption did not properly take account of the fact that formaldehyde-induced cytotoxicity and attendant cell proliferation make high-concentration intermittent exposure patterns inherently more risky than their lifetime continuous exposure equivalent. Since cell proliferation is known to be increased by as much as 20-fold relative to background replication rates at high formaldehyde concentrations, it is clear that CARB's assumption of equivalence may actually overstate the risk associated with low continuous lifetime exposure conditions by a corresponding factor of the same magnitude.

New data have already been collected at CIIT regarding cell proliferation rates in the rat during the course of chronic formaldehyde exposure. These data can and should be utilized directly in CARB's risk assessment process. They can be employed to estimate the parameters of carcinogenesis models that accommodate cell proliferation information, such as the two-stage growth model proposed by Moolgavkar and his co-workers. In this way, CARB can reduce the bias introduced into its human cancer risk

estimates that arise from its use of an incorrect and inappropriate dose-response model.

There are a number of factual inaccuracies in the CARB draft health assessment document that should be corrected. For example, when the Blair et al. (1986) epidemiology study is discussed on p 2-19, it is stated that Blair et al. "observed significantly elevated relative risks of mortality both for lung cancer (relative risk for hourly workers who had the substantial formaldehyde exposure, was 1.35) and for nasopharyngeal cancer (relative risk for wage earners was 2.0)." This statement gives the distinct impression that the study was convincingly positive.

Yet the authors themselves stated that "Workers exposed to formaldehyde had slight excesses for Hodgkin's disease and cancers of the lung and prostate, but these excesses were not consistently related to average, cumulative, or peak formaldehyde exposure levels." In addition, they stated that "Although there was a deficit for cancer of the buccal cavity and pharynx, mortality from certain subsites, i.e., the nasopharynx, and oropharynx, was elevated. These subsites did not, however, show a consistently rising risk with level of exposure." In conclusion, Blair et al., wrote "These data provide little evidence that mortality from cancer is associated with formaldehyde exposure at levels experienced by workers in this study."

These statements lead me to conclude that the results of the Blair et al. study would be equally if not perhaps more consistent with the hypothesis that no extra cancer risk was attributable to the workers' formaldehyde exposure. This certainly appears to be the conclusion of the study authors. It is also the conclusion of the blue ribbon epidemiology panel (UAREP 1988) after review of all of the existing epidemiology studies of formaldehyde-exposed workers: "1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure and 2) furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small."

In its discussion of Starr (1989, 1990), CARB asserts that "Starr used tumor incidence data which did not subtract out early mortality in the denominator and did not account for interim sacrifice in the numerator." This is not correct. The tumor incidence data employed by Starr (1989, 1990) was the same as that employed by Starr and Buck (1984). All interim-sacrificed animals were excluded from both the numerators and denominators, so as to permit a direct comparison of our results with the earlier risk

estimates that had been developed by Cohn (1981) for the Consumer Product Safety Commission.

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March 25, 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Formaldehyde
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Shiroma:

Enclosed are my comments on the Preliminary Draft Report on Formaldehyde prepared by the staffs of the Air Resources Board and the Department of Health Services. Unfortunately, I will not be able to attend the April 3, 1991 meeting. I would appreciate your bringing these comments to the attention of the appropriate individuals. Thank you for your consideration.

Sincerely,

James A. Swenberg

James A. Swenberg, DVM, Ph.D.
Professor, Environmental Sciences
and Engineering and Pathology

JAS/thb

Enclosure

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1. Introduction

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However, the best presently available scientific evidence provides a compelling basis for concluding that CARB and DHS have overstated the potential human cancer risks from formaldehyde exposure by a very substantial margin. Indeed, if only one component of this evidence, namely, the extent of formaldehyde-induced DNA-protein crosslinking, is *fully and properly* taken into account, then CARB's upper bound estimate of human cancer potency should be reduced by a factor of approximately 54-fold.

CARB's exaggeration of formaldehyde's cancer potency arises from the demonstrably invalid procedure they employed in extrapolating cancer risk between species.

CARB also assumed that different temporal exposure patterns corresponding to a given continuous lifetime exposure all yield the same cancer risk. Because this assumption stands in direct contradiction to the acknowledged amplifying effects of increased cell replication on the carcinogenic process at high, but not low, formaldehyde concentrations, it introduces additional conservative bias into CARB's upper bound estimates of human cancer risk, further exaggerating their risk estimates at low exposure levels by a factor of approximately 20-fold. Taken together, CARB's failure to fully and properly account for the DNA protein crosslink and cell proliferation data that is currently available imply an overestimation of human cancer risk from formaldehyde exposure by as much as 1,000-fold! These and other flaws in the CARB and DHS formaldehyde health assessment are discussed below in greater detail.

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REVIEW OF THE CALIFORNIA AIR RESOURCES BOARD'S

PROPOSED IDENTIFICATION OF FORMALDEHYDE

AS A TOXIC AIR CONTAMINANT

BY

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MARCH 25, 1991

I have reviewed with great interest the proposed California Air Resources Board's (CARB) preliminary draft on identifying formaldehyde as a toxic air contaminant. This document draws heavily on the earlier 1987 EPA document on formaldehyde and extends the information by adding recent publications. It does not review the 1990 EPA update in any detail, however. While I commend the writers of this document for incorporating the use of DNA-protein crosslinks (DPX) as the dose parameter, I seriously question the unit risk of 2.9×10^{-2}. The EPA 1990 update used the DPX data and calculated a unit risk of 7.0×10^{-4}. The EPA's unit risk used the monkey DPX data rather than a scaling factor. I do not understand how CARB can dismiss the monkey DPX data. The monkey data are generated in exactly the same manner that the rat data are. Surely, it is more accurate than some mathematical extrapolation based on body surface area. The net result is that CARB proposes a risk from formaldehyde that is 41-fold higher than that proposed by the EPA. If the objective of the CARB proposal is to present the most scientifically accurate risk assessment, it is clear that monkey DPX data should be the dose parameter. This change incorporates important pharmacokinetic differences between high and low exposures associated with saturation of formaldehyde dehydrogenase, the primary route of formaldehyde detoxication, and provides the best available parameter for interspecies scaling.

The major deficiency in the CARB document is its lack of utilization of our present knowledge of the role being played by cell proliferation in the dose response relationship for formaldehyde. It is now absolutely clear that cell proliferation is the driving force responsible for the observable nonlinearity in tumors. While this was suggested by many of the earlier studies, the new data being generated in the mechanistically based repeat rat bioassay conducted at CIIT leaves no doubt as to its importance. Some of these data are shown in Figure 1. The new study examined the induction of nasal cancer and cell proliferation in rats exposed to 0, 0.7, 2, 6, 10, or 15 ppm formaldehyde 6 hours/day, 5 days/week. Not only did this study confirm the shape of the concentration response, it also incorporated the very important 10 ppm concentration. The slope of the original and the new study

increases from 6 to 15 ppm by a factor of 21. The new 10 ppm tumor data provide a third point on this line demonstrating that this increase in slope is not just an abberration of the 15 ppm data. What is absolutely compelling, however, is the fact that the new 12 month exposure data on cell proliferation fall on exactly the same line (Figure 1.). These new data are crucial for understanding the highly nonlinear dose response for nasal cancer induction in rats.

When extrapolating from high to low formaldehyde exposures it is imperative that one understands that there is a series of changes that work in concert to lower the risk of cancer per unit dose. By using DPX as its measure of exposure, the CARB has incorporated most of the pharmacokinetic factors. What it hasn't recognized is that the major nonlinearity for observable nasal cancer occurs at concentrations above 6 ppm and that the pharmacokinetics are saturated and therefore linear between 6 and 15 ppm. Thus, while it is clear that good science dictates that DPX be used as the index of exposure and that this correctly decreases the estimated risk at concentrations below 6 ppm formaldehyde, it does not explain the striking nonlinearity in tumors between 6 and 15 ppm. It is obvious that an additional factor is involved. The new data of Monticello and Morgan strongly points to cell proliferation as that factor.

It is well known that cell proliferation is involved in multiple steps of the carcinogenic process. Cell proliferation elevates the likelihood of DNA binding by formaldehyde due to greater amounts of single stranded DNA in replicating cells. However, increased cell proliferation also increases the "fixation" of formaldehyde-induced DNA damage into mutations. This increase in mutations is the result of decreased time being available for DNA repair prior to DNA replication. Thus, even though the amount of DPX between 6 and 15 ppm formaldehyde is proportionate to concentration, the probability of mutations remains highly nonlinear due to marked increases in cell proliferation at 10 and 15 ppm. The effect of this nonlinear increase in cell proliferation does not stop at increasing the probability of mutation.

Cell proliferation is also required for clonal expansion of the initiated cell population. This is a critical step in multistage carcinogenesis. The likelihood of additional genetic events occurring in an initiated cell is proportional to the number

of initiated cells. The increased cell proliferation that is associated with 10-15 ppm formaldehyde results in clonal expansion of initiated cells, therefore increasing the probability of these necessary genetic events. Such clonal expansion was evident in the original bioassay in lesions diagnosed as atypical hyperplasia and has been even more carefully evaluated in the repeat studies of Monticello and Morgan.

The impact of this on the risk assessment is that the risk per unit formaldehyde is based on tumor incidence data from 15 ppm. Incorporation of DPX as the dosimeter only deals with the nonlinearities associated with pharmacokinetic factors that occur below 6 ppm. Thus, the risk assessment only corrects for these factors and ignores the major factor associated with high dose nonlinearity. If the CARB document is going to be scientifically defensible, it must be revised to incorporate this new understanding. If the effect of increased cell proliferation was simply multiplicative, the potential magnitude of this effect would be a factor of at least 20. If it is exponential, which is the most likely scenario, it could be several orders of magnitude. One cannot simply drop (ignore) the high dose data and revert to a two stage model. The formaldehyde data set represents one of the best characterized understandings of chemical carcinogenesis available today and should be used in its fullest to pave the way toward generating more accurate and scientifically defensible risk assessments in the future.

While I am not an epidemiologist, I am fairly familiar with the studies that have been conducted on formaldehyde. I am deeply concerned with the presentation of these data in the CARB document. Data are selectively used to support the contention that formaldehyde is carcinogenic in humans. In truth, the collective data are simply equivocal, ie. they are neither positive nor negative. The CARB document predicts upper confidence limits for human lung cancer. This endpoint is cited as being supported by the best available epidemiology study (Blair, 1986), yet this is not the conclusion drawn by that study, to say nothing of the fact that the study had no control for smoking. Perhaps the most compelling argument against formaldehyde being causal for human lung cancer comes when you examine the CARB document's Table C-1. An overwhelming proportion of the data demonstrate a lower number of deaths from lung cancer than expected under the null hypothesis

in formaldehyde-exposed populations. This lack of an effect is further supported by the frequent lack of exposure and duration correlations, and by inconsistencies between and within studies. The bias shown in the CARB document citation of data is unjustifiable and must be corrected.

The CARB document needs to clearly state the major uncertainty associated with projections of risk that are based on concentration x time (C x T) relationships. Research has clearly demonstrated that cell proliferation (Swenberg et al, 1983; Wilmer et al, 1987) and histopathology (Rusch et al, 1983; Wilmer et al, 1987) are driven by concentration, not the C x T product. The entire premise that environmental exposures to formaldehyde pose a carcinogenic risk to humans is based on C x T extrapolations of high dose data. To say the least, this premise is on extremely shaky ground. While I cannot prove that there is an absolute threshold for cancer at the low concentrations of formaldehyde encountered in the environment, it is highly likely that the slope of any real risk is close to zero. This slope would increase greatly if humans were subjected to concentrations of 6 ppm and higher. That, however, is not the case.

The CARB document on formaldehyde risk assessment states that "..an acceptable mathematical modelling approach is needed to predict cancer risks at the lower concentrations to which humans are ordinarily exposed." I fully agree with this statement. Unfortunately, the method used, ie GLOBAL86, cannot do this. I was amazed to see Moolgavkar, 1989, given as part of the support for the use of GLOBAL86 (although the actual reference for Moolgavkar was omitted from the references). All of Moolgavkar's publications that I am aware of in the last 5 years have stressed the need to incorporate cell proliferation data into risk assessment models. This is in fact what is needed to acceptably model the formaldehyde risk. While the complete data on cell proliferation have not yet been fully published, the data are available, ie Figure 1., and should be used. I am confident that an arrangement could be worked out with CIIT to gain access to these data in the short time before they are published. It makes no sense to begin new regulations without these data being incorporated into the risk assessment. While other aspects of the

CARB formaldehyde document will be briefly commented on below, the incorporation of the new cell proliferation data is clearly the most important.

page 1-3: In view of the excellent understanding of the mechanisms associated with formaldehyde's carcinogenicity, the use of an upper confidence limit from GLOBAL86 estimates is clearly overkill. Likewise, the potential hazard to human health is extremely low at the low concentrations associated with environmental exposure. Drawing undue attention to unlikely risks is counterproductive to improving human health because society fails to accept and regulate major causes of cancer such as smoking.

page 1-4: The human nasal cancer data are confounded by exposure to wood dust. The new CIIT study now provides rat data on 6 exposure groups.

page 1-6: The range of extrapolation is too low. The lowest statistically positive exposure is 10 ppm. Using the data in Table 5, the average environmental exposure to formaldehyde is about 34 ppb. This is an extrapolation range of 294.

page 2-1: The reported risks predicted from epidemiology studies have also been severely biased by selection. If you reported the predicted risks for pathologists, it would be greatly exaggerated from what has been found.

page 2-3: The Soffritti study should not be put on the same level as the Til and Tobe studies. It is very poorly documented and inconsistent within its own data sets, as well as with other studies run at higher and lower doses. Several attempts have been made by independent investigators to review the data. Unless some form of peer review can be done, it should be dropped.

page 2-5: It should be clearly stated that metaplasia of nasal epithelium is not related to the neoplastic process.

page 2-10: It is inappropriate to even suggest that the multistage model for risk assessment is based on the biological stages of carcinogenesis. It is merely the number of "stages" that fit a mathematical curve. There is no biology in it! If there was, cell proliferation data would be mandated.

pages 2-18, 19: There certainly are a number of uncertainties. I don't know how CARB calculated that humans are more sensitive than rats. The data on DPX

In rats versus monkeys clearly shows the opposite trend. CARB should reevaluate how they are using this.

page 2-21: The document never discusses the actual range of risk in which the true risk may lie.

pages B-1-8: The paper by Crosby et al (Environ. Mol. Mut., 12: 155-166, 1988) was not cited. This paper characterizes the mutational spectrum of formaldehyde-induced mutations. These data provide reasonable evidence that DPX are responsible for half of the mutations, ie large deletions. The other half of the mutations occur at AT base pairs, data consistent with formation of the very unstable N^6-hydroxymethyladenine adduct of formaldehyde.

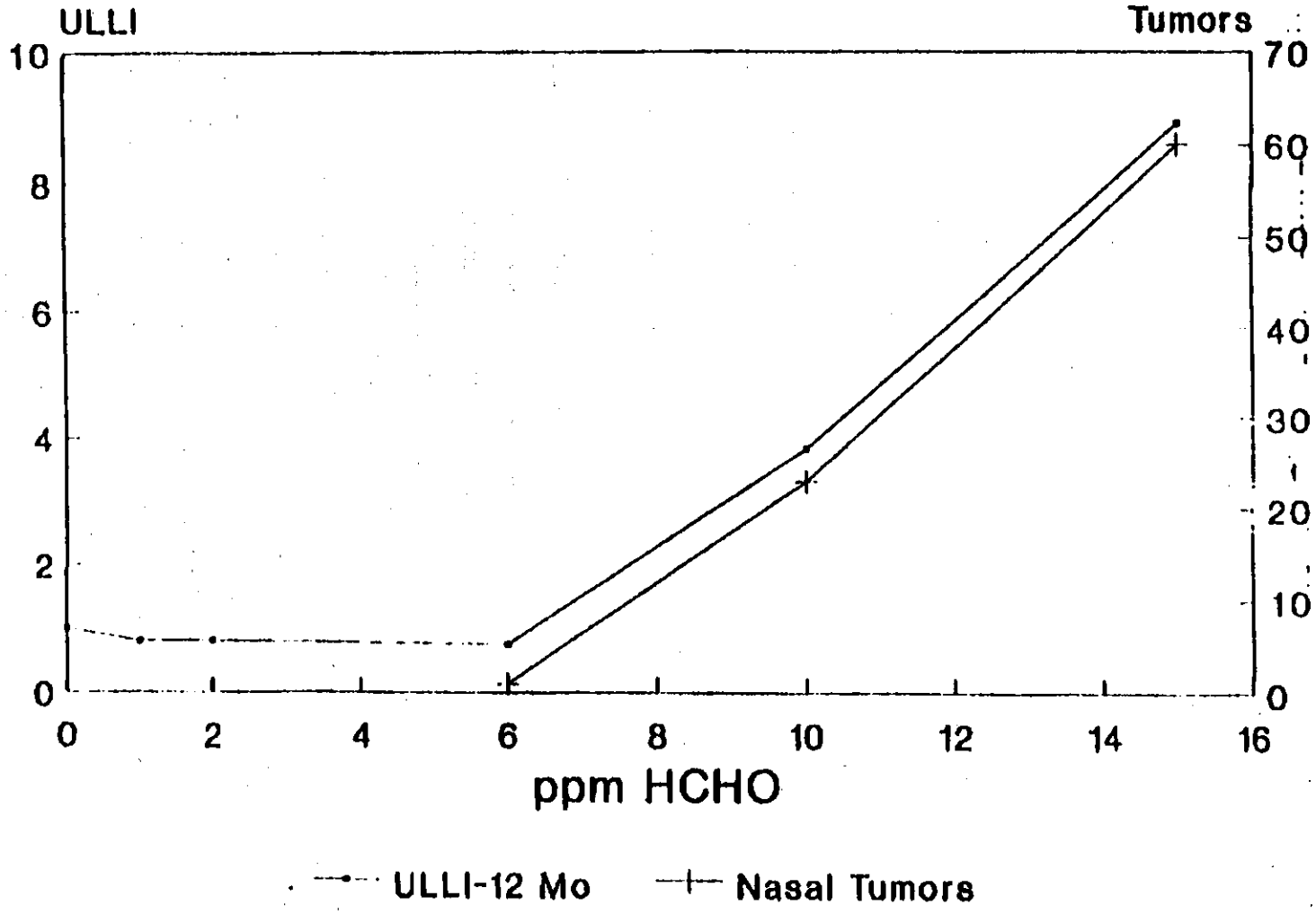

Figure 1.

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27th March, 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Formaldehyde
PO BOX 2815
SACRAMENTO, CA 95812

Dear Madam

Draft Report on Formaldehyde

Further to my discussions with Robert Krieger and Barbara Cook of your office, please find attached to this fax a copy of my resume, together with copies of two of the papers which I have written on the subject of formaldehyde. Other supporting documentation can be provided on request.

Your draft documentation is in the mail to me, so I cannot comment explicitly on the contents within the required timeframe. However, the information which I summarise below is of sufficient importance in your deliberation of the toxicity of formaldehyde that it merits serious consideration.

CANCER RISK

In evaluating cancer risks it is essential to consider the complete path by which a given cancer is supposed to occur. For example, laboratory tests can demonstrate a teratogenicity for formaldehyde, but because of formaldehyde's normal role in body chemistry and its reactivity (hence short half-life in blood) there is no mechanism by which the necessary high concentrations of formaldehyde could be transported to a foetus, except by such an extreme poisoning of the mother that it would likely be fatal to both. Also, the likely route would be by ingestion, rather than by inhalation.

Since we know that formaldehyde is a natural component in the atmosphere, we can conclude that formaldehyde cannot pose a significant risk at natural ambient levels. This is as a result of natural selection processes over the aeons of time.

Equally, the higher formaldehyde levels experienced by our ancestors as a result of cooking fires in their caves, would have ensured that today we do have a tolerance for significant concentrations of formaldehyde.

In the CIIT rat tests[1] it was demonstrated that the cancer was induced by prolonged excessive irritation of the rats' nasal passages. It was also shown that animals with a more human-like nasal physiology did not suffer the same elevated cancer risk as the rats at 15 ppm. One can therefore conclude that if people cannot smell or be irritated by formaldehyde, then the risk of formaldehyde induced cancer is effectively zero.

In my opinion, at levels below 1 ppm, the irritation is so minor in the cancer forming sense that at levels below 1 ppm, cancer risk is not an issue.

Despite a considerable amount of work, I am not aware of any study which has unambiguously demonstrated a sensitivity by any person to formaldehyde vapour alone.

IRRITATION RISK and OTHER HEALTH EFFECTS

In commenting on this aspect it is important to emphasise my background and specific experience and responsibility regarding formaldehyde. In 1981, when I left Cape Insulation Services Ltd. as Technical Director I was ultimately responsible for the technical performance of over 300,000 buildings insulated with urea formaldehyde foam (UFFI). The earliest buildings were insulated in 1959 by Thermalon, which was taken over by ICI Insulation Services in 1973, which in turn was taken over by Cape Insulation Services Ltd in 1977. I was Chairman of the British Standards Committee which drew up the Specification, BS 5617[2], the Code of Practice, BS 5618[3], in 1978, and the British Standards Institution (BSI) supervised Quality Assurance Scheme[4] inaugurated in 1979. UFFI continues to be installed in the UK under the UK Building Regulations, and to date over 2 million buildings have been successfully insulated.

Everett[5] has shown that indoor formaldehyde concentrations typically rise to a peak of around 0.3 ppm about two weeks after installation, which decays, with a half-life of 60 to 100 days, to around 0.1 ppm after a year. In one frame building he found a maximum of 1.6 ppm. From other work, peak concentrations of 0.5 to 0.75 ppm were not uncommon. Under the BSI scheme a card had to be left at each installation bringing people's attention to the fact that there might be a smell from the formaldehyde. BSI, as a part of their Quality Assurance Programme found a 0.2% complaint rate of formaldehyde irritation in the initial period, and only a 0.02% unresolved problem after 8 weeks, see attached 1982 BSI summary sheet for the industry. Note: with the tightening up of building survey requirements prior to

installation and with the development of lower formaldehyde emitting resins subsequent to 1982, formaldehyde has virtually ceased to be a complaint issue in the UK with respect to UFFI.

Formaldehyde complaints were always taken seriously in my Companies long before the formaldehyde scare arose in the US. Because of the high profile nature of these Companies, customers had no hesitation in enquiring about the smell, and all such calls were logged.

Note that the total number of buildings (176,486) insulated with UFFI in the UK from Oct '80 to Sept '82 exceeded the grand total of all buildings ever insulated in the United States and Canada combined.

Before 1978 we used Draegar tubes, and subsequently the chromatropic acid and MBTH methods combined with a portable formaldemeter when investigating formaldehyde complaints. From my experience, it takes a very well trained nose under ideal conditions to detect down to 0.3 ppm. Most people are not aware of formaldehyde below 0.5 ppm, many not even at 1 ppm. I attach one paper[6] which gives additional information on the frequency of various formaldehyde concentrations found in buildings in the UK, in none of which was there any awareness of the formaldehyde in the indoor air by the occupants.

One has therefore to question why there is no major problem in the UK with such a substantial installation base, and the banning of UFFI which occured in both the US and Canada in 1980/81 after far fewer installations. I believe that the most fundamental reason is that the majority of the American buildings insulated are of wood frame construction, whereas the majority of those in the UK are of masonry construction. Also the air-tightness of those in the UK is less because they do not experience the extreme cold of a continental climate in winter. As a result, in American homes, there was often a higher initial formaldehyde concentration and hence more irritation. However, the building tightness does not account for the higher incidence of longer term complaints. One must therefore conclude that <u>there must be another factor involved</u> in the prolonged American complaints.

In one complaint which I investigated in the UK they had a problem each spring. After a great deal of effort it was finally discovered that a bird had found a way into the eaves and regularly nested in the UFFI in the wall cavity. There were other cases where rats and mice nested in the UFFI.

The second attached paper[7] describes the successful effort to mitigate formaldehyde evolution from UFFI installed in the St Thomas More School in Essex, England, using treatment with pure ammonia gas injection into the UFFI. The first attempt was not completely successful, but the second reduced the indoor concentration to an average of only 0.03 ppm as measured the next day by the Health and Safety Executive. The amazing aspect was

that the two key people who claimed to be "sensitised" by the formaldehyde after each step reduction claimed that if anything the problem had got worse! The complaint was not therefore due to formaldehyde. It was afterward discovered that adjacent to the two critical rooms there were urinals leaking into the wall cavity. I believe that the installation of the UFFI blocked the normal cavity ventilation and the spores from the more concentrated rotting residues came into the adjacent rooms via the open suspended ceilings.

In another case in which I treated a private home which had formaldehyde concentrations above 0.3 ppm, the complainants' problem disappeared with reduction of the formaldehyde off-gassing from the UFFI using the ammonia gas injection procedure[8].

In co-operation with the University of Victoria, Formtek Technologies Inc demonstrated that damp UFFI in contact with sawdust would support the growth of stachybotris atra, a common wet rot fungus, and other fungii[9]. Stachybotris atra, in defending its territory against other fungii emits a mycotoxin which is the third most powerful poison known to man.

In investigating a seasonal complaint of induced heart problems related to sharp weather changes in Toronto in a house insulated with UFFI, I discovered that the humidifier was full of a black mold which proved to be stachybotris atra.

I persuaded the Canadian Federal Government in 1985 to conduct an initial investigation into the possible role of fungii in insulated buildings. Unfortunately they were unable to undertake a sufficiently comprehensive study to be able to come up with any definitive conclusion because of the sheer complexity of the issues involved.

When one examines the huge amount of data collected by the Canadian Government in investigating the UFFI issue, formaldehyde does not come out as being an unambiguous cause. In fact the data is so conflicting that it is difficult to see how formaldehyde could be the unique cause.

Barring the initial irritation effects, I believe that allergies and sensitisation to fungal spores and their mycotoxins is a far more probable cause of the claimed adverse long-term health effects. This also becomes apparent in many intractable sick building syndrome problems.

If the UK experience in masonry buildings, which are not so conducive to fungal growth, is compared to that in North America, one has to conclude that the unofficial UK maximum value of 0.5 ppm in domestic buildings is in fact a reasonable figure. It is based on the normally accepted lower detection threshold, whilst I believe that the 0.3 ppm level can be taken as the ultimate lower smell/irritation threshold for sensitive people.

Note that the claimed figure of 0.01 ppm as a lower detection threshold was probably a result of the experimental method used and not due to formaldehyde itself, which conclusion was indicated by the authors themselves in their paper[10].

Further information on the UFFI issues and analysis of the Canadian NRC research data on UFFI is contained in 2 reports for the UFFI Centre[11,12].

I believe the Essex case is no longer sub-judice. The draft report which I prepared and which contains the results of some 1,093 indoor formaldehyde measurements in 169 buildings could be made available if required[13] after obtaining clearance from Essex County Council.

CONCLUSIONS and RECOMMENDATIONS

In view of all of the above, and the extensive epidemiological data showing no increased risk of cancer as a result of exposure to significant concentrations of formaldehyde, I believe that the opportunity should now be taken to substantially down-rate the risks associated with exposure to formaldehyde vapour, as is proposed by the EPA.

1. Within the vapour concentrations proposed in this report, formaldehyde should not be considered as of carcinogenic potential.

2. Legislation on formaldehyde vapour concentrations should only be based on the minimisation of irritation, with criteria based on the classification of exposure, eg:

   0.4 ppm max 8h avg, for retirement homes and hospitals.

   0.5 ppm max 8h avg, for domestic and school environments.

   0.6 ppm max 8h avg, for office and shop type environments.

   1.0 ppm max 8h avg, for industrial environments.

3. For outside ambient air, I propose a total value of 0.1 ppm max 8h avg as a result of all local and natural sources of emission, on the basis that such an outdoor maximum should not substantially increase the risk that the above indoor figures should be exceeded.

   Since formaldehyde is at a natural equilibrium in the ambient environment, ie it is destroyed (half life of less than 12 hours) as well as being created naturally, and with normal atmospheric dilution, I believe that this maximum local figure provides an acceptable outdoor environmental criterion.

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Note: this submission does not purport to be a complete argument, but to place new information before the Air Resources Board. However, the recommendations given are not incompatible with those reached by others trying to achieve a reasonable and equitable set of criteria.

I trust that this perspective will allow you to come to reasonable conclusions regarding the desirable limits for formaldehyde vapour concentrations, based on its nuisance value, which are acceptable to the general public and which are not unreasonably stringent on commercial development.

Yours faithfully

P V L Barrett

Dr P V L Barrett

FOAM INSTALLED IN BUILDINGS MEETING THE REQUIREMENTS CLAUSE 4. BS 5618 : 1978 (Excluding Amendment No. 3)	1 Oct 1980 - 30 Sept 1982				1 June 1979 - 30 Sept 1
	Domestic Buildings		Others		All Buildings
TOTAL NUMBER OF BUILDINGS FOAMED = 176,486					
a) Existing	153,185		8241		151,309
b) New (less than 1 year old)	5,433		359		
c) Under construction	8,862		406		
REPORTS OF WATER PENETRATION					
a) Existing	793	[52]*	1	[1]*	430 [28]*
b) New	88	[162]	12	[334]	
c) Under construction	44	[50]	2	[49]	
VERIFIED REPORTS OF PRESENCE OF FORMALDEHYDE					
a) Existing	408	[27]	47	[57]	337 [22]
b) New	9	[17]	2	[56]	
c) Under construction	-		-		
EXTENDED PRESENCE OF FORMALDEHYDE					
a) Total number of reports (3)	417	(100%)	49	(100%)	337(100%
b) Lasting more than 14 days but less than 8 weeks	147	(35%)	36	(75%)	131 (39%
c) Lasting longer than 8 weeks	36	(9%)	11	(22%)	64 (19%
ROUTE BY WHICH FOAM/FORMALDEHYDE ENTERED BUILDING					
a) Reports of presence 14 days - 8 weeks	147		-		
(i) via gaps in inner leaf e.g. under bath/stairs	77		-		
(ii) via building/constructional faults	54		-		
b) Reports of presence longer than 8 weeks	36		-		
(i) via gaps in inner leaf e.g. under bath/stairs	12		-		
(ii) via building/constructional faults	12		-		
NUMBER OF INSTALLATIONS REPORTING PRESENCE OF FORMALDEHYDE WHICH REQUIRED ASSISTANCE FROM SYSTEM DESIGNER	36				

* [X] - representing X per 10,000 buildings foamed.

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Structural Survey

Volume Two Numb r 4

ISSN 0263-080X

Contents

Typeset by Omnus Graphics Ltd, Horsham. Printed by Whitstable Litho Ltd, Whitstable

Formaldehyde and urea formaldehyde cavity wall insulation

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Formaldehyde and UF foam cavity wall insulation

Urea formaldehyde (UF) foam cavity wall insulation was introduced into this country, from Denmark, in 1959. Relatively little was installed until after the oil crisis which followed the Arab-Israeli War of 1973. In total, some 1.5 million buildings have been insulated with it. UF foam is the cheapest material for retrofit cavity wall insulation. (All well-installed systems have a comparable heat resistance.)

Whilst the product has generally proved satisfactory, it has suffered two grillings in the media, including prime-time TV. The first concerned water penetration and the second alleged health effects from evolved formaldehyde fumes. The problem with the media is that 'Good news is bad news'. Hence the potential problems received wide coverage, and the counter argument, or resultant product evolution, much less.

Besides these issues, many people are skeptical about cavity wall insulation, because the product is unseen and its benefits are not directly measureable a potential dreamboat for a cowboy operator.

It is therefore essential that surveyors are fully briefed on the situation, so that they can properly advise clients involved in the sale and purchase of buildings insulated with UF foam.

Water penetration

The power of television is enormous. The first coverage occurred in February 1975 and involved water penetration – the market collapsed to a quarter of its size overnight. At the same time, the Secretary of State deemed that cavity wall insulation contravened Building Regulation C9(2) for England and Wales[1] (prevention of damp bridging cavity walls), and also was an alteration of a building, so requiring notification of the local authority, under A7, before work commences. In November 1975, Type Relaxation of C9(2) was introduced for existing buildings, streamlining the procedure for installation contractors who were registered with the Agrément Board (for any type of cavity wall insulation). Under Type Relaxation, registered contractors need only give the local authority seven days' notice of their intended work. Only if the local authority has reason to consider that there is a potential risk, based on its own information about the building, is a notification refused.

In 1978, BS 5617[2] and 5618[3] were published, laying down the Specification and the Code of Practice for the installation of UF foam. In 1979 the BSI scheme for the registration of installation contractors of assessed capability with UF foam was inaugurated. By 1980 the Agrément Board cover of UF foam had been phased out.

The Agrément Certificates and the BS Code lay down the types of construction for which the process is suitable regarding water penetration. The success of the schemes is given in the BSI survey of the contractors' records, showing that only 0.5 per cent of existing buildings insulated suffer subsequent water penetration, and these are usually resolved quite easily. The comparative figure for uninsulated buildings will never be known!

In 1983, the Third Amendment to the Building Regulations[4] revised clause C9, and the relevant section became C9(3) for which Type Relaxation applies for existing buildings.

Note that these controls and regulations are not applicable in Scotland and Northern Ireland because of different building regulations.

Formaldehyde evolution from UF foam

Certainly it has always been known that formaldehyde is evolved from the curing foam in the cavity, but as a result of normal UK construction practices this evolution is rarely noticed within the building. Even so, BS 5618, the Code of Practice for UF foam, when it was first published in 1978, insisted that a warning card be left with the occupiers after each installation. The card should state that there can occasionally be some irritation to the eyes, nose and throat, which can be relieved by increasing the degree of ventilation. If the irritation persists, then the installer should be contacted to investigate and remedy the cause. It was not regarded as a health risk. The BSI survey of installers revealed that only 0.3 per cent of customers contacted them regarding subsequent formaldehyde fumes.

The insulation of frame structures

Recently, a number of problems occurred during the insulation of the walls of buildings with frame structures. Figure 1 shows the construction details at the first floor ceiling band of one of the buildings. Because of the large gaps in both the external and the internal leaves, ventilation air could freely pass into the building via the cavity. There was no masonry inner leaf above the windows; the gap was filled by sheets of polystyrene wired onto the frame. When the cavity was filled with UF foam, the evolved formaldehyde was entrained into the building.

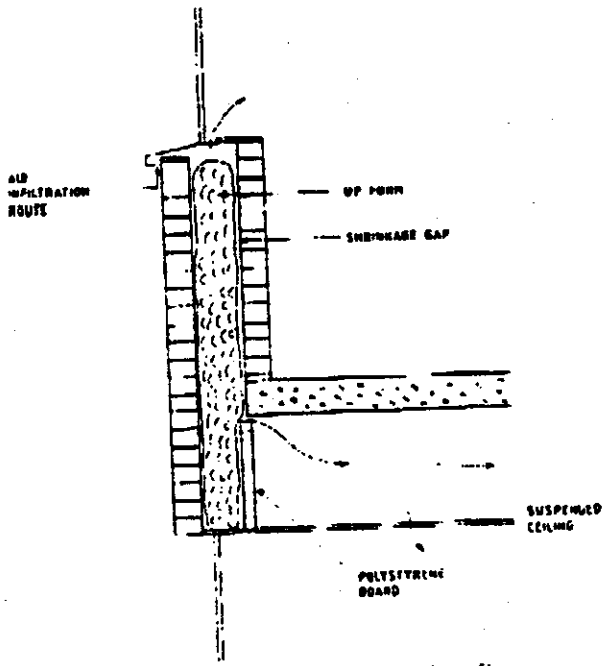


Figure 1 Sketch of construction at first floor ceiling band

As a result of these problems, the British Standards Institution re-examined the Code of Practice, BS 5618. Because frame structures are not normally used in the general housing stock (where UF foam has been predominantly used), specific guidance had not been incorporated within the general requirements.

Amendments to BS 5618

Amendments to BS 5618 were published on 30th November, 1982,[5] to ensure that unsuitable buildings are eliminated on the initial survey or that appropriate remedial action is taken prior to, or as a part of the contract.

The main points to consider are:

(a) The inner leaf is of essentially continuous masonry and that there are no large gaps in it leading to the occupiable part of the building. This means that the tops of cavities do not need to be sealed, unless there is a room in the space above, ie in the attic or a dormer room. Normal gaps around the ends of joists are acceptable. The space above a suspended ceiling should be considered as an occupiable part of the building.

In existing buildings, walls which are internally dry-lined or of fair-faced brick or blockwork are only suitable if the joints are well made — normally not the case — or the inner surface well sealed.

(b) As an additional precaution, untrucked vents into the occupiable parts of buildings must now be trunked.

(c) The cavity must not be open to a space from which a recirculating air system draws in air.

(d) Particular care is required when surveying buildings of a frame type construction, because gaps are more likely.

(e) Large gaps in the outer leaf, such as cavity vents or under windows should be sealed.

(i) After the installation, any foam which has penetrated the inner leaf into the occupiable part should be removed and the gap sealed.

(ii) If a problem does occur, to ensure prompt and effective remedial action, the British Standards Registered Firm Technical Panel drew up a set of industry guidelines, which is issued to every contractor in the scheme.

Note that for a variety of reasons, these precautions should also be applied to the other forms of retrofit cavity wall insulation.

As well as BS 5618, the Building Regulations in England and Wales were also tightened: a new Part S^4 was introduced, limiting the use of toxic substances in buildings. UF foam is deemed to satisfy these requirements if the material has been approved by BSI and installed by contractors operating under their registered firm scheme.

The American use of foam

As a result of developments in America, and the resultant interest in the UK problems, formaldehyde fumes from UF foam became the second subject for television coverage.

Unfortunately, the use of foam is not regulated in either the US or Canada. In addition, their houses are rarely of masonry construction, nearly all being of timber frame construction. There, the normal practice is to insulate the internal cavity, within the frame, between the studwork and the internal plasterboard. (This is forbidden for foam under BS 5618, because the foam cannot readily dry out, due to the high vapour resistances on either side of the insulation.) Because of frequent puncturing of the internal lining by electrical sockets etc, when foam was installed a proportion of the formaldehyde evolution took place into the building. In a number of cases this resulted in high internal concentrations, causing distressing irritation to the occupants. To make matters worse, proper remedial measures were not carried out, leaving some customers in great difficulties. The issue became political and Massachusetts banned its use.

The formaldehyde health scare

In 1976 the US CPSC (Consumer Product Safety Commission) was asked to investigate. This it did with crusading zeal, hoping to gain its laurels in consumer protection thereby. All the negative aspects were emphasised. Balanced and controlled studies were not the order of the day when investigating the effects on consumers. Consumer protection groups sprang up, such as 'SUFFER' — 'Save Us From Formaldehyde Environmental Repercussions'!

At the same time, a worker protection study was commissioned for the CIIT, the Chemicals Industry Institute of Toxicology, to investigate the potential cancer risk from high levels of formaldehyde in industry. Some 240 rats and mice were separately exposed to formaldehyde concentrations of 2, 6 and 15 parts per million (ppm), 6 hours a day, 5 days a week for up to 2 years. It must be appreciated that the ceiling value for workers in formaldehyde industries in the US is 3 ppm and in the UK it is 2 ppm. The irritation caused by 15 ppm is very intense.

Whilst no rats developed nasal tumours[6] at 2 ppm, 1.5 per cent of the rats at 6 ppm and 43 per cent at 15 ppm developed them. This contrasts with the mice tests where no tumours developed at either 2 or 6 ppm and 2.4 per cent were found at 15 ppm (two of the remaining 85, the others died in communal fights). Assuming that nasal tumours could be induced in humans in a similar way to the rats, the CPSC developed a mathematical model which predicted a low but positive risk to humans at levels down to 0.01 ppm. As a result of this and information from faulty installations, the CPSC banned the use of UF foam in the US. This was shortly followed by a ban in Canada and the institution of a multi-million dollar programme for either the removal of the foam from dwellings or major remedial action to seal up the walls. A whole host of illnesses and malaises were ascribed to the all-offending vapour.

The health aspects of formaldehyde

Although formaldehyde has been known for over 100 years and in extensive use since the turn of the century without major fears being aroused, surprisingly little was known about the health aspects. Doctors thought the situation ridiculous at first since every doctor had to do his stint dissecting samples preserved in formalin solution! Every school biology room has its preserved samples.

Formaldehyde is a part of our natural body chemistry and any absorbed low levels of formal-

dehyde are quickly broken down by natural enzymes within the body. However, formaldehyde vapour in sufficient concentrations does irritate the eyes, nose and throat. For most people the lowest concentration which they can detect by irritation is around 0.5 ppm. More sensitive people can detect down to 0.3 ppm.

Formaldehyde is ubiquitous and a cornerstone of modern industrial life. As such, the potential impact of the American health claims would be staggering, if proven. Therefore, an apparently disproportionate effort has been invested by industry and Government to establish the facts.

1 *Background levels*

Formaldehyde is evolved from plants. I have measured 0.03 ppm on a hot summer's day in a village garden. Outside air measurements typically vary from 0.003 to 0.02 ppm.

Formaldehyde is a component of exhaust fumes. Air concentrations of up to 0.2 ppm can be found on the streets of big cities.

2. *Concentrations in buildings*

I have analysed a survey of fomaldehyde concentrations in 17 local authority buildings which had not had their walls treated with UF foam and 14 which had been treated between two and eight years previously (without any problems). The results are shown on Figure 2. This shows no significant difference in the formaldehyde concentrations of rooms with untreated walls, compared with *rooms* with walls insulated between two and eight years previously.

Formaldehyde is clearly a normal and significant component of the building environment. By extrapolating the straight line in Figure 2, one can see that about 1 in 100 rooms of local authority buildings would be expected to have concentrations of 0.3 ppm and 1 in 1,000 around 0.4 ppm.

However, when UF foam is first installed, the internal concentrations of formaldehyde do increase. The peak concentration is normally less than 0.5 ppm, the level at which it becomes generally noticeable. The concentration decreases over the following few months, and by the end of a year the average is around 0.1 ppm.

3. *Health surveys*

The results of 16 epidemiological surveys, covering some 20,000 people involved with formaldehyde at their place of work, have been reported. The most recent involved some 7,000

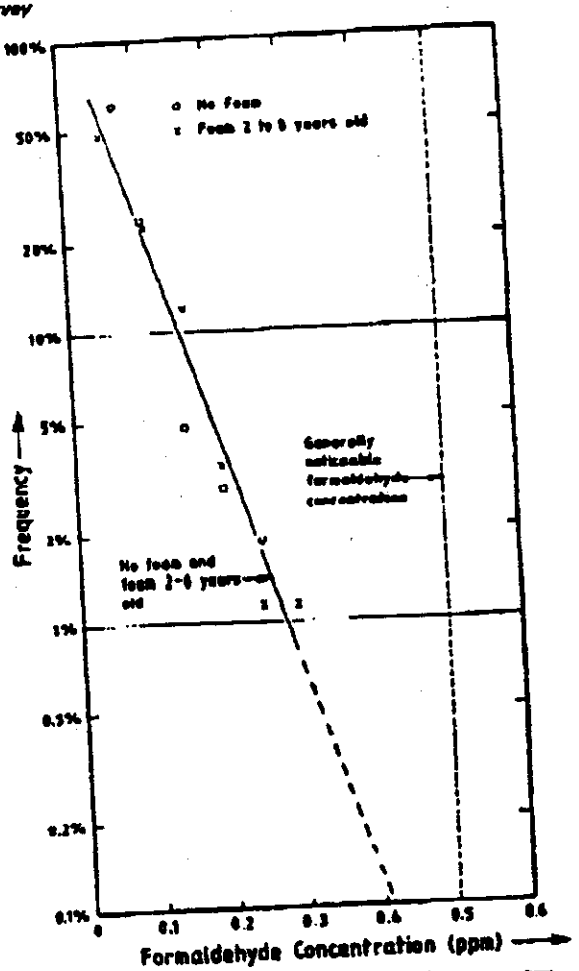


Figure 2 Frequency of formaldehyde concentrations

workers in the UK carried out by the Medical Research Council.[7] No significant increase in risk of cancer has been found, or any other long-term effects, even though some of the workers had previously been exposed to much higher levels than now permitted, since the maximum permitted concentration used to be 10 ppm.

4. *The rat study*

Because rats cannot breathe through their mouths, their nasal system is not comparable to man. In addition, it has since turned out that the '15' ppm animals had been exposed to 'an average daily high of a near-lethal 32.4 ppm'![8] The nasal infection which the rats suffered early on in the trials was another confusing factor. No other study

with different animals has shown up a significant increase in cancers. The only definite conclusion is that formaldehyde is carcinogenic to rats.

5. Conclusions on health

When the US Federal Court of Appeal considered all the information, it held[8] that 'record developed before the Commission (CPSC) did not contain the substantial evidence necessary to support the Commission's ban on use of urea-formaldehyde foam insulation' 'Rule Vacated'. When reviewed by the US Supreme Court of Justice on 25th August, 1983, they upheld the Federal Court of Appeal and the ban was lifted.

The position of the UK Government remains the statement in the House of Commons 'the Chief Medical Officer of the Department of Health and Social Security, who is the Government's senior adviser on health matters, has indicated that the completed studies of people exposed to formaldehyde vapour have not found any evidence that it causes cancer, changes in lung structure, or permanent impairment of lung function in man'.[9]

I believe a maximum concentration of 0.5 ppm should be set as a guideline for non-occupational environments, with some tolerance for short-term deviations.

It is clear that the mathematical model used by the Americans to forecast a significant risk of nasal cancers at 0.01 ppm is not tenable. Equally, the medical 'fact' that some people are sensitive to formaldehyde down to 0.05 ppm needs revision. Otherwise the cancers would be very common and sensitive people could not inhabit buildings!

Other potential sources

The investigations have considered the possibility of other chemicals used in the buildings being involved, other chemicals being evolved from the foam and dust particles causing allergic irritation. In November 1982, a BBC television 'Nationwide' programme covered formaldehyde from UF foam. In it Dr Nantel of Quebec, Canada, said that he was investigating other potentially dangerous chemicals in Canadian UF foam. However, checks by the BRE on UK foams found no other significant gases being evolved from UF foam, other than formaldehyde.

Very small quantities of tiny particles can be entrained by air movement off foam. However, only minute traces could be found inside even leaky buildings, and attempts in the UK to demonstrate reactions by sensitive people to dust from the foam have proved unsuccessful.

Indoor pollution

Since formaldehyde cannot be the cause of the majority of the reported problems, as the concentrations in complainant's buildings are generally within the normal indoor spectrum, attention is now turning to other indoor pollutants, which have been concentrated by excessive reductions in the air change rate. Radon, carbon dioxide, carbon monoxide, oxides or nitrogen and many others are now being studied. Formaldehyde has proved the catalyst in the opening of a Pandora's Box of potential airborne health problems in the home.

The clear message is: don't take energy saving too far by excessive reductions in ventilation.

Conclusions

The British Standard has been tightened up to exclude unsuitable buildings for the process. Noticeable concentrations of formaldehyde rarely occur. They cause temporary irritation, but are not a health risk.

The building must be surveyed for suitability, according to BS 5618.

UF foam cavity wall insulation is a satisfactory process when installed by a contractor registered under the British Standards Scheme of Firms of Assessed Capability.

REFERENCES

1 The Building Regulations 1976, Statutory Instrument 1976 No 1676.
2 BS 5617: 1978 Specification for urea-formaldehyde (UF) foam for thermal insulation of cavity walls.
3 BS 5618: 1978 Code of practice for thermal insulation of cavity walls (with masonry inner and outer leaves) by filling with urea-formaldehyde (UF) foam.
4 The Building (Third Amendment) Regulations 1983. Statutory Instrument 1983 No 195.
5 BS 5618: 1978 Amendment 4130, November 1982.
6 II & SI: Toxicity Review 2. Formaldehyde: HMSO 1981
7 Medical Research Council Environmental Epidemiology Unit, Formaldehyde Study, Interim Report, 24th June, 1983.
8 United States Court of Appeals, 5th Circuit, 7th April, 1983, 3632.
9 Hansard Official Report, 18th March, 1982: Vol 20, c 193. Also 7th May, 1982: Vol 23, c. 441.

FEATURE

uf foam — the curr nt situ tion

by Dr. Peter Barrett

There must be many worri people asking the question, "After uf foam, what's next on the hit list?" The truth of the matter is that there is no such thing as a product, whether insulation or not, which is absolutely safe when put into widespread use. Risk and safety are very emotive subjects but also ones to which the public takes a very schizophrenic approach. For instance if the public were so concerned, then they would not buy two storey houses because of the risk of serious injury from falling down stairs.

No insulation product is without risk, manufacturers and installers who advertise to the contrary are being dishonest. The core of the matter is, "What will society accept as a reasonable risk?" Society accepts that people are killed in accidents winning coal and oil from the ground. Many more will suffer in wars and hostilities when the available oil supplies can no longer meet the needs of society around the turn of the century, less than 20 years away. This is why insulation and energy conservation programmes have such an important part to play in extending the available energy resources.

As regards uf foam, if the use of the product was proven to produce an unreasonable health risk and there were suitable economic alternatives, then there would be no question that the product should be banned. Unfortunately particularly in the health field, it is relatively easy to develop theories as to how a product might be a risk but it is extremely difficult and costly to prove the contrary as many industries in the U.S. have found to their cost and exclamation.

Formaldehyde is one of the latest chemicals to face the cancer witch hunt in the U.S. The situation is made the more difficult because it has been around a long time and never went through the searching enquiry which modern chemicals have to before being released onto the market.

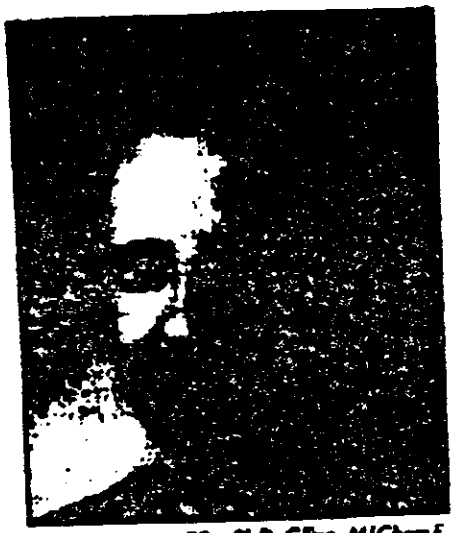
Another crucial aspect is the way the medical profession operates, there is no kudos in publishing painstakingly achieved negative information unless the subject is under the microscope. Only the other day I learnt of some Canadian research in which one patient was reported as reacting to uf foam, but the researcher failed to mention that after studies on 20 [illegible] he produced a single [illegible]

therefore, by default, heavily biased. So, in turn, the media cannot be blamed for quoting the published "facts".

It is certainly not unique to the formaldehyde scare that most people prefer to work with "tunnel vision". Theories have been developed where the unstated assumptions have not been questioned. A good example is that by the US Consumer Product Safety Commission

1. uf foam gives off formaldehyde.
2. The symptoms experienced by people in homes insulated with uf foam are in general similar to those caused by formaldehyde
3. Therefore formaldehyde given off by uf foam is the cause of the problem.

This has led to monumental arguments between the formaldehyde industry and the CPSC "side" over the interpretation of the "medical evidence" concerning people living in houses insulated with uf foam. The CPSC claims that a significant number of people react to low levels of formaldehyde but major users of formaldehyde, such as embalmers, biologists and pathologists, claim that their experience would not support such widespread low level effects. Therefore the charge has been made that the symptoms are due to the stress induced by a mass [illegible] and that formaldehyde is the

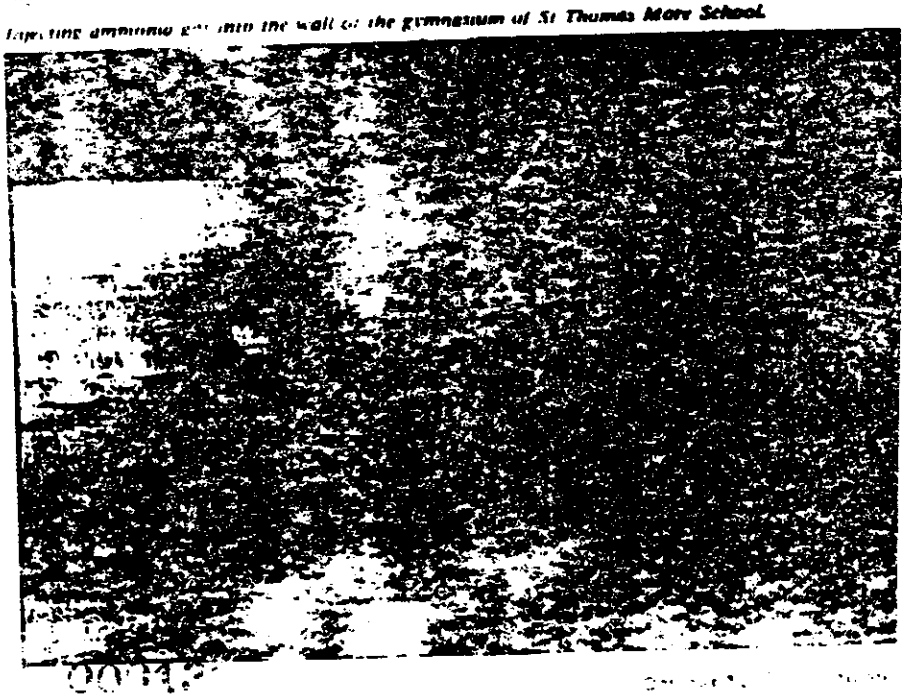


Dr. Peter Barrett BSc. PhD. CEng. MIChemE.

current scapegoat for all the unexplained aches and pains which our stressful society seems to be full of. All this is food and drink to the mass media and a convenient bandwagon for many "interested" parties. A fuller treatment would provide the basis for a bestselling fiction novel.

Last but not least is the accuracy of measurements of the formaldehyde concentration in air. Great strides have been made over the last few years to improve the techniques. Unfortunately the

Injecting ammonia gas into the wall of the gymnasium of St Thomas More School.

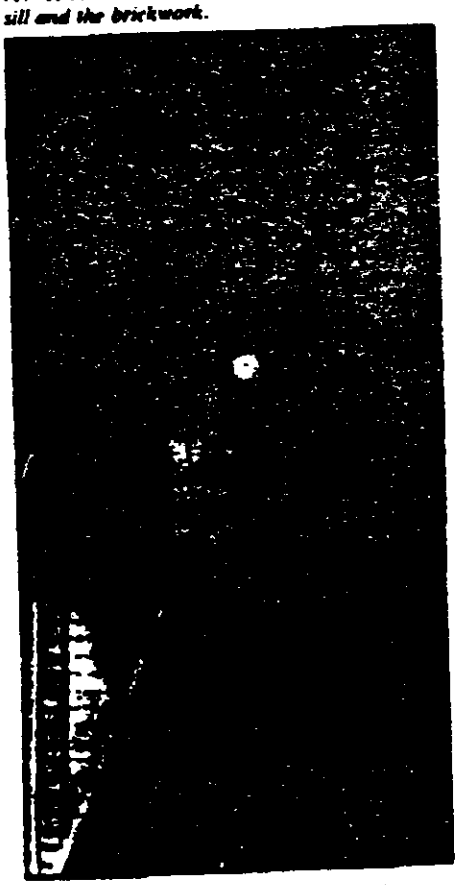


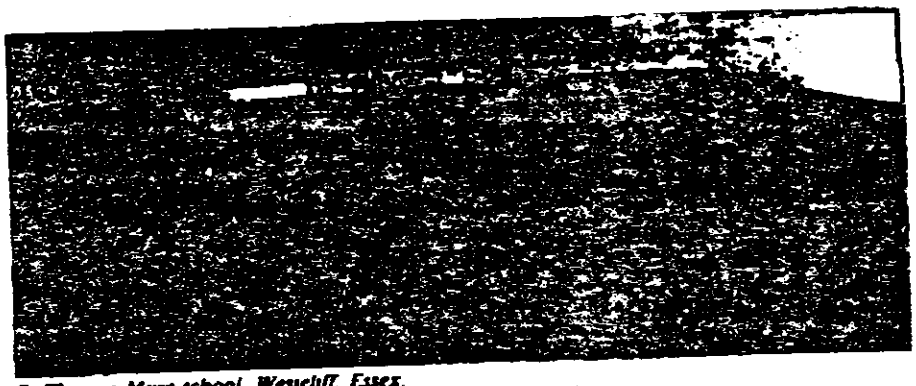
other side of the coin is that many earlier statements on the effects of various concentrations must be questioned because the measurements would now be regarded as unreliable.

So, in the middle of this confusing situation, where has the Essex experience now taken us? A new perspective is emerging which will hopefully allow a more reasoned attitude to prevail:

1. Formaldehyde is much more common than most people had previously suspected. In the outside air a typical concentration is 0.02ppm (parts per million by volume in air). The average concentration found this summer in 15 Essex schools uninsulated with uf foam was 0.065ppm. One school had an average of 0.14ppm and the highest room measurement was 0.24ppm.
2. Two ammonia gas treatments of the uf foam in the St Thomas More school reduced the formaldehyde concentrations to an average of 0.03ppm, yet some of the staff claimed that there were still adverse health effects in the school. In view of the emotion which had been generated over the issue, the County Council decided to relocate the school until a satisfactory remedial programme had been completed.

Picture of the gymnasium windows at St Thomas More School, showing the large gap between the underside of the aluminium window sill and the brickwork.





St Thomas More school, Wesrcliff, Essex.

3. The conclusion from (1) and (2) above is that there must be another factor involved related to the uf foam. This conclusion is supported by other evidence, as yet circumstantial, not just from Essex. It would also explain some of the American paradoxes.
4. The Health and Safety Executive has accepted that there could be another factor and has asked Dr Newman Taylor, Director of the Occupational Lung Disease Unit at Brompton Hospital, London, to conduct the necessary medical investigations. There are three possible permutations.
   a) The patients are sensitive to low levels of formaldehyde.
   b) The patients are allergic to a varying extent to minute particles of dust from the foam, in an analogous way to pollen causing hayfever or cat hairs causing an allergic reaction
   c) The patients are sensitive to some vapour which is given off from uf foam other than formaldehyde
5. Small quantities of fine uf foam dust have been measured in the air in St Thomas More school
6. The Building Research Establishment is developing apparatus to analyse for other vapours. So far the only vapours found of significance are formaldehyde and water vapour, confirming the ongoing Canadian research
7. The British Standards Institution is carrying out its own investigations and if it finds any significant data then this will be passed on to the medical team.
8. There is no question that in contrast to the majority of successful installations of uf foam in the UK, some of the buildings insulated under the recent contract in Essex did suffer an initial, higher than normal, concentration of formaldehyde, which caused irritation to a number of people. Action has been taken through the British Standards Institution to ensure that the Code of Practice will more clearly define those buildings which are unsuitable for the process. It is obvious that any action to reduce formaldehyde ingress would also reduce the ingress of any dust or other vapours. Straightforward remedial action to seal gaps and remove foam which had penetrated the inner leaf has resolved the majority of cases.

   It is important to have a perspective on the outstanding problems. Of the 93,000 people using the buildings insulated with uf foam under the 81/82 contract, only seven have had a strong reaction and two of these were cleaners who objected to the formaldehyde vapour in the early morning after the building had been closed up overnight.
9. So far, the circumstantial evidence indicates that the dust theory best fits the unexplained residual effects which a small proportion of people have experienced.

Because of the large number of people who could be unnecessarily alarmed by fear of the unknown, it is vital that the medical situation is clarified at the earliest opportunity. Fortunately the generally successful experience in the use of uf foam in the UK over 24 years would strongly indicate that there is no reason why it should not continue to be used within the criteria laid down in the revised BS Code of Practice.

One final note, allergies to dust particles are a fact of life. In addition, every retrofit form of loose insulation generates its own dust, whether beads, granules or fibre. As the use of each insulant increases, so it will probably be found that a very small, but differing, proportion of the population will be allergic to each. "Let he without sin cast the first stone" (ASA please note). The other systems may also need to consider whether the new restrictions on the use of foam are not equally applicable to them.

Dr Peter Barrett, of Peter Barrett Consultants, Welwyn Garden City, has been retained by Essex County Council as their technical consultant in regard to the formaldehyde problems which they have experienced following the insulation of 17 public buildings in 1981/2.

PETER BARRETT CONSULTANTS
Energy Conservation and Environmental Control
Dr. P.V.L. Barrett B.Sc.,Ph.D.,C.Eng.,M.I.Chem.E.,F.Inst.E.
807 Seamist Place, Victoria, BC, V8Y 2R4, Canada Tel: (604) 658-5183

RESUME

of

Dr PETER V L BARRETT

PERSONAL DATA:

Date of Birth: 24th July, 1941 *Married:* 26 years

Children: 2 sons, both at University, (Waterloo and RRMC).

Canadian Citizenship: 1989

EDUCATION & ASSOCIATIONS:

1963 BSc in Chemical Engineering from Imperial College, London, England (1st Class Honours)

1964 Completion of 5 year Student Apprenticeship with Ministry of Defence (Army Department) (similar to co-op courses)

1966 PhD in Chemical Engineering from Selwyn College, Cambridge, England

1968 Member of the Institute of Chemical Engineers

1982 Fellow of the Institute of Energy

1985 Member of the Air & Waste Management Association

CAREER SUMMARY

1967 Development Engineer for DuPont Co (UK) Ltd, Londonderry, Northern Ireland; working on neoprene and hylene plants. Saved $0.5M on improved design of chlorine and phosgene emergency release scrubbers, using a computer programme based on his PhD work. He saved a major toxic spill by redesigning the chlorobutadiene catalyst following an accident. He was project liaison officer with the US for the $8M dilution safety project.

1971 Research and Development Manager for Potterton International, London; manufacturer of central heating furnaces, gas and oil fired, residential and commercial. He managed the innovative research for the most successful wall mounted gas-fired boiler, the market leader for over 10 years.

1974 Technical Manager for ICI Insulation Service Ltd, Welwyn Garden City, Herts, England, the largest installers of UFFI in the UK. He was responsible for technical support to the Sales and Operations departments, as well as managing a UFFI research laboratory. ICI was unique, being both an installer and having its own chemical formulation backed by a research laboratory.

Throughout his time in ICI and Cape, the wall insulation industry was under severe media pressure because of poor performance by some small operators. He had to approve all advertising and PR for both companies. He was heavily employed as the National Technical Expert to give press interviews, seminars and technical papers as a central part of the campaign to regain respect for the industry. He chaired the British Standards Technical Committee which drew up the BS documents as well as the first BSI Quality Assurance Scheme applied to a contracting industry. The first problems arose around fears of rain penetration through external building walls; the second involved the formaldehyde scare, both of which were susuccessfully combated. UFFI is still being used with over 2 million installations.

1977 Take-over by Cape Industries Ltd, London. (The original specialisation of Cape was in asbestos.)

1979 Appointed Technical Director, Cape Insulation Services Ltd; range of insulation materials increased from UFFI to polyurethane, spray and pour, blown mineral fibre, weatherstripping and caulking, internal insulated lining systems, and polystyrene sheet systems. Turnover reached £13M. He carried out quality control work on a polyurethane installation in Argentina.

1981 Set up Peter Barrett Consultants.

1982 Appointed Technical Consultant to Essex County Council for advice on formaldehyde evolution from UF foam and appropriate remedial actions. This was the largest formaldehyde problem ever in the UK, and he was involved in numerous TV, radio and press interviews.

CAREER SUMMARY (cont)

The public relations and personnel procedures developed for the formaldehyde situation worked well when the Council was faced with subsequent problems over asbestos in school buildings.

1984 Set up Peter Barrett Consultants in Victoria, BC, Canada, when asked to come to Canada to apply his UK technical expertise to the Canadian situation. He had developed an ammonia gas treatment method which avoided the costly physical removal of the foam from the buildings.

1985 Appointed Vice-President Research and Development to Formtek Technologies Inc, Victoria, BC, Canada. Projects involved development of an ammonia gas based, in-situ, formaldehyde treatment of UFFI installed in wood-framed buildings, development of an ammonia gas treatment for particle board manufacturing plants, and development of the novel 'Tectonic' polyurethane, interlocking board insulation system. He played a major role in the instigation of a Federal UFFI fungal research programme. Formtek closed Sept '85 due to problems with construction financing.

1986 Under contract to the National Research Council as technical writer and to assist in the UFFI project wind-down, especially concerning formaldehyde and particle evolution from UFFI. He also liaised with the Federal Government for continuation of the UFFI programme by widening its scope to general indoor air quality research on a multi-disciplinary basis.

1987 Set up Peter Barrett Consultants (International) Inc in Victoria, BC, acting as President. He worked on marketing a medical heating pad into Europe, together with manufacturing proposals under license. However a patent disputed halted the entire market. He worked on proposals for the treatment of Hazardous Waste in BC and made presentations to the Committee. The Company completed a CIDA contract on the feasability of a pharmaceutical plant in Nigeria, then concentrated on raising the financing for the plant, as well as for a number of other West African and Chinese projects

As a part of the Company's brokerage activities, he assisted in the launch of the BC Business Network, and spoke at the launch in BC Place with the Minister, Mrs Grace McCarthy.

COMMITTEE WORK

72-74 Editorial Board of the "Chemical Engineer".

73-74 Inaugral Chairman, Nonsuch Section of the Institution of Chemical Engineers.

75-79 Appointed Chairman of the British Standards Working Panel which developed the Specification and Code of Practice, BS 5617 & 5618, for UFFI manufacture and installation, published in 1978.

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COMMITTE WORK (cont)

78-84 Member of the British Standards Quality Assurance Department Technical Panel which set up the Scheme for Firms of Assessed Capability in both the manufacture and installation of UFFI.

80-81 He organised the formation of the Cavity Foam Bureau and became its Secretary. He ran the day-to-day operations during the first two successful advertising campaigns to distance the UK UFFI industry from the North American problems. (The industry is still operating in the UK, with over 2 million buildings insulated.)

80-84 Member of the BS committees on plastic insulation materials, together with those developing methods to describe a building's exposure to wind-driven rain and a general method for the assessment of buildings for cavity wall insulation.

1982 Appointed National House Building Council representative on BS committees concerned with insulation materials.

1985 Attended Canadian General Standards meetings on polyurethane insulation and on vapour barriers.

1991 Programme Director for new Vancouver Island Chapter of the Air & Waste Management Association.

ADDITIONAL SKILLS

1. He developed a close working relationship with relevant government departments in the UK and Canada.

2. He is familiar with advertising and public relations in the handling of controversial issues.

3. He has developed a popular lecture style and he has written many articles, each tailored to the audience's expertise.

4. He has acted as technical expert in legal actions.

5. He operates his own word-processing using WRITER III, WORDSTAR 2000 and WORDPERFECT 5.1, desktop publishing using VENTURA PUBLISHER, spreadsheets using Lotus 1-2-3 and QUATTRO PRO, databases and accounting programming using dBASE III Plus, and basic programming using GW-BASIC and FORTRAN.

6. He has a very practical approach when it it comes to resolving problems, but the logic is soundly based, either on chemical engineering principles, which he has found to have a very wide applicability, or on practical common sense based on his wide experience.

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Energy Conservation and Environmental Control
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Fax: (604) 658-5183

To FAX: (916) 327-7212

28th March, 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Formaldehyde
PO BOX 2815
SACRAMENTO, CA 95812

Dear Madam

Draft Report on Formaldehyde
Addendum to submission of 27th March, 1991

If we take the UK UFFI installation base as 2.2 million buildings, and with a population of 52 million and a housing stock of 19 million, the number of people who have lived in homes freshly insulated with UFFI is at least 6 million.

I attach a graph of the results of the Essex survey expressed as a frequency distribution. For the 1981/82 contract, the buildings, mostly related to schools, had been insulated with UFFI some 4 to 10 months previously. By the time this survey was carried out, remedial action had been taken on many of the buildings where high readings had been found earlier. As an extreme example, an early Draegar reading in St Thomas More School was 2 ppm, and by the time of the survey the average had been reduced to 0.03 ppm.

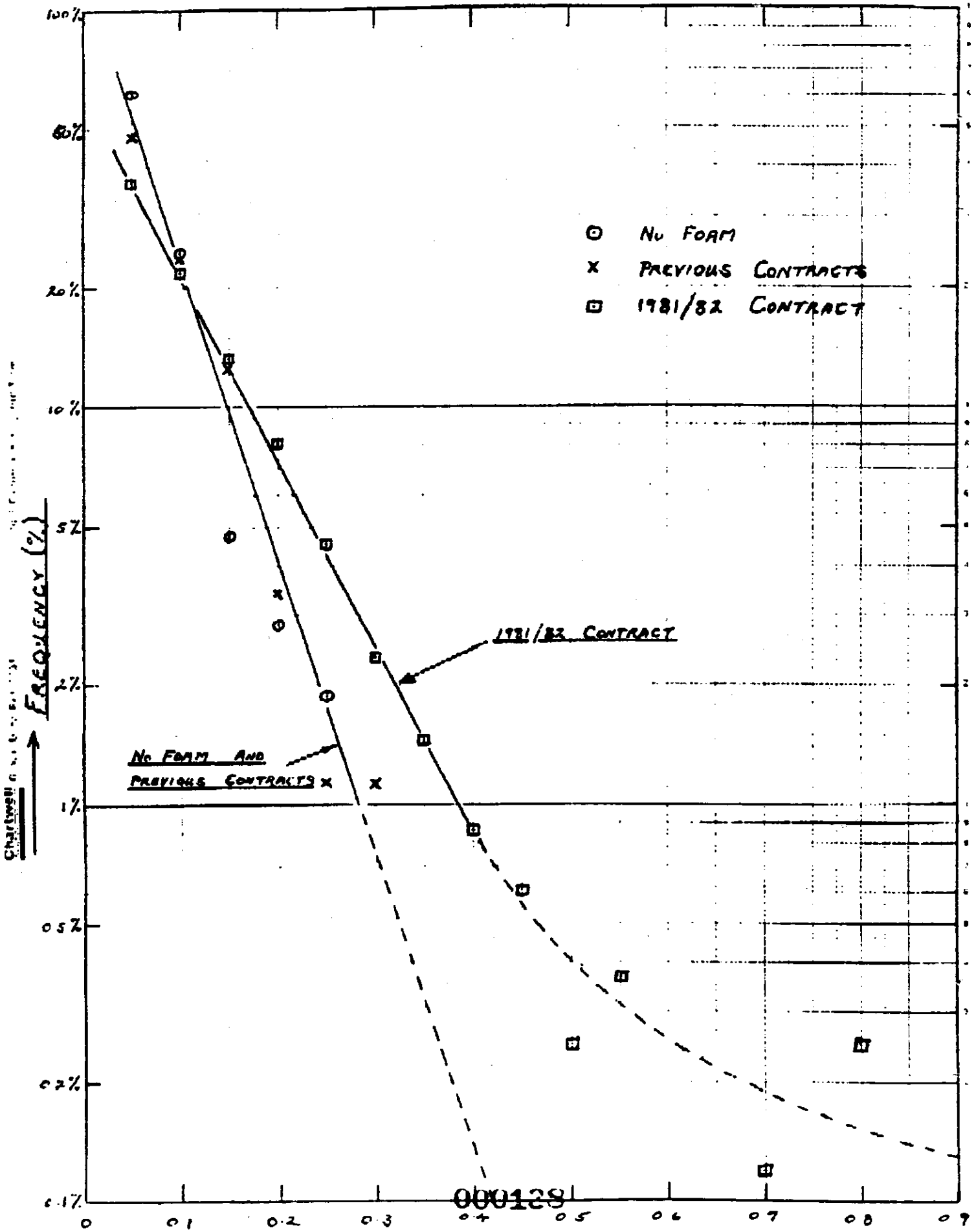
Bearing in mind the range of normal background concentrations in these buildings, see Fig, which I believe would prove fairly typical for the UK housing stock, there is no justification for making the formaldehyde standards any tighter than what I have proposed.

Yours faithfully,

PVL Barrett

Dr P V L Barrett

FIG 3 FREQUENCY OF FORMALDEHYDE CONCENTRATIONS



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BORDEN PACKAGING and INDUSTRIAL PRODUCTS
DOMESTIC AND INTERNATIONAL
DIVISION OF BORDEN, INC.

March 21, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Formaldehyde
P. O. Box 2815
Sacramento, CA 95812

Re: Comments on Draft Formaldehyde Air Toxics Documents

Dear Ms. Shiroma:

I am writing to provide Borden's comments on the Proposed Identification of Formaldehyde as an Air Toxic. We are encouraging consistency between the California DHS and U.S. Environmental Protection Agency risk assessments.

EPA has incorporated mechanistic data into their risk assessment. Additionally, scaling factors used by both agencies should be the same. Based on EPA's revised assessment, the lifetime daily dose exceeds 800 μg/day.

We request that the inclusion of formaldehyde on the air toxics list be evaluated consistent with the revised EPA assessment and that DHS support a consistent approach with EPA guidance.

Thank you for this opportunity to provide comments.

Sincerely,

Diane E. Strayer

Diane E. Strayer
Environmental Engineering Manager

DES/cjs

xc: M. Gruenwald
R. Springer

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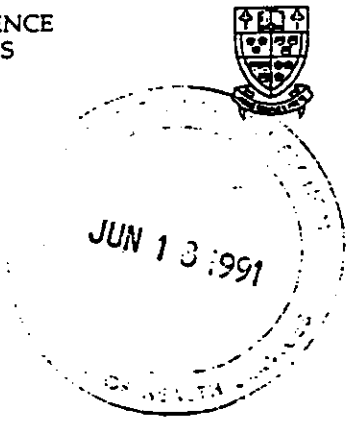

June 13, 1991

Dr. Stan Dawson
Dept. of Health Services
Air Toxicology and Epidemiology Section
2151 Berkeley Way, Annex 11
Berkeley, CA 94704

Dear Dr. Dawson:

I include our reply to the Formaldehyde Institute, Inc.'s comments to the State of California Air Resources Board.

The issue is of sufficient importance so that we will submit the exchange to a suitable journal. The key issue is whether or not cancer is affected by the healthy worker effect. If this is the case then mortality ratios, standardized on the basis of the general population as the referent, are difficult if not impossible to evaluate. In this case, we believe the evidence is firm. Calculations of relative risks of occupational hazards simply will have to be based on some sort of internal comparison. This is far from easy to accomplish especially as any estimate of a true relative risk based on internal comparisons underestimates this risk by considerable amounts because of unavoidable misclassification of workers into different exposure groups (I include a recent reprint discussing this problem).

I also include a copy of my curriculum vitae.

I hope our discussion is what you need.

Sincerely,

T. Sterling

Theodor D. Sterling
Professor

TDS/ac
encl.

THEODOR D STERLING AND ASSOCIATES LTD

CURRICULUM VITAE

Theodor D. Sterling

EDUCATION

B.A. (CUM LAUDE), 1949, M.A., 1952, University of Chicago; Ph.D., 1955, Tulane University.

PROFESSIONAL AFFILIATIONS

Present: Professor, The Faculty of Applied Science and School of Computing Science, Simon Fraser University.

Previous: Visiting Professor, Department of Statistics, Princeton University, (78). Chairman, Department of Computing Science, Simon Fraser University, (72-77). Professor in the Department of Applied Mathematics and Computer Science, Washington University, St. Louis, Missouri (66-72). Also Joint appointment as Professor in the Department of Sociology (66-68), and Visiting Professor in Computers and Humanities, Hebrew Union College, Cincinnati, Ohio (68-70). Professor Biostatistics and Director of the Computing Center, College of Medicine, University of Cincinnati, Ohio (58-66). Previously instructed in the Department of Statistics, Michigan State University and Department of Mathematics, University of Alabama.

PROFESSIONAL ACTIVITIES

ACM Committee on Scientific Freedom and Human Rights; President of the Computer Science Association of Canada (75-80); Chairman, Ombudsman Committee, Canadian Information Processing Society (73-80); Chairman, President of Biological Information Processing Organization (64-65); Chairman, CIPS Special Interest Groups, Humanization of Information Systems (73-80); Chairman, SIGCAS Committee of Information and Public Policy (72-); President of Missouri Chapter, American Association of Workers for the Blind (70-72); Member of the Panel for Biology, Management, and Social Sciences of the Mathematics Association of America (62-67); Chairman, Committee on Professional Activities of the Blind of the Association for Computing Machinery (63-71); Chairman, Ad Hoc Committee on Accreditation, Association for Computing Machinery (66-67); Committee on Radiation Dosimetry, American Association of Physicists in Medicine (66-69); National Lecturer for Association for Computing Machinery (72-3, 75-6).

EDITORIAL ACTIVITIES

Associate Editor - Canadian Journal of Statistics (73-78); Editorial Board - Canadian Occupation and Health Journal (84-86) and International Journal of Biomedical Computing (69-); Computers and Applied Mathematics (73-85), Humanist in Canada (73-83).

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GOVERNMENT AND OTHER SERVICES (Consultant/Advisor, Now and Previous)

In Canada: Treasury Board, Labour Canada, Canadian Standards Board; Department of National Revenue; Quebec Department of Consumer Affairs; Environment Canada, The Royal Commission (B.C.); Consumers Association of Canada; Society for Professional and Environmental Control. **In the U.S.:** NIH; PHS; EPA; FTC; FDA; NSI; OSHA; SRA; U.S. National Academy of Science/National Research Council; American Lung Association; Natural Resource Board (Wisconsin); Environmental Defense Fund, MECCA (Minnesota); Citizens Against Toxic Sprays (Oregon). **In Kuwait:** Ministry of Health. **In the Socialist Republic of Vietnam:** Ministry of Health.

PROFESSIONAL SOCIETIES:

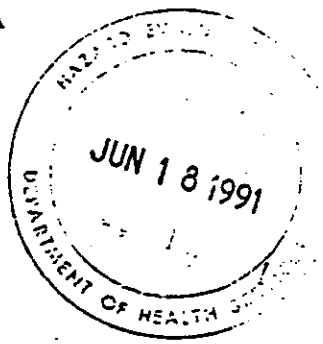
Can. Inf. Proc. Soc.; Can. Comp. Sci. Assoc.; Assoc. Comp. Machinery; Amer. Math. Assoc.; Math. Soc.; Inst. Math. Stat.; Amer. Stat. Assoc.; Biometric Soc.; N.Y. Acad. Sci.; Amer. Assoc. Phys. Med.; Int. Epidem. Assoc.; Soc. Epid. Res.; Amer. Assoc. Adv. Sci.; Amer. Coll. Epid.

HONORS AND AWARDS:

Fellow, Amer. Assoc. for Advancement of Science; Fellow, Amer. College of Epidemiology; Fellow, Amer. Stat. Assoc.; Fellow, Can. Com. of Scientists and Scholars; Sigma Xi; Pi Nu Epsilon, University Research Professor (1980-1981).

Published 8 books and approximately 300 scientific articles. Bibiliography available upon request.

BEFORE THE STATE OF CALIFORNIA
AIR RESOURCES BOARD



RESPONSE TO:
SUBMISSION BY THE FORMALDEHYDE INSTITUTE, INC.'S COMMENTS SUBMITTED BEFORE THE STATE OF CALIFORNIA AIR RESOURCES BOARD

("Comments Regarding Draft Document On Proposed Identification Of Formaldehyde As A Toxic Air Contaminant")

By Theodor D. Sterling and James J. Weinkam
Simon Fraser University, Burnaby, B.C., V5A 1S6

June 14, 1991

In A Preliminary Draft Document, the California Air Resource Board marshalls evidence for a "Proposed Identification of Formaldehyde as a Toxic Air Contaminant" (February, 1991). The Formaldehyde Institute, Inc. (a not-for-profit corporation whose membership consists of firms and trade associations representing all phases of a formaldehyde industry) submitted extensive comments and submissions by a number of scientists to that Air Resource Board Draft Document (Formaldehyde Institute, Inc., 1991). Comments regarding the Draft Document (on Proposed Identification of Formaldehyde as A Toxic Air Contaminant) disputed our findings concerning the association between formaldehyde exposure and lung cancer. The Formaldehyde Institute, Inc.'s submission also included special critical assessments of our work by a number of individuals including W.R. Gaffey; R.W. Morgan and O. Wong; M. Suh; G.M. Marsh, R.A. Stone, and D. Henderson; as well as by a reviewer who did not include his/her name (appended as Tab 14 in Formaldehyde Institute, Inc., 1991). These multitudinous comments are summarized by the Formaldehyde Institute's submission in eight "key points" on pages 38 and 39 of that document.

We respond here to these comments.

DOES THE HEALTHY WORKER EFFECT INCLUDE CANCER?

One basic issue on which conclusions about the carcinogenicity of formaldehyde appears to hinge, is whether or not the Healthy Worker Effect includes cancer.

That question is one of the key points of the Formaldehyde Institute's submission.

> *"Sterling's insistence on a healthy worker effect for cancer does not comport with the published literature".**

This key point not only summarizes one of the fundamental problems in the investigation of the carcinogenicity of formaldehyde as it emerges from the Blair et al reports (1986, 1989, 1990) but it is a fundamental issue with which all cohort studies of occupational carcinogens must deal. If the prevalence of cancer among employed individuals is indeed significantly and substantially less than it is among the general population, then it would not be valid to compare cancer mortality among employed persons with that of the general population - or, more precisely, use the general population as a standardizing referent for relative risk calculations. Rather, investigations of

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* The Formaldehyde Institute's use of "Sterling" is meant to imply "Sterling and Weinkam". It is never made clear why Dr. Weinkam's name is consistently deleted.

environmental or industrial carcinogens would have to base their conclusions on within cohort comparisons of workers who differ by exposure levels, or at least incorporate a correction for the Healthy Worker Effect.

The Healthy Worker Effect is generally recognized as an important source of bias or confounding. It arises because persons who are employed come from a class of individuals who are sufficiently healthy to obtain and hold employment. The general population however includes not only those who are employed but also those who are not. The later includes many who do not seek employment or have ceased working for reasons of health. Mortality is higher among the later than among the former so that the mortality of the total general population (or that residing in the larger region where an investigated occupational group lives) can be expected to be greater than that of a sample of employed individuals, that is, providing these employed individuals are not at some occupational risk.

The Healthy Worker Effect is easily recognized. It occurs when the Standardized Mortality Ratio (smr) computed with the general population as the referent is appreciably less than 1.0 (or, as it is sometimes given, less than 100). If persons who are employed come from a class of individuals who suffer less from cancer than those who are unemployed, then the Healthy Worker Effect will extend to the disease category of Cancer. Whether the Healthy Worker Effect does or does not include cancer can be easily determined by reviewing observed smrs for cancer in different studies.

We have done such a review and refer to our paper in *New Risks*. (Sterling and Weinkam, 1990). Table 2 of this report (reproduced here) lists the smr for All Causes and All Cancers reported by a number of studies between 1974 and 1985 that assess the effects of known or suspected carcinogens (dioxin and furans, metals, organic chemicals and solvents, polyaromatic and miscellaneous hydrocarbons, petrochemicals, PVC, radon, and rubber).* Smrs for <u>All Causes</u> were as low as 0.55 and were significantly lower than 1.0 in 32 out of 59 studies or in approximately 54% of them. Not a single one of the point estimates of smr for All Causes was as large as 1.0 and only 10 were .9 or greater. This clearly demonstrates that employed individuals have a lower mortality ratio from <u>All Causes</u> than does the general population.

More to the point for the issue under discussion here is that a similar Healthy Worker Effect is observed for the smrs for <u>All Cancers</u>. 17 of all smrs for cancer, or 29% of them, were

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* Our paper is also included as an Appendix.

Table 2. SMR's for ALL CAUSES and ALL CANCERS From a Sample From Occupation Health Studies of Working Populations Exposed to Known Carcinogens

Exposure	Reference	SMR for All Causes	SMR for All Cancers
DIOXINS & FURANS	Brown & Jones (1981)	0.89	0.89
	Ott *et al.* (1980a)	0.54*	0.28*
	Riihimaki (1982)	0.78*	0.71*
	Zack & Suskind (1980)	0.69*	1.00
METALS	Axelson *et al.* (1980)	0.99	0.90
	Cragle *et al.* (1984)	0.86*	0.94
		0.89*	1.10
	Elinder *et al.* (1985)	0.92	1.15
	Enterline & Marsh (1982)	0.84	1.03
		0.82*	1.03
	Godbold & Tompkins (1979)	0.75	0.94
	Hayes *et al.* (1979)	0.92	1.02
	Lemen *et al.* (1976)	0.93	1.54*
	Sheffet *et al.* (1982)	0.68*	0.85
	Wong *et al.* (1984)	0.88*	1.02
ORGANIC CHEMICALS & SOLVENTS	Alderson & Rattan (1980)	0.83	0.91
	Hoar & Pell (1981)	0.82*	0.69
		0.47*	0.50*
	Katz & Jowett (1981)	0.80	1.00
	Ott *et al.* (1980b)	0.71	0.76
		0.98	0.85
	Pasternack *et al.* (1977)	0.66*	1.23
	Polednak (1980)	0.86	0.94
	Wang & MacMahon (1979)	0.72	0.82
POLYAROMATIC & MISCELLANEOUS HYDORCARBONS	Jarvholm *et al.* (1981)	0.82*	0.65*
	Olin & Ahlbom (1982)	0.89*	1.32
	Olin (1978)	0.93	1.89*
		0.88	1.63*
	Paganini-Hill *et al.* (1980)	0.92	0.98
	Rockette & Arena (1983)	0.99	0.91*
	Werner & Carter (1981)	0.90	1.10
	Wong *et al.* (1985)	0.81*	0.93*
PETROCHEMICAL	Alderson & Rushton (1982)	0.84*	0.89*
	Austin & Schnatter (1983)	0.80*	0.87
	Decouflé (1978)	0.80*	1.05
	Divine *et al.* (1985)	0.75	0.75
	Hanis *et al.* (1982)	0.92*	0.92
	Rushton *et al.* (1983)	0.84*	0.95
	Rushton & Alderson (1980)	0.84*	0.89*
	Schottenfeld *et al.* (1981)	0.55*	0.72*
	Theriault *et al.* (1979)	0.78*	0.89
	Waxweiler *et al.* (1983)	0.80*	0.81*
	Wen *et al.* (1981)	0.88	0.96
	Wen *et al.* (1985)	0.78*	0.88
PVC	Fox & Collier (1977)	0.75	0.90
	Heldaas *et al.* (1984)	0.84*	1.14*
	Tabershaw & Gaffey (1974)	0.75*	1.10
RADON	Beral *et al.* (1985)	0.76	0.79*
	Checkoway *et al.* (1985)	0.73*	0.78*
	Gilbert & Marks (1979)	0.75	0.85
	Hadjimichael *et al.* (1983)	0.82*	0.85
	Smith & Doll (1981)	0.83*	0.82*
	Stayner *et al.* (1985)	0.85*	0.76
RUBBER	Delzell *et al.* (1981)	0.89	0.96
	Delzell & Monson (1981)	0.87	0.96
	Delzell & Monson (1982)	0.88	1.04
	Fox & Collier (1976)	0.98*	1.16*
	Monson & Nakano (1976)	0.65*	0.73*
	McMichael *et al.* (1974)	0.99	1.03

*Indicates statistical significant, as reported, with p equal to or less than 0.05 at least.

Reproduced from Sterling and Weinkam, 1990, pg. 590.

significantly less than 1.0 while only two of them, 3%, were significantly larger than 1.0. In fact, one of the smrs for All Cancers was as low as 0.28, indicating that in one study individuals working with dioxins and furans had 28% the cancer mortality of the general population.

These results coincide with our study of mortality among 250,000 U.S. veterans (Sterling and Weinkam, 1980) and also with those of others (see for instance Seltzer and Jablon, 1974).

Surely the large number of small smrs observed for All Cancers among workers exposed to demonstrated or suspected carcinogens is not due to the action of these carcinogens. They belong to a class of observations to which the name Healthy Worker Effect has been affixed. Very often this term is not used. Rather investigators refer to a "deficit" among the studied population. However whether we call it a deficit, a Healthy Worker Effect, or by any other name, it does indicate a major bias or confounding that applies to cancer just as it does to other diseases. This deficit or Healthy Worker Effect is real, obviously holds for cancer, and makes it very difficult to interpret the significance of estimates of relative risk based on mortality rates standardized on the general population.

Adjusting for the Healthy Worker Effect

The concern with Blair et al is that they standardized smrs to the general population. Yet they do observe a Healthy Worker Effect - in fact, they repeatedly refer to a "deficit" in mortality. We obtained and reanalyzed the Blair et al data, relying solely on internal comparison between high and low exposed subgroups of Blair et al's subjects. Our reanalysis was hampered by some misunderstandings about classification of workers in the data file we obtained from Dr. Blair as well as by some programming difficulties. However, our final analysis was presented in the *Journal of Occupational Medicine*, in 1989.

Table Three from our 1989 discussion reproduced below summarizes the outcome of the Categorical Analysis for simultaneously evaluating the effects of cumulative exposure (CX), length of exposure (LX), job type (JT) and age of mortality on cancers of the respiratory system. The headings for Tables 3 and 4 should read respiratory cancer, not lung cancer. It had been our intention to show the results for lung cancer in Table 3 but the result for all respiratory cancers were inadvertently published. However, the facts that errors were committed are regrettable but not as important as the final results of the corrected analysis that shows the association of formaldehyde exposure and the significantly elevated relative risk for respiratory cancers.

TABLE 2

Summary Of Categorical Analysis For Simultaneously Evaluating the Effects of Cumulative Exposure (CX), Length of Exposure (LX), Job Type (JT), and Age on Mortality from Lung Cancer (reproduced from Sterling and Weinkam, 1989, page 883.)

Factors	Estimate of Risk Ratio	90%CI	95%CI
CX,ppm			
<0.1	1.00		
0.1-0.5	1.21	0.89-1.64	0.84-1.74
0.5-2	1.19	0.83-1.70	0.78-1.83
2+	1.56	1.03-2.36	0.95-2.56
LX, yr			
<1	1.00		
1-5	0.77	0.55-1.06	0.52-1.13
5-10	0.68	0.44-1.06	0.41-1.15
10+	0.73	0.49-1.07	0.45-1.16
JT			
Salaried	1.00		
Hourly	1.61	1.19-2.17	1.12-2.31
Age, yr			
<40	1.00		
40-55	11.10	6.39-19.26	5.74-21.45
55+	67.44	39.51-115.13	35.59-127.79
Log likelihood			
df	79		
P	>.98		

When the relative risk of the lowest cumulative exposure group (receiving less than 0.1 ppm over their length of exposure) is taken as 1.00, an increasing relative risk ratio emerges which is significant for the highest level of exposure.

When cumulative exposure coefficients are considered individually, only the coefficient for high exposure approaches statistical significance. However, more important than individual confidence intervals is the analysis of trend for lung cancer risk with increasing level of exposure. To evaluate this trend, we applied the method of trend analysis of the coefficient of a log-linear model given by Rothman (1986, Chapter 16). Using scores of .3 ppm, 1.25 ppm, and 2.5 ppm for the three cumulative

exposure groups, the relative risk of a high cumulative group estimated from the fitted trend line is 1.53 with 95% confidence interval (1.02, 2.27) for all workers and 1.62 (.99, 2.65) for workers under 65 years of age. This indicates a significant trend of increasing lung cancer risk as a function of exposure. Trend analysis evaluates the pattern of change and so, according to Rothman estimates a single overall measure of a trend in effect rather than a set of separate effect estimates. (Rothman, 1986, page 336) A significantly elevated lung cancer risk for workers younger than 65 with high levels of cumulative exposure also merits special attention. It indicates a shift of lung cancer mortality towards younger ages among those occupationally exposed to formaldehyde.

HOW VALID IS THE FORMALDEHYDE INSTITUTE, INC.'S CRITICISM OF STERLING AND WEINKAM?

The Formaldehyde Institute, Inc. submitted a number of reviews of Sterling and Weinkam's work. Many of the statements and analyses made by these reviewers based on older versions of our manuscripts some of which had been circulated for review others had been submitted as discussion papers to Canadian and U.S. agencies. These many objections have been summarized by the Formaldehyde Institute, Inc.'s submission to the California Air Resource Board and we shall limit our discussion to those key points.

The most important of these key points, pertaining to the Healthy Worker Effect has already been discussed. We will now turn to the remaining key points of the Formaldehyde Institute's discussion.

> *"Sterling's reanalysis ignores the increased rate of lung cancer in the general population since World War II principally as a result of smoking. Sterling's failure to make this correction for time trends in respiratory cancer casts doubt on the validity of his observations of increased risk, given that lung cancer has doubled in the U.S. over the past 40 years. NCI took into account changes in lung cancer study analysis.*

Blair et al (1986) computed smrs using the general population as the referent. Since the follow up period spanned many years it was necessary to take the changing general lung cancer death rate into account.

The Sterling and Weinkam reanalysis computed relative risk of more exposed to less exposed workers. Within the study plants person years at risk were accumulated at all levels over the

entire follow up period. Since duration of exposure was also taken into account it is unlikely that calendar time would have any effect on the outcome.

> *"Sterling does not adequately support his two methods of analysis -- a categorical log-linear analysis and a Mantel-Haenzel analysis. The categorical log-linear model does not adequately fit the data, and there is no comment on whether the Mantel-Haenzel model fits the data. It appears that Sterling did not control for sex or race in the Mantel-Haenzel analysis. In both cases, Sterling failed to perform a trend test to show whether there was a significant trend."*

The log-linear model described in our final 1989 discussion and reproduced here fits the data very well. Log likelihood X^2 for goodness of fit = 53.56 for 79 d.f. ($p > .98$).

Separate analysis for white males gives similar results. Rothman's test for tread in the coefficients of the log-linear model shows a significant trend.

> *"Sterling's analysis inexplicably concludes that the shorter the duration of exposure, the greater the likelihood of cancer risk. This suggests that the observed cancers likely are due to a cause other than formaldehyde."*

This is not inexplicable at all. Our findings are:

1) Among those with the same cumulative lifetime exposure, the longer the time period over which that exposure was accumulated, the lower the relative risk. This makes sense because the average level of exposure would be lower for those who accumulate a given amount of exposure over a long period of time than for those who accumulated the same amount of exposure over a shorter time period.

2) Among those who accumulated their total exposure to formaldehyde over the same amount of time, the higher the cumulative exposure, the higher the relative risk. Again this makes sense, because those with higher cumulative exposure must have a higher average level of exposure.

> *"Sterling arbitrarily selected his exposure categories to maximize support for his theories."*

This is not true. The exposure categories in our final 1989 analysis are identical to those used by Blair et al for intensity of exposure and similar to those used for cumulative exposure and were chosen for that reason. We used 2.0 ppm rather than 5.5 ppm

as does Blair and Steward (1990) as the lower limit of the highest category of accumulated dose because when length of exposure was also considered, there were very few person years of observation with high cumulative exposure and short length of exposure.

> *"Sterling mischaracterizes the results of essentially negative epidemiology studies as providing evidence of carcinogenicity, and he improperly tries to explain away negative studies."*

We are not aware of having mischaracterized negative studies or improperly tried to explain away negative results nor does the Formaldehyde Institute furnish examples.

> *"Sterling's classification of hourly and salaried employees is simplistic, incomplete and selective."*

In our published analysis, we used the hourly vs. salaried designation as recorded on the data tape provided by Blair et al (1986). The flaw is then of Blair et al?

> *"Sterling uses confusing terminology and does not adequately explain the methods used or the raw data, which appears to differ significantly from the NCI data."*

No example of confusing terminology or inadequate explanations are given. We are not aware nor does the Formaldehyde Institute's Draft specify where the data we used differs in any way from the NCI data of the Blair et al study. Insofar as we used a taped copy of the Blair et al data, that last key point makes very little sense.

GENERAL COMMENTS

Although our published paper and our subsequent correction of an error in counting deaths (Sterling, 1989) is cited by the Formaldehyde Institute, Inc.'s submission in footnote 41, much of the discussion seems to relate to earlier, unpublished drafts. The numerous submissions about our work (in Tab 14) refer to preliminary analyses which were circulated for comments and critical evaluation. The analyses published were extensively revised. The Formaldehyde Institute's response claims that our report "*has led to further evaluation of the NCI data*". We seriously doubt that our report influenced Dr. Blair to do anything but his usual thorough analysis.

In his latest and extensive additional analysis published in 1990, Dr Blair examines virtually every conceivable measure of exposure in search of a dose response trend. However, in

considering cumulative exposure and length of exposure simultaneously (1990, Table VI, p. 691) he uses only 2 levels of duration (< 1 year and ≥ year) and a high lower limit (5.5 ppm - years) for the highest cumulative exposure category. As a result, there are no data for high exposure and short duration and there were an inadequate number of points to measure an association. When this shortcoming is corrected, elevated smrs for lung cancer reaches borderline significance for all ages and are statistically significant for ages younger than 65.

On the other hand, we used four levels of duration, and our highest cumulative exposure category includes 2.0 ppm - years and up (1989, Tables 3 and 4, p. 883). As a consequence, our management of the data ensures an adequate number of observations for all combinations of exposure and duration. Also we have already pointed out, trend analysis of the coefficients for cumulative exposure show a significant dose response trend. The differences between our results and Blair et al's might well be due to our inclusion of all respiratory cancers and to inappropriate grouping of data by Blair et al.

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Department of Labour, Occupational Safety and Health Administration, 29 CFR Parts 1910 and 1926: Occupational Exposure to Formaldehyde; Final Rule, Federal Register, Friday, December 4, 1987, 52:46189-46190.

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II.

ARB Staff Summary of Responses and Comments on the Preliminary Draft Part A

A) Chevron Environmental Health Center, Inc., March 26, 1991

1. **Comment:** The Air Resources Board (ARB) should consider extending the comment period on future drafts of this document.

Response: The ARB toxic air contaminant identification SRP process for formaldehyde began with the Request for Information from the public on November 10, 1987 and a formal request to DHS to review the health effects on March 24, 1988. There will have been two public comment periods: a 45 day preliminary draft report comment period (February 20 through March 27) and a 30 day draft report (SRP version) comment period (September 13 through October 15) prior to the October 22, 1991 SRP meeting. There was also a public workshop held during the preliminary draft comment period (April 3) to solicit comments. Should the SRP approve the report, there will also be a 45 day comment period on the final draft report before it is considered by the Board. We feel that this process, comment periods, and the workshop allow the public sufficient time to review and comment on the reports.

B) Hardwood Plywood Manufacturers Association (HPMA) and National Particleboard Association (NPA), March 26, 1991

1. **Comment:** HPMA and NPA comment that the Executive Summary in-home exposure time segment (62% or 14.9 hours) is overstated relative to the out-of-home exposure time segment (38% or 9.1 hours) of the 24 hour day.

Response: The table in the Executive Summary "Excess Potential Cancer Cases For California Exposure" has been changed to reflect a more realistic average daily exposure to formaldehyde indoors and outdoors. The out-of-home exposure estimate is no longer based solely on outdoor concentration data but has been split into an "Indoors - Away From Home" segment and an "Outdoors" segment. We have used recent data concerning Californians' activity patterns to apportion time spent in the different exposure locations. The new "Indoors - Away From Home" segment uses the best available indoor concentration data obtained from offices and public buildings in western states.

2. **Comment:** The out-of-home average statewide formaldehyde exposure of 4.4 ppbv, weighted by population, is significantly lower than other reported values made by other investigators for urban areas (i.e. CARB Part A, Table IV-3). Several studies show that formaldehyde concentrations found in urban areas are significantly higher than the statewide ambient average concentrations of formaldehyde. It is not likely that the large difference (by a factor of 2 to 12) can be explained only by differences in sampling times, and the time of day that the samples are taken.

Response: Our ambient data are used to determine statewide annual averages and overall exposure. These 24 hour average, composite data taken over an entire year predict a more accurate annual average exposure than short-term studies. However, short-term studies mentioned in the report will show maximum exposure levels at different periods of the day and "hot spot" exposures. These short-term studies mentioned in the report (pg. A-35) tested concentrations in the South Coast Air Basin (SoCAB) during daytime hours and showed that higher than ambient air concentrations are a result of possible early morning emissions from motor vehicles and/or afternoon photochemical reactions involving formaldehyde.

3. **Comment:** The in-home exposure assessment (as compared to the outdoor ambient data) relies on older data. There has been emphasis on reducing building product formaldehyde emissions from CPSC, EPA and HUD and also recent voluntary product standards that were not accounted for in the report. Since ARB uses older data before those standards for pressed wood products were implemented, then it is likely that there also has been significant reductions for in-home formaldehyde exposures.

Response: Formaldehyde emissions from pressed-wood products declined several years before the 1984 HUD emission limits were imposed due to advances in manufacturing techniques and competition within the industry. There is evidence that emissions declined markedly as early as 1982, including information presented by the Formaldehyde Institute during the April 3, 1991 workshop which showed steep reductions in particleboard emissions beginning in 1982. The exposure estimates were based on the best and most recent indoor concentration data available. Thoses data were obtained from studies conducted between 1983 and 1986 (Table IV-7, page A-50 and Table IV-8, pages A-53 and A-54) and thus reasonably reflect some of the large emission reductions that have occurred since the 1979-1981 period. Also, those data include older homes which presumably would have off-gassed most of the formaldehyde from their original building materials.

4. **Comment:** In respect to old data, the publication by CARB of the 1983 table from Pickrell (Page A-44; Table IV-5) is misleading, vastly out-of-date, and irrelevant in respect to current pressed wood products. Pressed wood product emission standards established by the U.S. Department of Housing and Urban Development (HUD) represent products with much lower emission rates than were available in the early 1980's as shown in CARB Table IV-5. Formaldehyde emission rates have also decreased for other listed products such as textiles and paper products, and UFFI has no relevance for new manufactured or conventional home construction.

Response: We concur that the sum of the emission rates listed in Table IV-5 may be somewhat higher than current rates; however, that table was intended to show relative emissions from different products. The utility of the information in the table is that the measurements for the

different products were made under similar conditions. Those numbers were not used in the calculation of our exposure estimates. We are unaware of any evidence that shows that relative emissions of the different products have changed significantly. We have noted on page A-45 in the document that UFFI is not used in new homes; however, many homes still have UFFI in them. Also, we have deleted "Typical" from the title of Table IV-5 and have added footnotes to the table to reflect this comment.

5. **Comment:** The sample size (64 homes) in the SAI report is inadequate to use in the exposure assessment and the data from that study show some unusual results.

Response: The ARB did not rely solely upon the SAI study as the basis for the exposure estimate (see pg. A-48). We also looked at data gathered from a number of studies of conventional homes conducted in California and in other areas of the United States (Table IV-8). Although California data were emphasized, data from other parts of the country, even from more recent studies with larger sample sizes, were generally comparable with the California data. There is no evidence that the SAI results are unusual. Also see response to comment no. 3 regarding the use of older data.

6. **Comment:** The exposures for the in-home segment have been overstated and for the out-of-home segment have been understated.

Response: See the response to comment no. 1.

7. **Comment:** Assuming that outdoor formaldehyde exposures can be used as an adequate surrogate for out-of-home exposures there is sufficient data which indicates that the 9.1 hours (38% of the time) that people spend out of the home would roughly coincide with the highest outdoor formaldehyde levels because of daylight hours (photochemical oxidation) and motor vehicles. Formaldehyde concentrations would also reach peak levels during daylight hours due to higher temperatures. Since these diurnal variations were not accounted for, formaldehyde exposures have been overstated for in-home exposures and understated for outside the home exposures.

Response: We did not use peak concentrations to calculate our risk estimates; instead we used a population-weighted annual average outdoor exposure and average indoor exposures. There are no representative measurements of diurnal variations of formaldehyde concnentrations inside California homes, and thus there is no evidence that peak indoor concentrations occur during daylight hours. Indoor formaldehyde concentrations are influenced not only by temperature, but also by other factors including ventilation and humidity. For example, in the large California mobile home survey (see page A-49), formaldehyde levels inside homes in Northern California were lower in the summer than in winter, possibly due to more opening of windows in the summer and/or decreased humidity (see ARB Technical Report ARB/RD-90-01).

8. **Comment:** The studies used by CARB (Sexton et al. and Rogozen et al.) contain little or no information on UF-bonded building materials although CARB states in several parts of the report that building materials made with urea-formaldehyde resins are the largest source of formaldehyde indoors.

Response: The studies we used to estimate indoor exposure were not used directly to draw conclusions regarding the sources of indoor formaldehyde; they were used to estimate average indoor concentrations. However, indoor concentration data from a variety of studies viewed in combination with source emissions data strongly implicate pressed wood products as the major contributors to indoor formaldehyde concentrations. For example, laboratory studies on pressed wood products have shown that increasing the load factor (the ratio of a source's surface area to the indoor air volume) will increase the formaldehyde concentration. In parallel, mobile homes contain a large amount of highly-emitting pressed wood products in a small air space and also tend to have high indoor formaldehyde concentrations. As another example, laboratory studies have shown that new pressed wood products tend to emit more formaldehyde than do older sources. In parallel, new homes (with new building materials) tend to have high indoor formaldehyde concentrations. Also, in-home measurements have generally ruled out the relative importance of some other potential formaldehyde sources. Several studies have found that cigarette smoke and combustion appliances do not appear to affect the average indoor concentration significantly. (See ARB Technical Report ARB/RD-90-01.)

9. **Comment:** The primary basis for making statements regarding the contribution of pressed wood products appears to be the 1983 Pickrell paper, which is outdated. Newer products have less emissions and have likely become less important than other indoor formaldehyde sources.

Response: The statements regarding the relative importance of pressed wood products were not based solely on one paper, but on an overview of indoor concentration and source emissions data. See the response to the previous comment and to comment no. 4.

10. **Comment:** The emission rates listed in Pickrell are essentially initial emissions and do not account for "emission decay" from UF-bonded wood panels. As a result UF-bonded wood products probably contribute little to formaldehyde levels in homes built before March 1980.

Response: It is important to stress that the emission rates listed in Table IV-5 were not used in calculating our exposure estimates. Our exposure estimates were based on indoor concentration data obtained from samples of homes of all ages, including older homes. We agree that the formaldehyde emissions decrease as products age and that the original building materials would generally contribute less to indoor formaldehyde levels in older homes. However, there is also a need to recognize that pressed wood products can still be the major source of elevated

formaldehyde levels in older homes when new materials are brought into the home as a consequence of remodeling or purchasing new furnishings. While we mention that the age of a source is a factor that influences formaldehyde concentrations in indoor air (page A-47), we have added a footnote to Table IV-5 that addresses the comment.

C) General Motors, March 27, 1991

1. **Comment:** The discussion of the direct emission of formaldehyde and the formation of formaldehyde from photochemical oxidation of hydrocarbons in the Executive Summary includes estimates in "tons per year" but the estimates are not referenced to a given year.

Response: The direct emissions of formaldehyde are based on the 1987 Emission Data System (EDS) estimates. This data has been added to the Executive Summary.

2. **Comment:** The CARB regulatory program for hydrocarbons has been reducing the emissions of both direct formaldehyde emissions and formaldehyde precursors for many years. The Executive Summary should address this.

Response: According to the ARB motor vehicle inventory, there has been a slight reduction in organic emissions from on-road vehicles, a slight increase in emissions from off-road vehicles with an overall decrease in emissions since 1987. This statement is included in the revised version of Part A (see pg. A-15).

3. **Comment:** ARB should use data from the Auto/Oil Air Quality Improvement Research Program to estimate future TOG and formaldehyde emissions from motor vehicles.

Response: The Auto/Oil data evaluated by ARB was used to create models for the effect of varying the properties of gasoline upon toxic emissions in exhaust. The models will only predict relative changes in emissions due to these variables in fuel content, thus, estimating future emissions may not be correct if one of these variables are changed or another fuel source is used.

4. **Comment:** The Executive Summary table "Excess Potential Cancer Cases For California Exposure" overstates the risk from outdoor exposure to formaldehyde, and should be revised to include additional categories of office and public buildings and rural area exposures.

Response: That table has been changed to reflect a more realistic average daily exposure to formaldehyde, which includes exposure inside offices and public buildings. See the response to the Hardwood Plywood Manufacturers Association and the National Particleboard Association comment no. 1.

5. **Comment:** The sources of personal exposures and risk are much more important than outdoor exposures to formaldehyde emissions from mobile sources.

Response: The preliminary draft provides a detailed discussion of both indoor and outdoor exposures. It appears that the majority of direct outdoor emissions still come from mobile sources. In addition, results from the 1987 SCAQS regarding the diurnal patterns of ambient formaldehyde concentrations in relation to other primary and secondary pollutants indicate that direct emissions from motor vehicles are the major source of ambient formaldehyde in urban areas during early morning hours. For a more detailed explanation refer to pg. 33 of the Part A document.

6. **Comment:** GM is concerned that risk from smoking in offices and public buildings may be a much more important source of exposure than the outdoor environment.

Response: The effect of smoking on formaldehyde concentrations inside offices and public buildings is very uncertain due to the lack of available information. We do not believe that smoking would be of primary importance in those environments though, because the average formaldehyde concentration in homes does not appear to be elevated significantly by the presence of smokers (see pg. A-47 of the report).

7. **Comment:** Lofroth et al. (1989) measured formaldehyde in environmental tobacco smoke (ETS) in experimental chambers and the air in a tavern at levels as high as 104 ug/m^3. Since people spend a significant fraction of their "out-of-home" time in taverns, this exposure and risk should not be ignored.

Response: It is not known whether ETS contributed significantly to the formaldehyde concentrations measured by Lofroth et al. inside the tavern, since no control measurements were made without smokers present. With respect to estimating exposures inside offices and public buildings, the revised assessment uses the best available indoor concentration data obtained from studies of those buildings conducted in western states. Those data are more representative of concentrations in offices and public buildings than the two individual measurements performed by Lofroth et al. in one tavern.

8. **Comment:** The population in urban areas should be used in assessing the risk in the urban environment and exposure to formaldehyde should be estimated for the rural population.

Response: The ARB air toxics ambient network represents a population of 20 million, most of which are in urban areas.

9. **Comment:** Time spent outdoors should take into account new data on human activity and behavioral patterns (Ott, 1988).

Response: Our exposure assessment uses data regarding the activity patterns of Californians obtained from an ARB-funded study conducted statewide in 1987 and 1988 (ARB contract no. A6-177-33). These are the best and most recent data available, and are representative of the activity patterns of Californians.

D) Timber Association of California, April 4, 1991

1. **Comment:** Both in the staff report and during the workshop, it was suggested that there are expected to be "hot spots" near "wood processing facilities". The term "wood processing facilities" gives the impression that all facilities handling wood, such as sawmills, remanufacturing mills etc. are potential "hot spot" sources. We believe that what is meant are facilities producing reconstituted wood products. We request that this be clarified in the report and that appropriate terminology be adopted.

Response: The term "wood processing plants" has been changed to read "facilities producing reconstituted wood products" in the Executive Summary and draft report.

2. **Comment:** The ARB air toxics monitoring network is oriented to urban exposure. Consequently, none of these monitoring sites are near reconstituted wood products facilities. Thus, the statements about potential wood products "hot spots" are entirely conjectural and have no supporting basis.

Response: We agree the ARB's toxic monitoring network does not indicate "hot spots." The discussion provided in the report is based on emission estimates from these types of sources. We plan to prioritize and estimate "hot spot" exposures in the control phase when formaldehyde is identified as a toxic air contaminant.

3. **Comment:** The 1987 SARA Title III data used in the report is clearly erroneous. We believe the two wood processing facilities in question have emissions to be some 10 times lower, from 111 TPY to 12 TPY. We are currently collecting information on formaldehyde emissions from reconstituted wood products facilities and will provide this information to ARB staff for incorporation into the report.

Response: As soon as this information is provided and quality checked, we will make the appropriate corrections. For now, we have adjusted and used updated 1989 SARA Title III numbers for estimates from these facilities (see pg. A-8).

E) Formaldehyde Institute, March 26, 1991

1. **Comment:** The preliminary draft document uses out-of-date residential exposure data from the early 1980's. Since then, voluntary efforts by manufacturers and standards sent by the Department of Housing and Urban Development (HUD, 1985) have reduced formaldehyde emissions from various products including urea-formaldehyde (UF) bonded products, textiles and fabrics.

Response: See response to HPLA & NPA comments 3 and 4.

2. **Comment:** In-home exposures are overstated relative to outdoor exposures. The preliminary draft document relies on relatively new atmospheric data (1988-1989), while the indoor exposure estimates are based on early 1980's data. Both atmospheric (outdoor) formaldehyde levels and in-home levels have likely declined since the early 1980's. Moreover, outdoor levels are high when most people are out of the home during daylight hours. Neither the Sexton, et al. study nor the Rogozen, et al. study relied on in the preliminary draft document describes homes with products with low formaldehyde-emitting characteristics.

Response: See response to HPLA & NPA comments 3, 7, and 9; also General Motors comment #4.

3. **Comment:** Formaldehyde emissions from wood products in the home decay significantly over time. Recent data indicates that initial emission level from particleboard decreases by half in one year or less (Zinn et al.). After one year, wood product emissions further decrease, but at a more moderate rate. Thus, UF-bonded pressed wood building materials make little or no contribution to formaldehyde levels in the older California housing stock (10 years or older).

Response: See response to HPLA & NPA comment 11.

F) Peter Barrett Consultants, March 28, 1991

1. **Comment:** Dr. Barrett comments based on the results of the Essex Survey of background concentrations of formaldehyde, standards should not be any tighter than his proposed levels.

Response: The identification of formaldehyde as a toxic air contaminant will not result in the establishment of health protective standards. These standards are not the responsibility of the ARB and are the result of other regulatory agency actions.

III.

DHS Staff Summary of Responses and Comments on the Preliminary Draft Part B

Response to Comments: CHEVRON

The following characterizations of the health-oriented comments quote only the headings of the actual text.

1. Comment: "ARB should ask DHS to update their cancer risk assesement to compare the most recent EPA analysis (1990) with their own."

Response: OEHHA staff discussed the U.S. EPA analysis with U.S. EPA staff. The U.S. EPA documents have been considered by OEHHA staff in preparation of the health assessment document. The DHS Draft Document did not discuss the U.S. EPA analysis because that document is clearly labeled as "an external review draft for review purposes only" The OEHHA staff's present responses to comments of the Fomaldehyde Institute and their consultants, Drs. J. Swenberg and T. Starr, discuss the differences. In brief, the revised version of the document now contains a dosimetrically adjusted contact scaling factor using the monkey data as well as the original purely allometric (generic) contact scaling factor. The case for the dosimetrically adjusted scaling factor is weakened by lack of knowledge of how the monkey's breathing may be partioned between nose and mouth and by how efficiently humans may bind fomaldehyde, compared to monkeys. The case for the allometric model is weakened by the apparent discrepancy that occurs in predicting the monkey tissue data from the rat data. So neither is used as a best estimate, but both help define the range of unit risks.

2. Comment: "ARB should have DHS update their analysis of the relationship between predicted and observed human cancer rates (pages 2-19 to 2-22)."

Response: The meta-analysis of Blair et al. (1990), while a useful review, has essentially no more useful quantitative information than does the Draft Document. The Draft Document compared human predictions based on animal studies to the data of the most appropriate human study in order to help evaluate the usefulness of the predictions based on the animal data. The consistency that the analysis found is agreement of their data with the upper portion of the range of predictions in the revised version of the document. Studies that observed less cancer are more consistent with the revised best estimate, which is well below the revised top of the range.

3. Comment: "The review of Toxicity and Carcinogenicity of Formaldehyde (page 2-2 through 2-5) should be revised to reflect the weak epidemiology link between formaldehyde exposure and human cancer."

Response: The Draft Document characterizes the weakness of the evidence in agreeing with the US Environmental Protection Agency and the International Agency for Research on Cancer, that the evidence is "limited," as stated on page 2-5 of the draft document. The meta-analysis of Blair et al. (1990) would actually imply that the evidence is close to sufficient to establish human carcinogenicity by concluding for one cancer "that it is is likely that the excesses of nasopharyngeal cancer observed were caused by exposure to formaldehyde."

4. Comment: "ARB should ask DHS to reconsider their decision that no threshold exists for the carcinogenic risk of airborne formaldehyde."

Response: At page 2-22 the Draft Document concludes a discussion of this issue with the statement "that there is a strong basis to assume that formaldehyde does not have a carcinogenic threshold." This statement does not imply any decision that "no threshold exists". On the contrary the context is that of proceeding in the face of considerable uncertainty to make best estimates of risk within a background of the California guidelines (DHS, 1985), which do "not include the concept of 'thresholds' unless clear and convincing evidence is presented to demonstrate their existence for a specified carcinogen in specified circumstances." The quantitative risk calculations estimate the excess risk, which is the risk above background effects such as those due to endogenous levels of fomaldehyde, referred to by the commenter and mentioned at page 2-2 of the Draft Document. The range of extrapolation from the animal data to human levels indoors is less than 100-fold. Furthermore, the consideration of the dosimetric adjustment and cell proliferation indicate that those factors do not argue for a threshold of carcinogenicity within the range of extrapolation.

RESPONSE TO COMMENTS: GENERAL MOTORS

Part B: Health Assessment of Formaldehyde

1. Comment: "In general, GM scientists agree with the document's conclusion that there is sufficient evidence that high concentrations of formaldehyde produce tumors in experimental animals. There is, however, a considerable uncertainty whether or not the documentation is sufficient to show that formaldehyde "should not be considered to have a carcinogenic threshold. (Summary, page 1-5)."

   Response: As discussed in the Draft Document at page 2-22, there is evidence of genotoxicity in several tests and of DNA-protein crosslinks at 0.3 ppm, suggesting that formaldehyde does not have a carcinogenic threshold in the observable range. There is uncertainty due to the abrupt rise in risk with dose in the animal bioassay. However, the extrapolation from experimental doses to human levels indoors is only 80-fold. Thus, the level producing tumors in animals is much closer to human exposure levels than for many other chemicals.

2. Comment: "If the DHS Staff accepts the molecular dosimetry data as an index of a more accurate dose.....providing a more accurate risk assessment, it should also pragmatically recognize the possibility of a discrete threshold for the tumor producing action of formaldehyde exposures. Or at least, the high level of uncertainty in our understanding of the tumorigenic response and in the extrapolation of high doses to low ambient concentrations should be explicitly discussed in the document."
   "General Motors believes strongly, that by referring to the Casanova-Heck studies and accepting the molecular dosimetry approach, DHS staff should no longer insist on 'having not found evidence of a carcinogenic threshold of formaldehyde' (page 1-3). Because of the presence of defense systems and the non-linear response, the DHS assumption of DNA-crosslinking mechanisms as an index of the tissue dose requires that the statement in the Summary be changed and the 'provisional' risk extrapolation models modified so that the possibility of a no-effect level is recognized."

   Response: Both these quotes assert, without explaining why, that the acceptance of molecular dosimetry somehow implies the plausibility of a threshold or no-effect level. On the contrary the use of the molecular dosimetry data is consistent with no threshold, as pointed out on page 1-3 of the Draft Document. With the additional use of the proliferation model in the revised version the exposure response curve becomes nearly linear at concentrations below 5 ppm. Nevertheless, the revised version has qualified the determination on that page to state that the evidence against a threshold outweighs the evidence for it. The discussion of the threshold issue at page 2-22 in the Draft Document contains an indication of uncertainty. The revised version contains a discussion of results of using cell

proliferation models, providing a further demonstration of uncertainty.

3. Comment: "In addition, General Motors feels that the risk assessment should include discussion on the alternative possibility that the tumors may be product of epigenetic mechanisms (such as an increased cell proliferation)..."

Response: The revised version of the document presents cell proliferation models that include epigenetic mechanisms. As indicated in the revised version, the risk estimates increase somewhat when cell proliferation effect are explicitly incorporated in the model.

Response to Comments: FORMALDEHYDE INSTITUTE

These comments are characterized by quoting the Executive Summary and the most relevant specific comments in the text. Numbering of comments corresponds to the order in the Executive Summary.

(1) Summary Comment: "Although the Draft Document has the worthy goal of seeking to update EPA's 1987 risk assessment, it does not properly incorporate all of the relevant mechanistic information regarding formaldehyde. EPA recently has issued a revision to its risk assessment yielding a prediction of risk much lower -- by a factor of 10 to 100 -- than that provided in the Draft Document. Further, cell proliferation data are available; incorporation of that data would further reduce the prediction of risk by over one order of magnitude. The Draft Document should be revised to reflect EPA's updated analysis and the other available data." p. 2

Comment 1a "The Draft Document relies extensively on the 1987 formaldehyde risk assessment document prepared by the U.S. Environmental Protection Agency. However, the Draft Document fails to recognize that, in September 1990, USEPA issued a draft revision to its risk assessment document that properly incorporated the mechanistic data for formaldehyde -- DNA cross-linking data in the rat and monkey -- that had become available during the intervening three years. The difference between the Draft Document's approach and USEPA's approach is stark. When both the mechanistic data and the scaling factor are taken into account, USEPA's 1990 unit estimate of incremental risk is 10 to 100 times less than that presented in the Draft Document." p. 5

Response: The Office of Environmental Health Hazard Assessment (OEHHA) has revised the Draft Document of January 1990 to take into account explicitly the available information concerning both these two issues, the use of the monkey cross-linking data in addition to those of the rat and the use of cell proliferation data. Both of these procedures are considered in the revised range of risks. The response to T. Starr's Comment 1 outlines the effect of the new analysis on the estimates of risk. Not only is the best estimate reduced 4-fold, but bottom of the range is reduced over 20-fold. In regard to USEPA, the September 1990 document is clearly labeled with the disclaimer, "external review draft for review purposes only and does not constitute policy." The document of June, 1991, is identically labelled. Neither document has been approved by appropriate peer review, the Science Advisory Board, and that board has seriously questioned the use of the monkey tissue data at a recent meeting. Thus the OEHHA staff has minimized citation of both those documents in the formal document, which has the objective of putting forward the reliable scientific information.

Comment 1b "As the Draft Document notes, there is strong evidence that the cancer observed in rats at high doses is related to the 'cytotoxic' effects of those high doses, thus indicating that cancer will not occur at low doses. CIIT research showed that a 10 to 20-fold increase in cell replication occurs when rats are exposed to 6 or 15 ppm." p. 7

Response: A greater rate of cell proliferation due to cytotoxicity at the higher exposures does not in any way imply that carcinogenesis will not

occur at significant rates at lower exposures. The long-term CIIT experiments showed that cell proliferation was near background but cancer incidence was above background at 6 ppm.

Comment 1c "In addition, at doses that do not increase cell proliferation, biological protective mechanisms (e.g., cell repair, detoxification, mucus secretion and mucus reactions with formaldehyde, and immunologic, tumor-associated rejection mechanisms) prevent or mitigate carcinogenic effects of formaldehyde....However, the Draft Document does not adequately account for all of the recent mechanistic data." p. 7-8

Response: The revised version of the document has incorporated both the commenter's specific suggestions about the need to incorporate additional mechanistic data. No further incorporations appear appropriate at this time.

Comment 1d "As EPA stated, the predicted risk level using the rat DNA cross-linking data is believed to overestimate true risk for three reasons...(1).data showing lower DNA cross-linking in monkeys are more significant to the likely effect in humans...(2) airborne concentration is a more important exposure parameter than total dose ...(3) recent data also show the importance of cytotoxicity and cell proliferation in carcinogenesis.", p. 17-18

Response: The revised version reflects specific analyses conducted for points (1) and (3). Thus, the information has been incorporated into the range of risks. The risk that is due to administered concentration, beyond administered dose, is incorporated in part by the use of cross-link data in the rat, as used in the Draft Document and in part by use of proliferation data in the revised version.

Comment 1e Although EPA deferred consideration of cell proliferation data pending further work, "further data is (sic) now available, and incorporation of that (sic) data would further reduce the prediction of risk by over an order of magnitude." p. 18

Reponse: The revised version shows that the most likely estimate of the effect of using the proliferation model is to raise the multistage result by 40%.

(2) Summary Comment: "The risk assessment uses an interspecies scaling factor which significantly overestimates the true risk of formaldehyde exposure." p. 2-3

Comment 2a "There is no basis for the Draft Document's use of a theoretical scaling factor adopting the position that humans are more susceptible to formaldehdye than the rat. In the case of formaldehyde, extensive available data show that humans are less susceptible to the effects of formaldehdye. These data include the fact that humans, unlike the rat, are not obligatory nose breathers and the recent data showing that monkeys had lower levels of DNA cross-linking than did rats." p. 19

Response: The revised version no longer adopts as a best estimate the generically derived contact scaling factor, which would appear to make

humans more sensitive than rats. Nor does it adopt a dosimetrically adjusted contact scaling factor, based on the monkey data, which would appear to make the human appear less sensitive than the rat. However, both of these scaling factors help define a range of upper confidence limits on unit risk. The revised version adopts as a best estimate the default (body-area) scaling because of the lack of a clear case for either the generic contact scaling factor or the dosimetrically adjusted factor.

(3) Summary Comment: "The Draft Document does not provide a balanced discussion of the formaldehyde epidemiology data. In particular, the epidemiology data regarding lung cancer do not show excess risk attributable to formaldehyde." p. 3

Comment 3a "The Draft Document's discussion of the human cancer data is one-sided and does not provide an overview of the extensive epidemiology data base. The Draft Document -- implying that many sites are in excess (ignoring that sporadic excess may be due to chance and other factors), asserting that formaldehyde may cause cancer at remote sites, and contending that very low formaldehyde levels elevate cancer risk -- differs from the positions taken by consensus panels and from a review of the epidemiology data taken as a whole. In the discussion of lung and pharyngeal cancer, the Draft Document cites Blair, Vaughan and Acheson without giving full weight to the published conclusions of each of these well-credentialed investigators."

Reponse: Appendix C contains an extensive review of the epidemiology data. Evidence of carcinogenicity from a review of all those is limited, as made clear in the Draft Document at page 1-2. IARC has also concluded that the evidence for carcinogenicity in humans is limited. Panels have found evidence for carcinogenicity in human studies alone to be equivocal, and investigators such as those cited by the commenter have been extremely cautious in attributing carcinogenicity to formaldehyde as a result of their own studies. A recent review of the epidemiological evidence by Blair et al. (1990) begins the concluding paragraph, "In summary, we conclude that it is likely that the excesses of nasopharyngeal cancer observed were caused by exposure to formaldehyde."

Comment 3b "The Draft Document improperly attempts to compare the results of animal-based risk assessment to claimed excesses of lung cancer in the epidemiology studies. In fact, there is not overall excess of lung cancer in the epidemiologic studies that can properly be attributed to formaldehyde. p. 36

Response: The document seeks to provide a modest check on predictions of the animal based model, and the epidemiology data provides the opportunity for respiratory-tract cancers. See also responses to Comment 5 of T. Starr and Comment 7b of J. Swenberg.

Comment 3c "The Draft Document improperly references the now-discredited Sterling and Weinkham analysis."

Response: Drs. Sterling and Weinkham have prepared a written rebuttal to this comment and the staff have reviewed their submittal. Sterling and Weinkham's (1989b) most relevant finding for this risk assessment is that,

when appropriately accounted, there is a dose-response trend for overall respiratory tract cancers in the Blair et al. (1986) data. None of the critiques offered on Sterling and Weinkhams's work confronts this finding directly. In view of the controversy and the importance of the issue, the staff believes that this finding of an upward trend with cumulative exposure needs further corroboration.

Comment 3d "Contrary to the Draft Document, there is no evidence that distant site tumors are related to formaldehyde. p. 45

Response: The Draft Document reviewed the data on such human studies in Appendix C. The commenter does not cite any particular objectionable statement in the Draft Document.

(4) Summary Comment "The Draft Document improperly concludes that formaldehyde is genotoxic in vivo."

Comment 4a "The Draft Document's discussion of genotoxicity is one-sided, ignoring relevant evidence that formaldehyde is not genotoxic in vivo. While formaldehyde has been shown to be weakly genotoxic in vitro, it does not have the same effect in the intact, healthy, live animal."

Response: As pointed out in the IARC (1987) monograph, formaldehyde is clearly genotoxic in vitro in drosophila, as well as bacteria. Some human studies have been positive. Unanimity of results is not required for the classification of an agent as genotoxic. An agent need only to be genotoxic by one mechanism to be genotoxic.

(5) Summary Comment: "The Draft Document relies upon poorly-conducted studies in deriving a conclusion that formaldehyde is likely to be carcinogenic by the oral route." p 4

Comment 5a "Contrary to the discussion in the Draft Document, the well-conducted studies regarding the effects of ingested formaldehyde indicate that there are no such effects, even at high exposure levels." p. 50

Response: See the response to J. Swenberg's comment for page 2-3.

(6) Summary Comment: "The Draft Document incorrectly suggests that benign tumors are meaningful in assessing cancer risk of formaldehyde."

Comment 6a "The Draft Document suggests that the benign tumors found in the CIIT study are a meaningful response. Extensive evidence shows that benign tumors are not indicators of risk for formaldehyde because: (1) the benign tumors observed -- polyploid adenomas -- were of an entirely different cell type than squamous cell carcinomas whose benign counterpart is papillomas; (2) such tumors did not progress to squamous cell carcinomas, which are the cancers observed in rats after exposure to extremely high levels of formaldehyde; and (3) the incidence of benign tumors is not statistically signficiant and lacks any dose-response relationship." p. 49

Response: The Draft Document follows USEPA's (1987) decision not to use the polypoid adenoma data in the quantitive risk assessment. There remains

the suggestion that these tumors when combined with actual tumors do form an impressive continuum of response, even though these tumors are generally considered not to be a predecessor of the squamous cell carcinomas that dominated the rat nasal response.

(7) Summary Comment: "The Draft Document gives undue weight to a few poorly-controlled studies finding hyperplasia in exposed workers." p. 53

Comment 7a "The Draft Document improperly relies upon recent Scandinavian reports showing squamous metaplasia and in a few cases mild dysplasia in the nasal mucosa, in small samplings of formaldehyde-exposed workers." p. 53

Response: Such findings in small studies are of concern. Certainly they are consistent with the above statement of Blair et al. (1990), quoted in response to Comment 3a. Small studies would tend to underestimate cancer risk due to their low power. The determination of cancer in a small human study should not be quickly dismissed.

8. Summary Comment: "EPA is in the final stages of its process to issue the revised risk assessment in final form. A brief delay would enable California to reflect the expert analysis by EPA and its outside reviewers and would avoid the uncertainty that would be raised by inconsistent approaches to risk assessment." p. 58

Response: With two draft reports completed by USEPA and two reviews held by its Scientific Advisory Board, the USEPA's basic inputs to the assessment appear to be made. Staff have reviewed these drafts and have discussed them with U.S. EPA scientists. It is not clear that consistency will be achieved by waiting. The U.S. EPA drafts will now undergo lengthy review and discussion. For example, the EPA staff report that their preference for using the risk predictions based on monkey data has now been called in question publicly by members of EPA's Science Advisory Board. Meanwhile the regulatory program needs this assessment to provide the basic information to develop a prudent program to protect public health in California.

Response to Comments: T STARR

(The numbers below refer to the commenter's order of paragraphs. The letters refer to the OEHHA staff's designation of subparagraphs).

1. Comment: If accurate, the 22,900 extra cancer cases estimated for the state, nearly one case per thousand individuals, would be alarmingly large. However, the ARB and DHS have overstated the risk in two ways. One way was in not taking account of the DNA-protein crosslinks "fully and properly," leading to a 54-fold overestimate. The other way was in assuming that different temporal exposure patterns with the same continuous lifetime exposure all yield the same cancer risk. This assumption is "in direct contradiction to the acknowledged amplifying effects of increased cell replication on the carcinogenic process at high, but not low formaldehyde concentrations," leading to further 20-fold overestimate. Taken together, the two overestimates imply an overstatement of risk by as much as 1000-fold.

Response: The revised version of the document explores the two points raised here and does adopt a 4-fold reduction in the best estimate of the upper confidence limit for extra cancer cases in California. First, as explained in the response to Comment 3a below, the use of the monkey-rat DPX data results in an 18-fold reduced estimate of risk, not a 54-fold reduction. OEHHA staff have concluded that neither the generic contact scaling adopted in the Draft Document nor the dosimetrically adjusted value, which gives the 18-fold reduction, can be used as a best estimate, but rather the default scaling, which is in between, is most appropriate. Second, as explained in response to Comment 4a below, there is no basis for the assertion that a proliferation increase of 20 at high exposures implies any decrease of risk at low exposures due to proliferation. The calculations show that the most likely effect of including proliferation in the model is actually a 40% increase in the estimates of upper confidence limit for unit risk.

2. Comment: The document uses a model developed by Casanova et al. (1989) to predict the level of DNA-protein crosslinks (DPX) as the independent variable or measure of dose rate in fitting the multistage model to the rat bioassay data. This model "provides a reasonably accurate description of the relationship between DPX and airborne formaldehyde concentration, but it also consistently overpredicts the DPX levels observed in rats exposed to low concentrations. For example, the prediction of the CARB equation is 14% higher than the value observed at 0.3 ppm for 6 hours exposure. Such overpredictions are expected at concentrations of concern, 0.075 ppm and lower." This conservative bias should be corrected, even though small compared to the two sources of overprediction mentioned in Comment 1.

Response: An important advantage of a model prediction is to smooth out the random variability in just such data as these. Careful inspection of Fig. 5 of Casanova et al. (1989) shows that this model relationship appears highly plausible in its smoothing, over the whole range of data. Thus, the model is based on all available points. To claim that one point is over or under prediction is inappropriate since the model provides a better estimate of the central tendency of the points. The measured level of DPX at 2 ppm is substantially higher, compared to predictions, than the value at 0.3 ppm is low, but the trend is quite clearly given by the model

3. Comment: Appendix A of the document develops two different scaling factors to extrapolate risks from rats to humans by determining equivalent airborne concentrations. Using the same two approaches to extrapolate from rats to monkeys shows that the resulting predictions are totally inconsistent with the DPX measurements of Heck et al. (1989). At the lowest airborne formaldehyde concentration, 0.7 ppm, for which measurements were made in both rats and monkeys, the observed monkey DPX value was 10.8-fold lower than the rat value. Thus the default scaling overpredicts the monkey DPX by 10.7-fold while the contact scaling overpredicts the monkey DPX by 24.9-fold. Also, the default scaling prediction for humans from rats is 13-fold greater and the contact scaling is 54 times greater than the DPX observations in monkeys. "The associated human cancer risks that CARB has estimated are thus clearly overstated by these very same substantial factors."
Despite the objection in the Draft Document at page 2-8, "the monkey DPX data can and should be used to estimate human cancer risk, as has been demonstrated and recommended by Starr (1990) and, subsequently, by EPA in the recent draft revision (EPA, 1990) of its 1987 formaldehyde health assessment document. It should also be noted that in October 1990, EPA's Science Advisory Board concurred with this recommendation."...
"At the present time, the Rhesus monkey provides the best available animal model for DPX formation in humans exposed to formaldehyde. Heck et al. (1989), Starr (1989, 1990), EPA (1990), and CARB have all noted that the monkey is far closer to the human than the rat in terms of its respiratory anatomy, physiology, and breathing patterns. Until direct measurements of DPX in humans are available, the most plausible and scientifically defensible assumption is that humans develop DPX following formaldehyde exposure to the same extent as do monkeys. CARB must not casually dismiss these data, as they provide the best available scientific information relevant to estimating a human cancer potency factor for formaldehyde."

Response: The commenter's analysis compares effects in only the nasal passages, yet the monkey data demonstrates DPX and therefore risk of cancer well beyond the nasal passages A complete comparison of the relative cancer risk is not possible due to the incomplete data available on the distribution of formaldehyde throughout monkey respiratory tract. To partially take into account this overall effect, the revised version of the document presents an analysis using the rat-to-monkey comparison in the development of a metabolically adjusted contact scaling factor. The result, is an 18-fold adjustment below the best value in the Draft Document. This result compares with the implied 54-fold lower adjustment by the commenter. This result is 4-fold lower than the best value of the revised version. The revised version does not adopt the dosimetrically adjusted scaling factor as the best estimate for the following reasons:

(1) Rats may have more ability to detoxify formaldehyde than humans due to the rats' higher glutathione levels and enzymatic activities, compared to humans. Thus, humans may be more sensitive to formaldehyde. The measured low binding in monkeys implies very high detoxification or other elimination of formaldehyde. The mechanism for this effect does not have a clear explanation.
(2) It is unclear how the partitioning of the oral and nasal breathing in the monkey compares with the rats' nasal breathing or the typical human breathing patterns.
(3) The underlying cancer predisposition factors for lung in monkeys is unclear. Data are not available which indicate that respiratory cancer

in monkeys correlates better with human respiratory cancer than rat respiratory cancer.

(4) The available monkey data do not describe formaldehyde binding throughout the complete respiratory tract. Human data seem to indicate that the primary risk factor from formaldehdye exposure is lung cancer in particular and respiratory cancer in general. Elevated cancer rates have been reported in humans for the lung, nasal passages, nasopharynx and buccal cavity. Consequently, comparison of exposure between rats and monkeys, isolated to a small area of the respiratory tract does not consider the complete carcinogenic picture for humans.

On the other hand the generic contact scaling factor is not well supported for formaldehyde. Therefore, for formaldehyde staff concluded that there was not a clear case to depart from the default (body-surface-area) scaling.

4a. Comment: The document assumes, as have federal agencies in the past, that cumulative lifetime dose is the proper measure of carcinogenicity, whereas EPA in their 1990 draft document noted that "cytotoxicity and attendent cell proliferation make high-concentration intermittent exposure patterns inherently more risky than their lifetime continuous exposure equivalent. Since cell proliferation is known to be increased by as much as 20-fold relative to background replication rates at high formaldehyde concentrations, it is clear that CARB's assumption of equivalence may actually overstate the risk associated with low continuous lifetime exposure conditions by a corresponding factor of the same magnitude."

Response: The revised version, like the Draft Document, weights administered exposure more heavily than time by virtue of using tissue dose to predict cancer risk. Proliferation effects may explain why the risks are so high at the highest exposure with substantial proliferation, as noted in the proliferation model reported in the revised version. However, the cancer bioassay did report tumors at 5.6 ppm, where long-term proliferation effects were not above background, and that result has a major influence on the low-exposure extrapolation. So the cell proliferation effects at the high exposure appear to have little effect on risk at low exposures, where long-term cell proliferation is at background levels. The proliferation modeling results gave a 40% increase in UCL for unit risk, contrary to the commenter's expectation of a decrease by as much as 20-fold.

4b. Comment: "New data have already been collected at CIIT regarding cell proliferation rates in the rat during the course of chronic formaldehyde exposure. These data can and should be utilized directly in CARB's risk assessment process. They can be employed to estimate the parameters of carcinogenesis models that accommodate cell proliferation information, such as the two-stage growth model proposed by Moolgavkar and his co-workers. In this way, CARB can reduce the bias introduced into its human cancer risk estimates that arise from its use of an incorrect and inappropriate dose-response model."

Response: The revised version of the document now contains results for proliferation models using data collected at CIIT. The computations with these data show an increase in the risk estimate, contrary to predictions of the commenter.

5. Comment: "There are a number of factual inaccuracies in the CARB draft health assessment document that should be corrected." For example, the statement at p 2-19 gives the distinct impression that the study of Blair it al. (1986) was convincingly positive, yet the authors themselves concluded otherwise. The statements of the authors lead the commenter "to conclude that the results of the Blair et al. study would be equally if not perhaps more consistent with the hypothesis that no extra cancer risk was attributable to the workers' formaldehyde exposure. This certainly appears to be the conclusion of the study authors. It is also the conclusion of the blue ribbon epidemiology panel (UAREP 1988) after review of all of the existing epidemiology studies of formaldehyde-exposed workers: '(1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure and 2) furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small'."

Response: At this point in the text, the Draft Document reports data from the Blair et al. (1986) study, along with the relevant information that the relative risk was significantly elevated. The Draft Document discusses the study at pages 2-4 - 2-21. As explained at those pages, the analysis in the Draft Document does not find the study convincingly positive because of the point raised by Blair et al. (1986) about lack of a dose-response relationship. However, the results of the corrected reanalysis of Sterling and Weinkham (1989a, b) stand as a challenge to the conclusion of Blair et al (1986).

6. Comment: "In its discussion of Starr (1989, 1990), CARB asserts that 'Starr used tumor incidence data which did not subtract out early mortality in the denominator and did not account for interim sacrifice in the numerator'. This is not correct. The tumor incidence data employed by Starr (1989, 1990) was the same as that employed by Starr and Buck (1984). All interim-sacrificed animals were excluded from both the numerators and denominators, so as to permit a direct comparison of our results with the earlier risk estimates that had been developed by Cohn (1981) for the Consumer Product Safety Commission."

Response: The staff agrees with this comment. The revised version of the document eliminates the phrase, "and did not account for interim sacrifice in the numerator."

Response to Comments: SWENBERG

(The numbers below refer to the commenter's order of paragraphs. The letters refer to the OEHHA staff's designation of subparagraphs).

1a. Comment: The document draws heavily on the 1987 EPA document and does not review the 1990 EPA update in any detail.

Response: The Draft Document (January 1991) covered the material that the OEHHA staff considered to be most relevant in the 1990 EPA update but no citation of that update was appropriate because it is "an external draft for review purposes only," as stated in the front of the EPA update. Thus, the information in the 1990 draft was considered and was discussed with U. S. EPA scientists. The revised version (September 1991) incorporates more of the information in the latest U. S. EPA drafts (June 1991). However, direct citation is kept to a minimum since both the U. S. EPA drafts are for review and have not been approved by the U. S. EPA's Science Advisory Board.

1b. Comment: "While I commend the writers of this document for incorporating the use of DNA-protein crosslinks (DPX) as the dose parameter, I seriously question the unit risk of 2.9×10^{-2}." This risk is 41 times higher than that of the EPA 1990 update, which used the monkey DPX data rather than a scaling factor. How can the CARB dismiss the monkey data, which are generated in exactly the same manner that the rat data are? "If the objective of the CARB proposal is to present the most scientifically accurate risk assessment, it is clear that monkey DPX data should be the dose parameter. This change incorporates important pharmacokinetic differences between high and low exposures associated with saturation of formaldehyde dehydrogenase, the primary route of formaldehyde detoxication..."

Response: The January document did not use the monkey data for the reasons stated at page 2-8, "The lack of cancer bioassay data for monkeys limits the usefulness of the binding data in monkeys, because it is not known how susceptible monkeys are to formaldehyde-induced carcinogenesis." As stated on page 2-22, "the monkey data do not appear to be adequate, and those data do not include the entire conducting airways, as would be necessary to extrapolate from rat nasal tumors to human lung tumors." It is not clear how the use of the monkey data would incorporate important pharmacokinetic differences between high and low dose exposures. Nevertheless, the revised document does contain a section using the monkey data, and values generated from the data are incorporated into the range. Staff do not consider the monkey data to be the best adjustment due to difficulty of extrapolating those data to the complete respiratory tract and due to the lack of information on the suceptibility of monkeys to lung carcinogenesis. The extrapolation is especially problematic without information on the partition of nose and mouth breathing in monkeys.

2. Comment: "The major deficiency in the CARB document is its lack of utilization of our present knowledge of the role being played by cell proliferation in the dose response relationship for formaldehyde. It is now absolutely clear that cell proliferation is the driving force responsible for the observable nonlinearity in tumors," as suggested by

many of the earlier studies. There is compelling support for this thesis in a new unpublished CIIT study which confirmed the trend of the previous cancer bioassay and showed a strikingly similar shape of curve for cell proliferation.

Response: The comment asserts that the steepening nature of the tumor exposure-response curve is due primarily to cell proliferation. The commenter presents some evidence that the profound steepening in this case may be strongly influenced by formaldehyde induced proliferation. Staff acknowledge the major concerns of this comment, and for that reason conducted several analysis to evaluate the impact of all proliferation on formaldehyde carcinogenesis. Even so, the GLOBAL86 version of the multistage model can account reasonably well for such an effect. In the revised version of the risk assessment several cell proliferation approaches using the data cited by the commenter show that explicit inclusion of the proliferation rate has, in the most likely cases, only a very limited effect on estimates of upper confidence limit on unit risk.

3. Comment: "When extrapolating from high to low formaldehyde exposures it is imperative that one understands that there is a series of changes that work in concert to lower the risk of cancer per unit dose." While CARB has incorporated most of the pharmacokinetic factors by using DPX, "it hasn't recognized...that the major nonlinearity for observable nasal cancer occurs at concentrations above 6 ppm and that the pharmacokinetics are saturated and therefore linear between 6 and 15 ppm. Thus, while it is clear that good science dictates that DPX be used as the index of exposure and that this correctly decreases the estimated risk at concentrations below 6 ppm formaldehyde, it does not explain the striking nonlinearity in tumors between 6 and 15 ppm. It is obvious that an additional factor is involved. The new data of Monticello and Morgan strongly points to cell proliferation as that factor".

Response: The excellent fit of the three-stage tissue-based model based on DPX shows that that model has sufficient flexibility to be consistent with the striking steepness in the cancer bioassay above 6 ppm. See also response to Comment 2.

4. Comment: Increases of cell proliferation lead to increases of mutation due to decreased time for DNA repair. "Thus, even though the amount of DPX between 6 and 15 ppm formaldehyde is proportionate to concentration, the probability of mutations remains highly nonlinear due to marked increases in cell proliferation at 10 and 15 ppm."

Response: The DPX are not proportional to applied concentration from 6 ppm to 15 ppm in either the rat or the monkey, according to data in Heck et al. (1989). The proliferation evidence alluded to by the commenter does suggest a possible role for cell proliferation at those exposures. In part for those reasons, estimates of risk based on the cell proliferation model are incorporated into the range of risks.

5. Comment: "Cell proliferation is also required for clonal expansion of the initiated cell population. This is a critical step in multistage carcinogenesis. The likelihood of additional genetic events occuring in an initiated cell is proportional to the number of initiated cells. The

increased cell proliferation that is associated with 10-15 ppm formaldehyde results in clonal expansion of initiated cells, therefore increasing the probability of these necessary genetic events. Such clonal expansion was evident in the original bioassay in lesions diagnosed as atypical hyperplasia and has been even more carefully evaluated in the repeat studies of Monticello and Morgan."

Response: Available measurements of cell proliferation for formaldehyde have not provided distinct enough characterizations of the proliferating cells to classify them as initiated. The observed cell proliferation may not reflect the clonal expansion of initiated cells. However, the proliferation model presented in the revised version of the document does consider the possibility of the clonal expansion of initiated (premalignant) cells being reflected in the observed proliferation.

6. Comment: "The impact of this on the risk assessment is that the risk per unit formaldehyde is based on tumor incidence data from 15 ppm. Incorporation of DPX as the dosimeter only deals with the nonlinearities associated with pharmacokinetic factors that occur below 6 ppm. Thus, the risk assessment only corrects for these factors and ignores the major factor associated with high dose nonlinearity. If the CARB document is going to be scientifically defensible, it must be revised to incorporate this new understanding. If the effect of increased cell proliferation was simply multiplicative, the potential magnitude of this effect would be a factor of at least 20. If it is exponential, which is the most likely scenario, it could be several orders of magnitude. One cannot simply drop (ignore) the high dose data and revert to a two state model. The formaldehyde data set represents one of the best characterized understandings of chemical carcinogenesis available today and should be used in its fullest to pave the way toward generating more accurate and scientifically defensible risk assessments in the future."

Response: The commenter clearly overstates the importance of cell proliferation in formaldehyde risk assessment. Furthermore, it is the lower doses that are most important for the multistage model. Nonlinearity at the higher doses does not play a major factor in extrapolation. The revised assessment gives results for this proliferation effect. See response to Comment 2.

7a. Comment: "Data are selectively used to support the contention that formaldehyde is carcinogenic in humans. In truth, the collective data are simply equivocal, i.e., they are neither positive nor negative. While I am not an epidemiologist, I am fairly familiar with the studies that have been conducted on formaldehyde. I am deeply concerned with the presentation of these data in the CARB document."

Response: As indicated in the document, the epidemiologic data for formaldehyde are limited. This is in agreement with the International Agency for Research on Cancer's conclusion. Appendix C of the Draft Document reviews the available epidemiological studies and summarizes their quantitative results. Some of the larger of these studies are consistent with a carcinogenic effect, as reported at pages 2-3, 2-4 and 2-5. In the past, staff have conducted risk assessments on limited human data. In this case, staff use the human data for comparison purposes only.

7b. Comment: "The CARB document predicts upper confidence limits for human lung cancer. This endpoint is cited as being supported by the best available epidemiology study (Blair, 1986), yet this is not the conclusion drawn by that study, to say nothing of the fact that the study had no control for smoking."

Response: At page 2-21 the Draft Document notes that a modeling prediction from nasal tumors in rats is consistent with observations of lung cancer in workers exposed to formaldehyde and points out that such consistency lends support for that modeling prediction based on carcinogenesis of the respiratory tract. The Draft Document discusses the smoking issue and the finding of a lack of consistent correlation of lung cancer with intensity or other measures of exposure in Blair et al. (1986), pointing out that those points are not inconsistent with a carcinogenic effect. It is important that animal extrapolations to human risk be compared with humans data when they are available. Otherwise it is difficult to determine whether the risk predicted is a possible upper bound for human risk. In this case, the animal data were compared with the best available human study. The human data were found not to be inconsistent with the animal data.

7c. Comment: "Perhaps the most compelling argument against formaldehyde being causal for human lung cancer comes when you examine the CARB document's Table C-1. An overwhelming proportion of the data demonstrate a lower number of deaths from lung cancer than expected under the null hypothesis in formaldehyde-exposed populations. This lack of an effect is further supported by the frequent lack of exposure and duration correlations, and by inconsistencies between and within studies. The bias shown in the CARB document citation of data is unjustifiable and must be corrected."

Response: Although the studies reviewed in Appendix C did show variable results, the two largest industrial studies involving significant exposure to formaldehyde both found elevated rates of lung cancer that were unlikely to be due to chance. The industrial cohort studies are reasonably consistent with regard to respiratory tract cancer excesses, when one takes into account exposure levels. The Stayner study (Stayner et al., 1988) involved a large cohort, but the exposures were lower than for the Blair (Blair et al., 1986) and Acheson (Acheson et al., 1984) studies. Some increases in risk in respiratory tract cancer were reported, but, with the exception of buccal cancer, they were small. While the Wong study (Wong, 1983) did not find overall increases in risk, the exposures were unknown and may have been low.

The lower number of deaths from lung cancer than expected under the null hypothesis in formaldehyde-exposed populations has a potential explanation, called by epidemiologists "the healthy worker effect." Sterling and Weinkham in their response to the Formaldehyde Institute present the case that the healthy worker effect may apply to cancer. Neither the Draft Document nor the revised version rely on human epidemiological data; so this issue is not presented here in detail. Still the issue can be addressed with the Blair et al (1986) study by considering comparisons between exposed and non-exposed workers. The overall respiratory tract cancer SMR among exposed workers of 1.12 can be compared to the respiratory tract cancer SMR of 0.95 for non-exposed workers. It is

reasonable to compare these two directly and to adjust the SMR for exposed workers upwards by about 5% to 1.18 (1.12/.95 = 1.18), taking account of healthy worker effect. The result is an approximate 50% increase in excess risk. Thus the healthy worker effect bias adds to the importance of the findings for causal inference, and may become important in risk estimation.

The "frequent" lack of exposure and duration correlations and the inconsistencies between and within studies could arise from a number of causes, but the effect of formaldehyde irritancy, especially in connection with smoking, would appear to be the most likeley confounder, as explained briefly on page 2-21 in the Draft Document in connection with Blair et al (1986). Again, this issue is not pursued here in detail because neither the Draft Document nor the revised version rely on human epidemiological data.

8a. Comment: "The CARB document needs to clearly state the major uncertainty associated with projections of risk that are based on concentration x time (CxT) relationships." Histopathology and cell proliferation are driven by concentration while the document assumes that carcinogenesis is driven by the product of concentration and time, an assumption that "is on extremely shaky ground.

Response: The concentration that the commenter refers to is that of applied exposure. The Draft Document used tissue concentration x time for the basis of the risk assessment, which weights applied concentration more heavily than linearly as concentration increases. All proliferation results and some reports of histopathology have shown strict increases with applied concentration but very complex relationships with time, including reduced levels with increasing time. See page 2-6 of the Draft Document.

8b. Comment: "it is highly likely that the slope of any real risk is close to zero. This slope would increase greatly if humans were subjected to concentrations of 6 ppm and higher. That, however, is not the case."

Response: The main goal of the quantitative risk assessment is to predict these very small slopes or potencies.

9. Comment: The model used in the document, GLOBAL86, is not acceptible to predict cancer risks at the lower concentrations to which humans are ordinarily exposed... The document's citation of a recent Moolgavkar reference as support for the use of GLOBAL86 is amazing in view of that author's stressing "the need to incorporate cell proliferation data into risk assessment models. All of Moolgavkar's publications that I am aware of in the last 5 years have stressed the need to incorporate cell proliferation data into risk assessment models. This is in fact what is needed to acceptably model the formaldehyde risk... It makes no sense to begin new regulations without using the new data displayed in Figure 1 of the comments. The cell proliferation data could be obtained from CIIT in time for use."

Response: The revised version of the document includes a cell proliferation model based on an approximate formula of Moolgavkar. As pointed out in the response to Comment 2 , the most likely results from this model do not differ much from the multistage model results. The upper

confidence limit on unit risk increases in most cases by 40% with the explicit use of the suggested proliferation data.

Comments referred to specific pages in the Draft Document.

Comment, page 1-3: "In view of the excellent understanding of the mechanisms associated with formaldehyde's carcinogenicity, the use of an upper confidence limit from GLOBAL86 estimates is clearly overkill. Likewise, the potential hazard to human health is extremely low at the low concentrations associated with environmental exposure. Drawing undue attention to unlikely risks is counterproductive to improving human health because society fails to accept and regulate major causes of cancer such as smoking."

Response: This point is discussed in response to Comments 2 and 9 and others. The issue of environmental tobacco smoke is under great scrutiny for regulation throughout the country. Formaldehyde is a substantial component of tobacco smoke.

Comment, page 1-4: "The human nasal cancer data are confounded by exposure to wood dust. The new CIIT study now provides rat data on 6 exposure groups."

Response: The association of human nasal cancer with formaldehyde exposure is somewhat less persuasive than the association of human nasopharyngeal cancer (Blair, 1990b). Still, both need to be included in this very brief summary.

Comment, page 1-6: "The range of extrapolation is too low. The lowest statistically positive exposure is 10 ppm. Using the data in Table 5, the average environmental exposure to formaldehyde is about 34 ppb. This is an extrapolation range of 294."

Response: The rat exposure of 14.3 ppm has a lifetime equivalent exposure of 2.6 ppm. For an average human exposure of 34 ppb this gives ratio or range of extrapolation of 76, which rounds to 100. Using the new average human exposure of 42 ppb gives a range of extrapolation of 62, and using a lower exposure value as positive in the rat bioassay would give an even lower value. This range of extrapolation is much lower then usually occurs in animal-to-human extrapolation. In most cases extrapolations of 100,000 to 1,000,000-fold are required. For formaldehyde, the range of extrapolation is only 100. This provides much more certainty to the formaldehyde risks compared to most environmental cancer risks.

Comment, page 2-1: "The reported risks predicted from epidemiology studies have also been severely biased by selection. If you reported the predicted risks for pathologists, it would be greatly exaggerated from what has been found."

Response: As reviewed in Appendix C, the increases in respiratory tract cancer found in the industrial workers were not found among professionals. Indeed, the lung cancer rates are much lower than expected. In part, this would be due to the lower smoking rates which have been found among professionals, yet the Stroup study (Stroup et al., 1986) made comparisons

with psychiatrists and still found low lung cancer rates. However, the lack of increased lung cancer risks among persons exposed to embalming solutions does not provide evidence against formaldehyde being a human lung carcinogen. The most important reason for this conclusion is that the time-weighted average exposures were low. For example, the estimated time-weighted average exposure for embalmers was only 0.02 ppm, which is in marked contrast to time-weighted averages around 1 ppm for some industrial workers. See also the responses for Comments 7a,7b,7c.

Comment, page 2-3: "The Soffritti study should not be put on the same level as the Til and Tobe studies. It is very poorly documented and inconsistent within its own data sets, as well as with other studies run at higher and lower doses. Several attempts have been made by independent investigators to review the data. Unless some form of peer review can be done, it should be dropped."

Response: The Draft Document offers the Soffritti study as a published work. No published rebuttal or critique that could be used in the document has yet come to the staff's attention. Because the work is recently published, the staff will remain alert for any published rebuttal, especially in connection with concerns about intake by the oral route.

Comment, page 2-5: "It should be clearly stated that metaplasia of nasal epithelium is not related to the neoplastic process."

Response: The OEHHA staff does not have the information at this time to warrant the statement that the nasal metaplasia is not related to the neoplastic process in the human studies alluded to on this page of the Draft Document. The first sentence of the first full paragraph has been changed (indicated by underlining) to refer to "histological changes, some of which are potentially precancerous lesions".

Comment, page 2-10: "It is inappropriate to even suggest that the multistage model for risk assessment is based on the biological stages of carcinogenesis. It is merely the number of "stages" that fit a mathematical curve. There is no biology in it! If there was, cell proliferation data would be mandated."

Response: The text refers to the biological plausibility of the multistage model in comparison to other available models that have been presented as alternatives in past risk assessments. The biology in it is the description of a multistage mutation process, which is a special simpler case of the more general approach that Moolgavkar developed in order to include cell kinetics.

Comment, page 2-18, 19: "There certainly are a number of uncertainties. I don't know how CARB calculated that humans are more sensitive than rats. The data on DPX in rats versus monkeys clearly shows the opposite trend. CARB should reevaluate how they are using this."

Response: The revised version of the document explores this issue in developing approaches to interspecies scaling.

Comment, page 2-21: "The document never discusses the actual range of risk in which the true risk may lie."

Response: The Draft Document discusses the predicted range of risk briefly on page 2-22. It is difficult to see how to discuss any other range of risk which would be generally as useful. The current range of risk incorporates all relevant scientific data brought to staff's attention.

Comment, page B-1-8: "The paper by Crosby et al. (Environ. Mol. Mut., 12:155-166, 1988) was not cited. This paper characterizes the mutational spectrum of formaldehyde-induced mutations. These data provide reasonable evidence that DPX are responsible for half of the mutations, i.e., large deletions. The other half of the mutations occur at AT base pairs, data consistent with formation of the very unstable N^6-hydroxymethyladenine adduct of formaldehyde."

Response: The main body of the revised version of the document now cites this reference.

Response to Comments (27 and 28 March, 1991): Peter Barrett Consultants

1. Comment: Dr. Barrett had not received the document and was unable to comment on its contents. He sent a copy of his resume, papers which he authored, and general comments on the cancer risk, irritation risk and other health effects of formaldehyde.

Response: The OEHHA staff have reviewed the material, which comments on the USEPA document of September 1990. The OEHHA staff did not find the proposed procedures to be directly applicable to the analysis in the risk assessment document.

Response to Comment: Borden Inc.

1. Comment: Borden request that the inclusion of formaldehyde on the air toxics list be evaluated consistent with the revised U.S. EPA assessment and that DHS support a consistent approach with EPA guidance.

Response: The OEHHA staff have revised the risk numbers for formaldehyde with data considered to be most relevant from the EPA updates (1990). However, direct citation has been kept to a minimum since the U.S. EPA's Science Advisory Board has not approved an updated document on formaldehyde (See Response to Comments by J. Swenberg 1a.).

PART C ADDENDUM

PUBLIC COMMENTS AND RESPONSES TO THE DRAFT SRP VERSION OF THE FORMALDEHYDE REPORT

Prepared by the Staffs of the Air Resources Board
and the Office of Environmental Health Hazard Assessment

January 1992

Part C Addendum contains the comments received from the public during the September 20, 1991 through October 18, 1991 public review period for the Draft SRP Version of the formaldehyde report. The responses of the Air Resources Board and the Office of Environmental Health Hazard Assessment to those comments are also contained in this Addendum.

Contents of the Addendum to Part C

I.

Comment Letters Received on the Draft SRP Version of the Formaldehyde Identification Reports, Part A and B

Hardwood Plywood Manufacturers Assn.
1825 Michael Faraday Drive
Reston, Virginia 22090
703/435-2900

National Particleboard Association
18928 Premiere Court
Gaithersburg, Maryland 20879
301/670-0604

October 14, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
ATTN: Formaldehyde
P.O. Box 2815
1219 K Street
Sacramento, CA 95812

SUBJECT: Comments on Proposed Identification of Formaldehyde As A Toxic Air Contaminant Part A - Exposure Assessment; and Part C Public Comments and ARB/OEHHA Staff Responses - SRP Draft Versions

Dear Ms. Shiroma:

The Hardwood Plywood Manufacturers Association (HPMA) and the National Particleboard Association (NPA) - representing manufacturers of hardwood plywood, particleboard and medium density fiberboard (MDF) - have reviewed the September 1991 SRP version formaldehyde draft documents prepared by the California Air Resources Board. While the Air Resources Board has incorporated some changes, as suggested by HPMA and NPA in our March 26, 1991 comments, in the new SRP Part A - Exposure Assessment draft, we believe that ARB continues to over emphasize the influence of current low emitting urea-formaldehyde (UF) bonded wood based panel products on home formaldehyde levels.

Wood panel products made with UF adhesives include two reconstituted wood products - particleboard and medium density fiberboard (MDF). Hardwood plywood is made of distinct layers of wood and is not classified as a reconstituted wood product. (See Page A-42, Part A - SRP Version).

Our industries continue to be frustrated about the inability to free themselves from the reputation of higher formaldehyde emission potential ascribed to our products of the late 1970s and early 1980s. In general, during the past 5 to 10 years, reductions in emissions of between 75 to 90% have been made from UF-bonded hardwood plywood, particleboard and MDF. Almost all of the exposure information cited by ARB in the September 1991 SRP version documents is based on data developed during the early

1980s in homes built before low emitting UF-bonded wood products became widely used in the market. None of the information cited by ARB fully considers the emission reductions from UF-bonded wood products that have continued to occur into the mid and late 1980s, and the 1990s.

We have attached comments and a response to some specific issues related to formaldehyde exposure and wood panel products as addressed in our earlier March 26, 1991 letter. Serious deficiencies remain in the ARB September 1991 draft documents and we believe that these deficiencies must be corrected before a meaningful assessment of formaldehyde exposure can be made. We appreciate the opportunity of reviewing the documents.

Sincerely,

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William H. McCredie
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Enclosures:Comments and Three Appendices

October 14, 1991

Comments on Proposed Identification of Formaldehyde As A Toxic Air Contaminant Part A - Exposure Assessment; and Part C Public Comments and ARB/OEHHA Staff Responses - SRP Draft Versions

I. GENERAL COMMENTS

A. Home Studies Emphasized by ARB are Among the Best That are Available.

Studies used by the state to characterize exposures in homes are probably among the best that are available. ARB did not present a compendium of "complaint" homes, which has been the case in certain investigations by other states and agencies. Home studies emphasized included those having the largest number of homes surveyed (the 1984-1985 Sexton et al. mobile home study, for example), and included homes that appear to be reasonably representative of homes in the state.

The Science Applications, Inc. 1983 study (Rogozen et al.) in conventional homes has been acknowledged by its own authors as having a small sample size. The authors of this study recommended that a stratified sampling design study be conducted in a minimum of 500 homes if factors related to indoor concentrations of formaldehyde were to be assessed. Nevertheless, the Rogozen study remains as the largest study among California conventional homes (70 homes surveyed), and was well-conducted.

The primary difficulty is that the studies available for characterizing California homes relate to homes built in the early 1980s and prior to that time. These studies contained

virtually no information on the loading rates (usage) of wood products, and indeed, little information on formaldehyde containing materials and formaldehyde sources. The problem is not that the studies were bad; they appeared to be well-conducted. Like all studies of this type they were limited by funding resources and, thus, limited in scope. Now they are outdated, at least in the context of being relevant to formaldehyde release from the current generation of wood products.

B. The Reference to the Urea-Formaldehyde Foam Insulation (UFFI) Ban is Not in Accordance with the Facts.

We have found that regulatory investigations often perpetuate certain myths. This has been characteristic of agency investigations of formaldehyde, both at the state and federal level. As a case in point the following appears on page A-45 of the Part A SRP version draft in reference to the UFFI ban:

> "The ban was challenged successfully on procedural grounds (but not on its technical merit) in the U.S. Court of Appeals (1983) by UFFI and formaldehyde manufacturers."

This statement may have appeared in the popular press or be someone's perception of what happened but it has little resemblance to the actual findings of the Fifth Circuit Court of Appeals. The Opinion of that Court (April 7, 1983) contained seven general areas: I. The Product; II. The Rulemaking; III. Standard of Review; IV. The Risk of Cancer from UFFI; V. Acute Irritant Effects; VI. The Consumer Product Safety Act vs. the Federal Hazard Substances Act; and VII. Conclusion.

The Opinion, while including an analysis of procedural issues, emphasized technical and health issues. Section IV - The Risk of Cancer from UFFI - was the single largest section of the Opinion and contained a discussion of formaldehyde exposure studies, the CIIT animal experiments, epidemiology, and risk assessment. The conclusion of the Court was very specific as to the principal reason why the ban was vacated.

> "VII. CONCLUSION
> We are not unmindful that regulating in the face of scientific uncertainty within ever-tightening budgetary constraints presents the Commission with a difficult task. We nevertheless cannot abdicate our role in the regulatory process. Congress and our circuit's precedents require us to take a "harder look" to determine whether rules adopted under the Consumer Product Safety Act are supported by substantial evidence. That look discloses that the evidence is lacking here. The Commission's rule banning UFFI is VACATED."

The key phrase in the conclusion is "regulating in the face of scientific uncertainty." There is some parallelism in the "scientific uncertainty", referenced by the Fifth Circuit, and the ARB analysis in respect to exposure data from California homes built in the early 1980s, the virtual absence of information on wood product use in such homes, and the publication of <u>only</u> "point" cancer estimates based on <u>only</u> "upper bound risk" mathematical model risk estimates.

II. SPECIFIC COMMENTS

A. <u>In-home exposures are likely overstated relative to outdoor exposures</u>.

In March 26, 1991 comments, HPMA and NPA contrasted the ARB out-of-home exposures of 4.4 ppbv, weighted by population, as

being significantly different (by factor of about 2 to 12) from earlier ambient formaldehyde concentration data described by other observers (Rogozen-1984, and Scott Research Laboratories-1969; for example). We stated that we did not think that the magnitude of difference between the current cited ARB ambient values and other higher ambient formaldehyde levels could be explained only by differences in sampling times, the time of day samples are taken, and changes having occurred in recent years to reduce outside levels of formaldehyde.

In examining the Part C ARB/OEHHA staff response and the data itself, we agree that the sampling technique used in determining outside exposures based on 24-hour average composites over a year (between September 1988 and August 1989) is a superior technique to that used by earlier investigators. With the growth that has occurred in California in the past 10 to 20 years, we still remain surprised that the levels are now this low (4.4 ppbv).

If the outside levels of formaldehyde have changed due to reductions in formaldehyde release from motor vehicles and from other outside sources, which apparently is the case, then the decrease in these levels would be reflected indoors. Outside ambient levels are one component of inside home levels. The use of 1988-1989 home outside ambient levels by ARB would likely require some adjustment of indoor levels reported in the early 1980s in making any meaningful home indoor projections for 1989 and beyond. Alternatively, new home studies could be conducted to determine current home levels of formaldehyde.

B. Flawed 24-hour exposure patterns for California citizens.

ARB has modified exposure patterns to better reflect 24-hour living patterns for California citizens. Thus, persons not

"at home" would be exposed to something other than atmospheric formaldehyde of 4.4 ppbv for 6 hours of the day when they are at work, at school or shopping. While the use of formaldehyde levels in commercial and institutional building, as a surrogate for the away from home exposure segment, does increase the exposures for that part of the day, the use of such data represents a technical improvement in exposure assessment. Segmenting exposure assessment into three elements: at home (14.9 hours), away from home (6 hours) and outdoors (3.1 hours) is a more logical way of exposure assessment than that used in the February 1991 draft ARB reports.

We are less familiar with the technical literature on formaldehyde levels in office and institutional buildings except to know that relatively little formaldehyde level data is available for these types of buildings, as compared with homes. We have no specific comments, at this time, on the levels selected for the away from home segment nor for the time elements associated with the three time segments of exposure.

C. The importance of UF bonded wood products as a formaldehyde emission source is overstated.

Although the addition of notes to the Pickrell table (Page A-44, Part A - SRP Version) in response to our March 26, 1991 comments are helpful, we do not believe that the Pickrell table should even be included in the ARB Part A report. The Pickrell information was published in 1983 and has little relevance to emission characteristics of current low emitting UF-bonded wood panel products. The ARB staff acknowledges that the emission rates in the Pickrell table "may be somewhat higher than current rates" (Page 155, Part C - SRP version); however, the following statements, still appear, unmodified or only slightly modified,

in the September 1991 draft Part A report.

> "By far the largest source of formaldehyde indoors is pressed wood products made with urea-formaldehyde resins" (Page A-1)

> "Formaldehyde concentrations are generally much higher indoors than outdoors due to the abundance of building materials and consumer products in buildings that emit formaldehyde." (Page A-41)

> "Building materials (especially pressed wood products made with formaldehyde resins), because they emit relatively large amounts of formaldehyde and are present in large quantities, make the most significant contribution to indoor formaldehyde concentrations." (Page A-42)

> "In general, building materials tend to be the highest emitters, followed by combustion sources, paper products, new clothes, draperies and other fabrics." (Page A-42)

Except for UFFI, which has disappeared from the market, the most pronounced reductions in emissions from any products containing formaldehyde has probably been within the urea-formaldehyde wood panel products group. Particleboard and hardwood plywood products were subject to U.S. Department of Housing and Urban Development manufactured home emission level requirements in February 1985. A State of Minnesota statute (June 1985) established requirements similar to HUD, except that medium density fiberboard was included as a regulated product in addition to particleboard and hardwood plywood. The Minnesota rule also applies to all types of building structures.

To support the fact that ARB has over emphasized the importance

of wood products in contributing to indoor formaldehyde levels, we have focused principally on studies in California manufactured and conventional homes as cited by ARB. Tables 1 and 2 (Pages 20 and 21 of these comments) contain information on manufactured (mobile) and conventional homes, respectively. Reference to these tables will be made from time to time as points are emphasized or our previous March 26, 1991 comments are amplified.

1. Older Home Data do not Reflect Emission Rate Reduction Patterns from Different Pressed Wood Products.

The particleboard, hardwood plywood and medium density fiberboard industry sectors have exhibited different patterns of formaldehyde reduction. The SRP version draft states that . . .

> "Formaldehyde emissions from pressed-wood products declined several years before the 1984 HUD emission limits were imposed due to advances in manufacturing techniques and competition within the industry. There is evidence that emissions declined markedly as early as 1982, including information presented by the Formaldehyde Institute during the April 3, 1991 workshop which showed steep reductions in particleboard emissions beginning in 1982." (Page 155, Part C - SRP Version)

The Formaldehyde Institute presented two histograms on April 3, 1991: one for particleboard and one for hardwood plywood. An additional histogram for medium density fiberboard, not previously presented, has also been prepared for these comments. The histograms, as appearing in Appendix 1, are representative of the patterns of formaldehyde emission reduction for each of three UF-bonded products.

a. Particleboard

Formaldehyde emission data for particleboard from 1979

through 1988, as illustrated in Appendix 1, demonstrates that emission reductions have been made throughout the decade. The 1982 data represents survey information from plants voluntarily having their product tested at the National Particleboard Association laboratory - the state-of-the-art of the particleboard industry at the time. No data was presented for 1983 because insufficient industry-wide information was available to NPA at that time. Data presented for 1984 through 1988 represents annual large chamber test (FTM 2-1985 and ASTM E 1333-90) data and includes products from virtually all U.S. particleboard manufacturers. From the early part of the decade to the later part two things occurred: 1) more and more particleboard products were made with improved low-emitting UF adhesives, and 2) further gains in emission reduction occurred - from 62% emission reduction by 1982 to 83-84% emission reduction in the 1985 to 1988 period.

b. Hardwood Plywood

The initial focus during 1979 and the early 1980s was on hardwood plywood wall paneling, a building product extensively used in the 1970s in manufactured (mobile) homes for interior wall finish. Early basic information about formaldehyde emission characteristics from hardwood plywood wall paneling was developed in 1979-1981, concurrent with the refinement of formaldehyde test methods by the industry.

The hardwood plywood industry, having a greater number of small and medium sized manufacturers and being more fragmented than the particleboard industry, lagged slightly behind the particleboard sector in bringing relatively large quantities of low emitting hardwood plywood to the market.

While there was, no doubt, some reduction in emissions from hardwood plywood during the early 1980s, there was insufficient technical data from enough manufacturers for HPMA to make any meaningful judgement on reductions within the industry at large during 1982, 1983 and 1984 (see Appendix 1). The 1985 HUD regulation and Minnesota statute were the primary factors leading to the development of sufficient data to characterize the industry. Thus, while some emission reduction occurred early in the decade (1982-1984), these improvements were exhibited by a relatively small number of hardwood plywood manufacturers. Most of the emission reduction improvement from both hardwood plywood wall panels and hardwood plywood industrial panels (used as components for cabinets and furniture) occurred in the mid and late 1980s as illustrated in the histogram in Appendix 1.

c. Medium Density Fiberboard

In respect to formaldehyde emission potential, the principal concern in the late 1970s and early 1980s was with UF-bonded building materials: particleboard decking for manufactured homes, particleboard underlayment for conventional homes, and hardwood plywood wall paneling. These building products were used at relatively high loading rates in some homes during that time.

Medium density fiberboard products, as components in kitchen cabinets and furniture, were generally used at lower loading rates in manufactured homes. Probably for that reason MDF was not addressed in the HUD formaldehyde rule (effective date - February 1985). Important regulatory benchmarks related to reductions of emissions from MDF included the

state of Minnesota statute of June 1985 (which covered MDF) and the development of an industry voluntary formaldehyde emission standard for MDF by the National Particleboard Association in 1987.

The pattern of emission reduction of MDF, thus, has been somewhat different than that of particleboard and hardwood plywood with much of the reduction in formaldehyde emissions from MDF coming late in the decade as shown on the histogram in Appendix 1.

In summary, there was some emission reduction, particularly among particleboard building products, in the early part of the 1980s. Further improvements in particleboard products occurred as the decade progressed from 1985 and beyond. The most dramatic decrease in emission from hardwood plywood occurred in the mid and late 1980s. The pattern for MDF appears to be similar to hardwood plywood except emission reduction, from the industry at large, occurred during the later part of the decade.

The California Department of Health Services study (Sexton and Liu) supports these comments about particleboard and is consistent of our understanding of the patterns of emission reduction from UF-bonded wood products. Liu (8) states:

"But data presented in Table IA show that the homes manufactured in 1982 and 1983 have formaldehyde levels lower than those homes manufactured between 1978 and 1981. The reason for this apparent discrepancy is probably due to the fact that building materials of mobile homes have been changing during the past few years. The particle-board (sic) industry has been gradually introducing products with lower formaldehyde emission rates to meet the Department of Housing and Urban Development's regulation (18) and the mobile home

industry has simultaneously been increasing the use of building materials that emit less formaldehyde."

The Liu data from Table 1A for 1978-1983 homes is presented:

Home Age (year)	Apparent Year of Construction	Number of Homes	Geometric Mean
1	1983	115	0.077
2	1982	106	0.093
3	1981	47	0.112
4	1980	20	0.124
5	1979	17	0.097
6	1978	15	0.096

This data supports our comments that some low emitting building products (primarily particleboard) were being introduced in 1982 and 1983. The 1978-1983 newer home Liu data, however, contains a component (1978-1981) prior to the introduction of much low formaldehyde emitting wood product in the market. The 1982 and 1983 homes, demonstrating lower mean values, did not include the full contribution of emission reductions identified with particleboard in the mid and late 1980s. Moreover, there was likely little low emitting hardwood plywood and MDF used in the 1982 and 1983 homes surveyed by Liu and Sexton.

2. Changes in Usage of UF-Bonded Wood Building Products Have Not Been Considered by ARB

a. Building Products

Home formaldehyde level studies performed during the early 1980s period do not include populations of homes representative of reduced usage of hardwood plywood and particleboard building products. Hardwood plywood manufacturing is a mature industry. The use of industrial hardwood plywood

products as components for furniture and cabinets has remained fairly stable over the past ten to twenty years; however, hardwood plywood wall paneling use has decreased significantly during the past twenty years. Appendix 2 includes a table showing total hardwood plywood wall paneling production in the U.S. from 1968 through 1990. While there was considerable decline in the use of this product during the late 1970s, there has been a further reduction of about 30% in shipments from the 1981-1983 period to 1990: from about 1,550 million square feet surface measure to about 1,050 million square feet surface measure.

The use of UF-bonded particleboard building products for decking in manufactured homes and for underlayment in conventional homes has also changed over the past 10 years. Decking production has declined from levels of about 200 million sq. ft. (3/4" basis) in the early 1980s to about 125 million sq. ft. in 1990. Underlayment has declined from levels of about 800 million sq. ft. in the early 1980s to about 350 million in 1990. These flooring building products have been replaced, in most cases, by either phenol-formaldehyde (PF) bonded oriented strand board or PF-bonded softwood plywood. PF-bonded wood products, in general, have lower formaldehyde emissions than UF-bonded products.

The Manufactured Housing Institute, representing the mobile home industry, recently submitted results of a product use survey to the Environmental Protection Agency for that agency's continuing investigation of formaldehyde release from pressed wood products. This survey substantiates the dramatic drop in use of hardwood plywood wall paneling. MHI reports that only 2.7% of surveyed mobile homes contained wall paneling. Urea-formaldehyde made particleboard decking now represents only about 48% of the market

according to the MHI survey; this compares to nearly 90% of the market in the early 1980s. The change in usage of UF-bonded wood panel building products has to be considered by the state of California in order for ARB to draw any meaningful conclusions for the year 1991, the year of this analysis.

b. Furniture and Cabinets

Hardwood plywood industrial panels, particleboard and MDF have been extensively used in the manufacture of furniture and cabinets for a number of years. Indeed, these products compete with each other for use as sides, fronts and shelving components.

There is limited data about emission characteristics from furniture and cabinets and, in particular, the effects of laminates and finishes on formaldehyde emissions. Alexandersson et al, (1) has described a study among workers in Sweden exposed to formaldehyde in acid-hardening lacquers and paints. Presumably such finishes could contribute to home formaldehyde levels when applied to wood products used in furniture and cabinets, whether the wood products were made with formaldehyde containing adhesives or not.

In recent years there has been a significant growth in the use of thin, flexible, decorative, film overlays for wood product components used in cabinets and certain items of furniture. An HPMA study demonstrates that a 2-mil thin, flexible, vinyl overlay applied to hardwood plywood reduced formaldehyde emission rates by 90 to 95% (5). The NPA has recently published a technical bulletin on "Formaldehyde Emission Barriers" for particleboard and medium density fiberboard (see Appendix 3). The bulletin discusses the effects of various materials that act

as diffusion barriers when applied to UF-bonded wood products. Industry surveys show that in 1989 there were over 8 billion sq. feet of plastic and paper laminates sold in the U.S. all capable of significantly reducing formaldehyde emissions.

The general adoption of low emitting UF adhesives in the mid and late 1980s and the OSHA formaldehyde workplace rule (1987) has led to the expanded use of low emitting UF-bonded components in furniture and cabinets. While there is little quantitative data available from furniture and cabinets, historical emission pattern information presented in Appendix 1 indicates that the contribution of airborne formaldehyde from UF-bonded hardwood plywood, particleboard and MDF is substantially less in the late 1980s than in the early 1980s. This has, no doubt, led to reduced emission potential from cabinets and furniture containing UF-bonded wood product components.

3. <u>There is a Reduction of Emissions Over Time From UF-Bonded Wood Products (decay) and This Must be Considered in Making Exposure Assessments.</u>

Unlike certain indoor formaldehyde sources such as outside ambient levels, cigarette smoking, and unvented gas appliances whose formaldehyde emissions continue over time, formaldehyde emissions from wood products decay over time. Urea-formaldehyde adhesive formulations for particleboard and hardwood plywood always have an excess of formaldehyde to urea in order that the wood product remains well-bonded. The use of low molar ratio formaldehyde to urea adhesives in recent years has led to a significant reduction in the amount of available "free" formaldehyde in bonded boards; however, some excess formaldehyde still remains in new improved adhesive formulations. There is residual formaldehyde in wood products, unbound to urea but held

mechanically or loosely bound to wood.

After the UF-bonded wood product is made, a sharp decline or decay of formaldehyde emission occurs early in the life of the wood product (the first year) as the "free" formaldehyde is released. The sharp or rapid decay phase is followed by a more moderate decay phase. While there is disagreement about the shape of the formaldehyde emission decay profile curve, virtually all recognize that there are changes in the rate of formaldehyde emissions from wood products over time.

The wood products industry has developed data that supports a decay profile consisting of a half-life of one year or less in the first year, followed by a more gradual decay. Industry has used, as a default value for the later years, a 2.92 year half-life as reported by Versar Inc. (16) in work for the Environmental Protection Agency. Several papers on decay are included in Appendix 3.

The relevance of this formaldehyde decay phenomenon is that low emitting UF-bonded building products used in new homes - particleboard decking and underlayment and hardwood plywood wall panels - make a contribution to home formaldehyde levels for a relatively short period of time. Versar Inc. (17) has estimated that only 5.6% of detached conventional homes and 8.7% of attached conventional homes contain particleboard underlayment. HPMA (6) has projected, using the Versar exposure model (16), that particleboard underlayment makes a contribution to indoor formaldehyde levels for only 4.1 years above an assumed background level of 0.03 ppm in average conventional homes containing that product. If decay were to be examined in the context of California homes, only new homes would likely include

any significant contribution from this wood panel product. Formaldehyde home levels in new 1991 homes, that contain UF-bonded building products, would likely be influenced by these products only for the first 4 to 5 years.

In making broad statewide exposure assessments, the age of the housing stock must be considered. We understand that about 80% of the housing stock in California is 10 years old or older. There is, therefore, only a small percentage of California conventional homes - probably less than 1% - where particleboard underlayment would have any meaningful influence on home formaldehyde levels.

4. The ARB Staff's Comments to the Contrary, California Home Level Studies Cited by ARB Do Not Support the Assertions that . . .

> **"Building materials (especially pressed wood products made with formaldehyde resins) . . . make the most significant contribution to indoor formaldehyde concentrations" (Page A-42, Part A - SRP Version) . . . and . . .**

> **"However, there is also a need to recognize that pressed wood products can still be the major source of elevated formaldehyde levels in older homes when new materials are brought into the home as a consequence of remodeling or purchasing new furnishings." (Pages 157-158, Part C - SRP Version)**

Table 1 and Table 2 (Pages 20 and 21) lists the major studies cited by ARB in California homes: Sexton and Liu, Rogozen, Colombe and Clayton Environmental Consultants (Singh). There was virtually no information related to the use of wood products, particularly wood building products, in either mobile or conventional homes described in any of the studies.

In examining the well recognized phenomenon of emission decay from wood products, only the mobile home data reported by Sexton et al. (13), Colombe et al. (3), and Clayton (14) had any significant number of new homes in the study populations. Only the later conducted Sexton and Liu study (1984 and 1985) included any homes where any real quantities of low formaldehyde emitting UF-bonded wood products were used. Even in this study many of the 0-6 year old homes did not contain low formaldehyde emitting UF-bonded wood panel products.

The California conventional home data includes very few new homes and the results and conclusions in these studies do not support the ARB contention that wood products represent the most significant contribution to formaldehyde levels in California homes. Indeed, other formaldehyde emission sources were cited.

In the largest study cited by ARB in conventional homes (Rogozen), the average age of the 64 home segment was over 20 years. Rogozen et al. (12) reports that only 7 homes were less than 5 years old in the total sample of 70 conventional homes. Because of the change in formaldehyde release from UF-bonded wood products over time (decay), very little contribution to home formaldehyde levels could be expected from UF-bonded wood building products.

The only reference to the possible use of wood products by Rogozen was in 6 homes containing new kitchen cabinets (56 ppbv) which were compared with 59 homes (49.3 ppbv) that did not have new kitchen cabinets. A difference of less than 7 ppbv hardly supports the hypothesis that UF-bonded wood products make a major contribution to home formaldehyde levels in older homes.

Moreover, improvements characteristic of current UF-bonded wood panel products would result in lower contribution to formaldehyde levels in 1991 homes than those wood products that may have been present in kitchen cabinets at the time of the Rogozen analysis in 1983.

The ARB/OEHHA staff response (Part C) to the March 26, 1991 HPMA/NPA comments have indicated that "California data were emphasized" (Page 156); and that . . .

> "indoor concentration data from a variety of studies viewed in combination with source emissions data strongly implicate pressed wood products as the major contributors to indoor formaldehyde concentrations" (Page 157) . . . and . . .

> "Also, in-home measurements have generally ruled out the relative importance of some other potential formaldehyde sources. Several studies have found that cigarette smoke and combustion appliances do not appear to affect the average indoor concentration significantly." (Page 157)

We are astonished at how little the ARB/OEHHA reviewers recall the conclusion of the principal California conventional home study cited by ARB. In the Summary and Conclusion section of Part 5 - Survey of Formaldehyde in the Indoor Environment of the Rogozen study (pages 5-46 and 5-47), the authors do not once mention wood products. The primary formaldehyde sources cited were related to homes where cigarettes were smoked and gas cooking fuel was used:

> "our data suggest that homes in which cigarettes are smoked will have higher indoor air HCHO concentrations than homes in which cigarettes are not smoked, by an average of approximately 9 ppb. Homes in which

cigarettes are smoked and gas cooking fuel is used are likely to have higher indoor HCHO concentrations than homes with no cigarette smoking and electric cooking, by an average of 19 ppb."

The Sexton study of 51 conventional homes was a pilot study subsequent to a survey in over 600 California mobile homes where diffusion samplers were mailed to participants. Sexton (1986) did not report any information on wood products and made no assessment of formaldehyde emitters in the conventional homes surveyed.

Table 1 - Formaldehyde Concentrations Cited by ARB in California Mobile Homes

Study	Avg. Conc. (ppbv)	Range (ppbv)	No. of Homes	When Sampled	Age Profile of Homes	Wood Product Usage	Sampling	Remarks
Sexton et al., 1986	72 78 (see remarks)	<10-464 17-314	663 Summer 523 Winter	Jul.-Aug. 1984 Feb.-March 1985	59% 0-4 yrs. 41% Over 4 yrs. 56% 0-4 yrs. 44% Over 4 yrs.	No information No information	LBL 7-day passive diffusion sampler	Average concentration reported as geometric mean. Arithmetic mean reported was 91 ppbv (summer and winter)
Liu et al., 1986	See footnote 1 below							
Rogozen et al., 1984	114	68-144	3	Jan.-Feb. 1983	No information	No information	LBL 7-day passive diffusion sampler	Large variation between three homes: 68, 130 and 144 ppbv
Colombe et al., 1983	160[2] 110[2]	50-300 30-150	10 Park 1 14 Park 2	June-July 1982	Most homes 1-2 yrs. old Most homes 2-4 yrs. old	No information	3M 8-hour passive diffusion sampler exposed for 7 days	Potential participants selected by letter: "we made no effort to contact the occupants who did not answer the initial letter. This could be a source of selection bias."
Clayton Environmental Consultants, 1982	210	<20-675[3]	81	1980 and early 1981	49% homes 1 yr. or less 51% homes more than 1 yr.	No[4] information	Impingers with pararosaniline analysis 4-hour sampling time	Includes 16 unoccupied homes and 65 occupied homes. Several other sampling techniques and methods of analysis were evaluated.

[1]This is the same study (California Department of Health Services) described by Sexton et al. (1986) above, except that Liu described other aspects of the work. The 470 home described by Liu were the number of homes monitored both in summer and winter. Liu was a coauthor of the Sexton (1986) paper; Sexton was a coauthor of the Liu (1986) paper.

[2]There is some confusion about the Colombe data. The text of the paper states that the average concentration in Park 1 was 0.11 ppm and that of Park 2 was 0.16 ppm. The histogram (Figure 4) in the paper shows the reverse: $\bar{x}$ = 0.16 ppm for Park 1; $\bar{x}$ = 0.11 for Park 2. Moreover, it appears that the mean value of 0.11 for Park 2 was based on 11 homes, not 14. ARB apparently mischaracterized the 0.16 ppm mean value as 116 ppbv.

[3]Reported by Clayton in mg/m³; converted to ppbv this range would be <20-675 ppbv.

[4]Four experimental homes built in Indiana as described by Clayton (14) did contain specific information on usage rates of pressed wood products. A separate report (15) was prepared describing these experimental manufactured homes. That report was coauthored by persons from Clayton, HPMA and NPA.

Table 2 - Formaldehyde Concentrations Cited by ARB in California Conventional Homes

Study	Avg. Conc. (ppbv)	Range (ppbv)	No. of Homes	When Sampled	Age Profile of Homes	Wood Product Usage	Sampling	Remarks
Rogozen et al., 1984	50 85	18-120 46-153	64 (older) 6 (new)	Jan.-June 1983	Avg. age 20+ years	Limited information; see remarks	LBL 7-day passive diffusion sampler	Avg. conc. of homes with new kitchen cabinets (N=5) was 56 ppb. Avg. conc. of homes with no new kitchen cabinets (N=59) was 49.3 ppb.
Sexton et al., 1986	35 (see remarks)	13-85 (whole house)	51	January 1984	4% of homes less than 2 yrs. old; 96% of homes 6 yrs. old or older	No information	LBL 7-day passive diffusion sampler	Avg. conc. reported as geometric mean. Arithmetic mean reported was 38 ppbv.
Wagner 1982	See footnote 1 below							

[1]The report by Wagner was unavailable to these reviewers at the time of this analysis. Since the report was published in 1982, the 12 homes surveyed would have been built prior to that date. If there had been any newer homes in the Wagner study, it is unlikely that they would have contained any significant quantities of wood products made with low-emitting formaldehyde adhesives.

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HARDWOOD PLYWOOD MANUFACTURERS ASSOCIATION

5/1/1991

ESTIMATED NATURAL HARDWOOD AND DECORATIVE HARDWOOD WALL PANELING PRODUCTION

Year	Natural Hardwood Paneling mil ft² sur. meas.	%	Hardwood Decorative Paneling mil ft² sur. meas.	%	Total Hardwood Plywood Paneling mil ft² sur. meas.	%	Other Paneling mil ft² sur. meas.
1990	113	11	940	89	1053	100	1,288
1989	129	11	1073	89	1202	100	1,310
1988	151	11	1275	89	1426	100	1,388
1987	155	10	1450	90	1605	100	1,348
1986	135	8	1465	92	1600	100	1,273
1985	172	11	1428	89	1600	100	1,188
1984	191	11	1507	89	1698	100	1,228
1983	285	18	1327	82	1612	100	1,141
1982	298	21	1148	79	1446	100	1,034
1981	345	22	1231	78	1576	100	1,077
1980	480	22	1696	78	2176	100	1,257
1979	416	15	2408	85	2824	100	1,128
1978	357	10	3145	90	3502	100	1,080
1977	376	11	3141	89	3517	100	1,382
1976	415	12	3035	88	3450	100	1,409
1975	430	14	2688	86	3118	100	1,178
1974	558	16	2938	84	3496	100	1,674
1973	742	17	3574	83	4316	100	1,207
1972	974	18	4343	82	5317	100	1,223
1971	1168	22	4066	78	5234	100	1,232
1970	716	17	3421	83	4137	100	688
1969	785	21	2946	79	3731	100	382
1968	668	23	2253	77	2921	100	---

NOTES: 1) Figures for hardwood plywood wall paneling are from HPMA annual surveys that have been adjusted to include projections for companies that did not report during the survey year.

2) Decorative paneling includes lauan and other similar species that are colortoned, printed, paper overlayed and vinyl overlayed.

3) Figures for Other includes softwood plywood, hardboard, gypsum, and particleboard paneling but does not include figures for all sources and understates the actual quantity in the category.

WP5.0:Estpanel.pro

1825 Michael Faraday Drive, P.O. Box 2789, Reston, VA 22090
Phone: 703/435-2900 FAX: 703/435-2537

HISTORICAL SUMMARY

YEAR	PARTICLEBOARD[3,4] (Thousand Square Feet - 3/4 inch Basis) TOTAL	INDUSTRIAL	UNDERLAYMENT	MOBILE HOME DECKING	MEDIUM DENSITY FIBERBOARD[3] (msf)	SHIPMENT VALUE[5] ($1,000,000) PTB	MDF	AVERAGE PRICE[5] (Dollars/msf) PTB	MDF
1959	255,356								
1960	231,998								
1961	291,327								
1962	366,028		105,667						
1963	455,813		118,876						
1964	591,697		162,325						
1965	753,006		282,556			79.1		113	
1966	947,612		375,948			88.7		100	
1967	1,074,195		456,531			97.1		92	
1968	1,391,177		547,450			141.9		103	
1969	1,681,933		551,855			200.8		124	
1970	1,731,451		596,427			159.4		96	
1971	2,359,221		753,411			206.3		90	
1972	3,079,123		941,353			284.9		94	
1973	3,460,450	2,107,532	890,935	461,983		389.4		114	
1974	3,074,535	1,859,624	901,353	313,558		347.4		115	
1975	2,502,580	1,492,032	784,007	226,541	215,496	272.6	31.4	106	177
1976	3,188,911	1,535,713	1,092,321	276,968	280,036	364.9	54.4	115	195
1977	3,569,451	1,825,450	1,096,564	289,154	441,354	484.9	84.9	136	206
1978	3,720,369	1,829,745	1,148,858	274,139	508,416	518.4	114.9	220	225
1979	3,376,488	1,674,906	1,103,965	264,849	506,728	574.8	136.7	170	270
1980	2,949,897	1,501,746	885,756	223,430	493,140	531.1	145.2	180	294
1981	2,869,352	1,531,309	780,487	218,476	516,102	536.6	175.4	187	340
1982	2,393,066	1,306,651	653,728	176,997	445,157	469.2	144.8	196	324
1983	3,009,343	1,730,329	797,897	190,157	604,323	607.0	198.0	202	328
1984	3,195,586	1,943,442	729,679	157,553	633,974	697.4	216.5	218	341
1985	3,330,517	2,015,544	756,772	159,213	684,593	675.9	242.5	203	354
1986	3,602,757	2,239,246	742,761	154,530	780,598	768.1	267.3	213	342
1987	3,705,560	2,468,378	627,729	156,464	899,282	832.5	303.1	225	337
1988	3,829,021	2,739,806	513,945	142,126	938,717	856.6	301.4	224	321
1989	3,858,226	2,933,072	325,678	126,251	970,001	882.1	314.6	229	324
1990	3,806,018	2,926,274	343,324	123,789	949,915	822.4	310.7	216	327

[1] Certifiable Board - Particleboard manufactured to have Formaldehyde Emissions at or below 0.30 parts per million at 0.13 square feet per cubic foot loading and 0.5 air change per hour; or MDF manufactured to have Formaldehyde Emissions at or below 0.30 parts per million at 1) 0.08 square feet per cubic foot loading or 2) 0.13 square feet per cubic foot loading and 0.5 air change per hour. Board manufactured to be certifiable is not necessarily third party certified.

[2] MDF certifiable at 0.08 square feet per cubic foot loading includes MDF certifiable at 0.13 square feet per cubic foot loading.

[3] In 1978, NPA began utilizing data based on shipments. Prior to 1978, all data was based on production.

[4] Particleboard shipment and production data does not include extruded board. Data from one waferboard plant is included in the 1970-1981 figures. The output of the plant is probably less than 2% of the total.

[5] Extruded particleboard is included in the value of shipments and price figures prior to 1977. Extruded board accounts for less than 10% of the total production between 1963 and 1969, and 2% or less of the total production from 1969 through 1976.

Manufactured Housing Institute

1745 Jefferson Davis Hwy., Suite 511
Arlington, Virginia 22202

Tel: (703) 979-6620
Fax: (703) 486-0938

September 27, 1991

Mr. George Semeniuk
Chemical Control Division
Office of Pesticides and
Toxic Substances
Environmental Protection Agency
East Tower (TS-794)
401 M Street, SW
Washington, D.C. 20460

Dear George:

This follows up the June 13 meeting our staff had in your office concerning formaldehyde releases from pressed wood products used in home construction. We indicated that we would advise you when we had completed a survey of panels and boards used in the assembly of manufactured homes.

As the enclosed summary of the survey reflects, we asked our members to indicate the quantity used for eight types of panels and boards. The responses represented the production of over 69,000 homes, or about 42% of the anticipated total industry production for 1991.

In our survey we asked for manufacturers' test results for any recent tests they conducted on formaldehyde levels in HUD-code homes. No information was provided by our members.

When you have had the opportunity to review the survey results, if you have any questions, please do not hesitate to contact me.

Sincerely,

Frank

Frank Walter, P.E.
Vice President
Technical Activities

Enclosure

cc: Linda Smith, Assistant Administrator
for Pesticides and Toxic Substances, EPA
G. Robert Fuller, HUD Manufactured Housing & Construction Stds. Div.
David Nimmer, HUD Office of Manufactured Housing and Regulatory Functions
Steve Winistorfer, Forest Products Laboratories

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FORMALDEHYDE-CONTAINING MATERIALS SURVEY RESULTS

The Manufactured Housing Institute conducted a member survey of formaldehyde resin use in wood paneling, flooring and cabinets over the 1991 summer. Responses accounted for 69,087 manufactured homes* produced or planned for assembly in 1991, or about 42% of the total industry's expected production. As such, they are statistically significant.

The survey results are as follows:

TYPE OF MATERIAL	TOTAL REPORTED HOMES USING	% OF REPORTED HOMES USING
Gypsum wallboard	67,223	97.3
UF hardwood panel walls	1,880	2.72
Med.-density UF fiberboard vanity fronts	50,997	73.8
Med.-density UF fiberboard kitchen cabinet fronts	45,469	65.8
UF particleboard decking	33,157	48.0
PF oriented strandboard decking	31,230	45.2
PF plywood decking	12,807	18.54
PF particleboard decking	1,604	2.32

* Manufactured homes (sometimes referred to as HUD code homes) are constructed to the federal Manufactured Home Construction and Safety Standards (24 CFR 3280)

The figures show gypsum wallboard, which does not contain formaldehyde, was used in nearly all homes produced, compared with UF resin-based hardwood paneling, which was used in less than 3 percent. UF particleboard and PF oriented strandboard were nearly tied for decking/flooring use, while PF particleboard decking/flooring was used in about 2 percent of the homes. Medium-denisty UF fiberboard vanity fronts are used in nearly three-quarters of manufactured homes.

September 27, 1991

Appendix 3

Technical Information on Diffusion Barriers and Decay

Effect of a Decorative Vinyl Overlay on Formaldehyde Emission - 1984

NPA Technical Bulletin - Formaldehyde Emission Barriers for Particleboard and Medium Density Fiberboard (MDF) - 1991

A Perspective on Home Occupant Exposures to Formaldehyde Gas from UF-Bonded Hardwood Plywood and Particleboard Building Products - 1990

HPMA and KCMA Letter of August 15, 1991 to EPA and Decay Profiles for Formaldehyde Emissions from UF-Bonded Wood Products - August 15, 1991

Appendix 1

Histograms

Reduction in Formaldehyde Emissions - Particleboard

Reduction in Formaldehyde Emissions - Hardwood Plywood

Reduction in Formaldehyde Emissions - MDF

Appendix 2

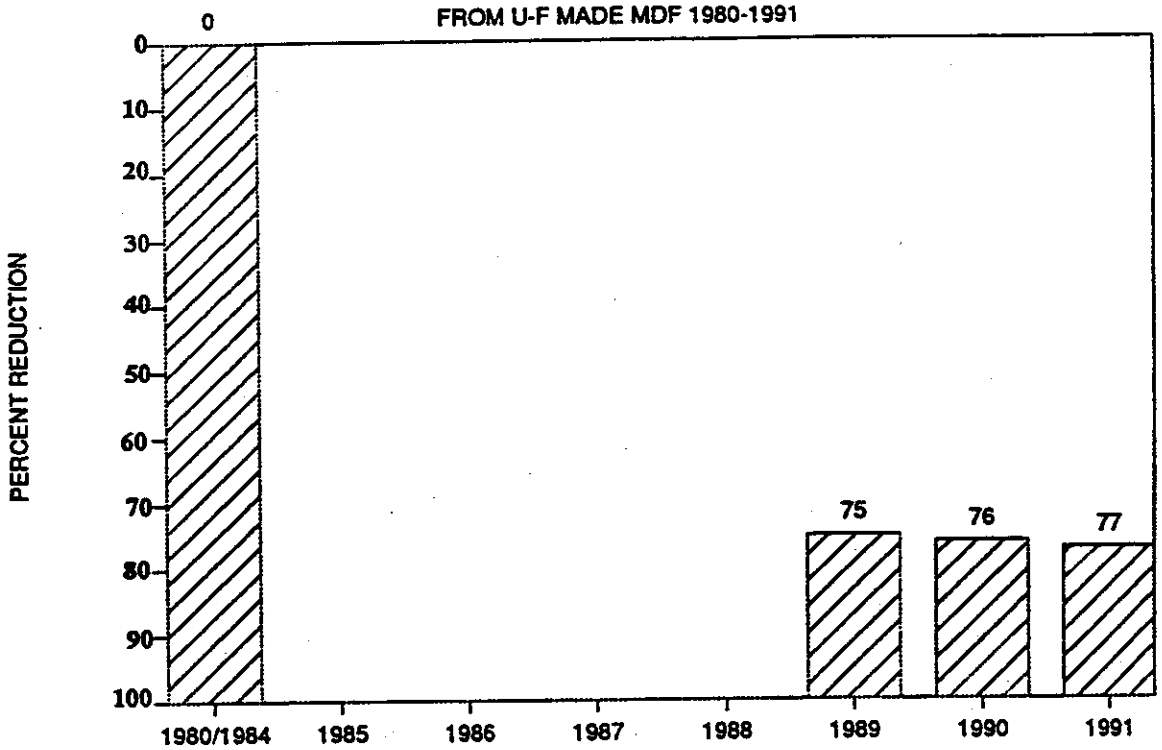
Changing Use Patterns

Estimated Natural Hardwood and Decorative Hardwood Wall Paneling Production - 5/1/91

Historical Summary of particleboard and medium density fiberboard production data - 1990

Manufactured Housing Institute letter of September 27, 1991 to EPA and Formaldehyde-Containing Materials Survey Results

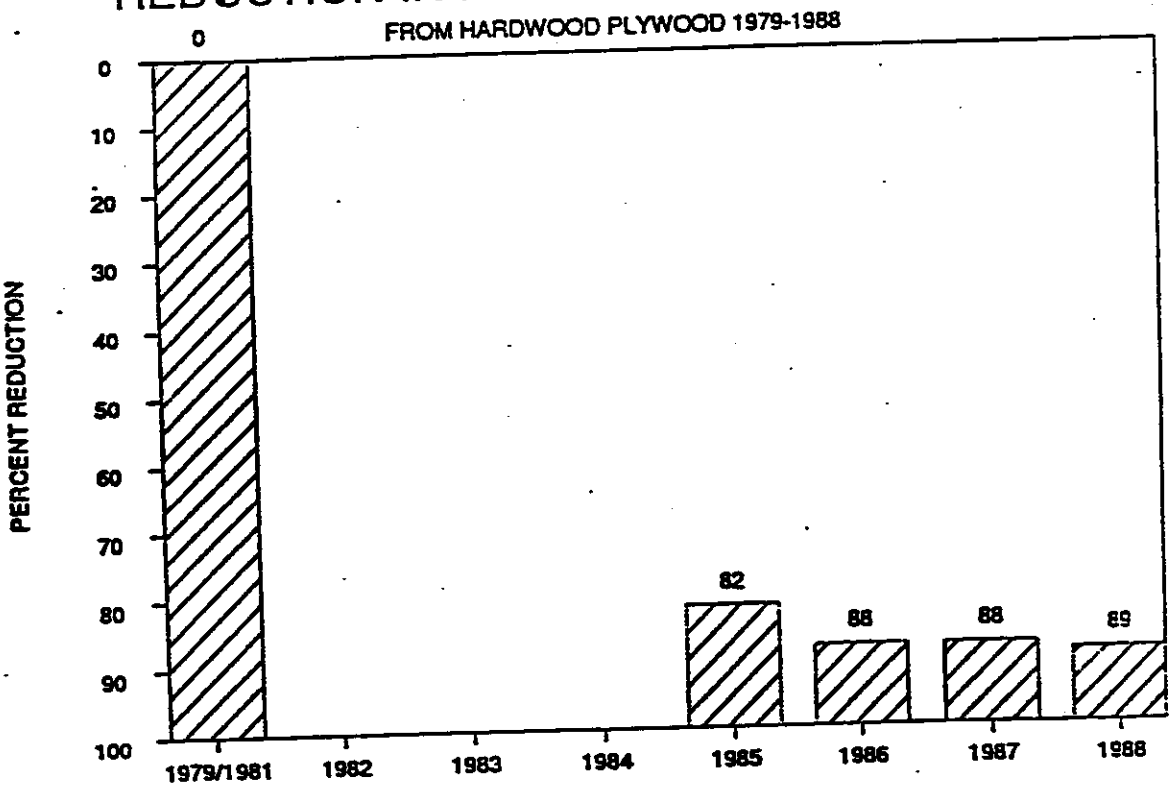
REDUCTION IN FORMALDEHYDE EMISSIONS



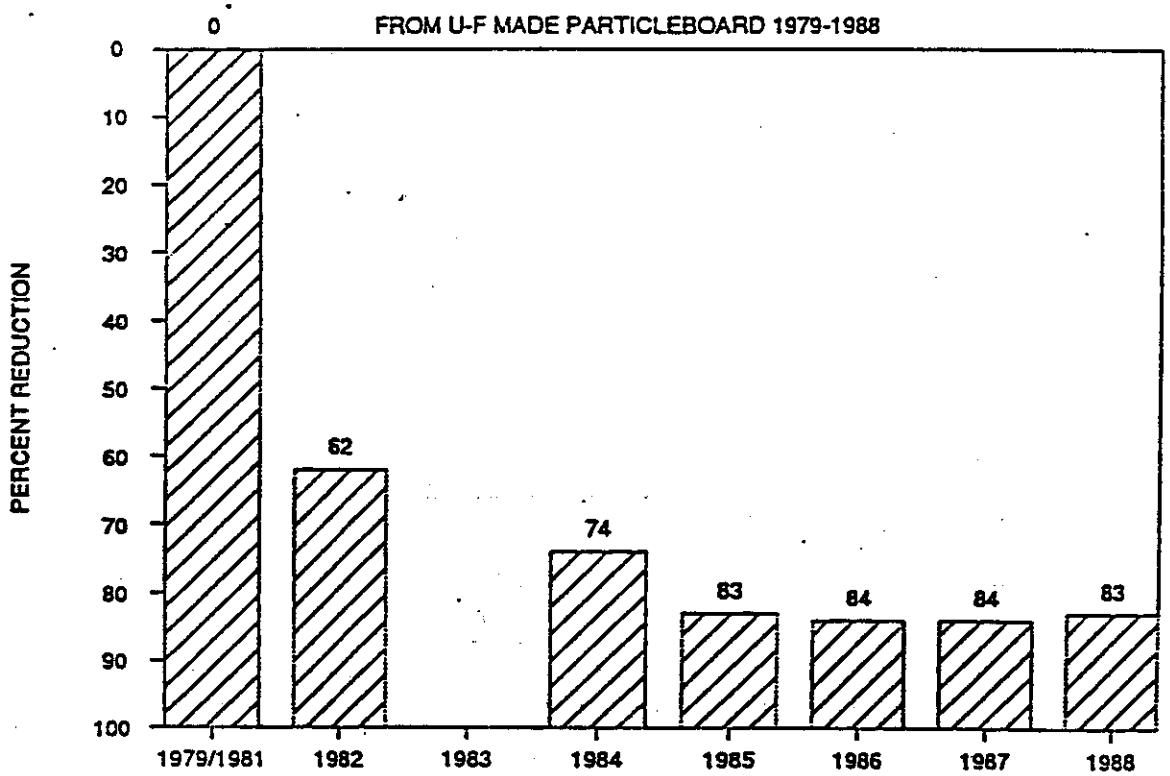
Notes: 1) Insufficient Industry Wide Data For 1985, 1986, 1987, 1988

2) Data For 1991 as of August 1, 1991

REDUCTION IN FORMALDEHYDE EMISSIONS



REDUCTION IN FORMALDEHYDE EMISSIONS



The Formaldehyde Institute

1330 Connecticut Avenue, NW ▫ Suite 300 ▫ Washington, DC 20036-1702 ▫ 202.659.0060

October 18, 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
1219 K Street
Sacramento, California 95812

Re: Formaldehyde

Dear Ms. Shiroma:

Enclosed are two copies of the preliminary comments of the Formaldehyde Institute, Inc. respecting the September 1991 "SPR Draft Version" of the "Proposed Identification of Formaldehyde as a Toxic Air Contaminant."

The Institute's opportunity for review of the current version has been inhibited by the short period since issuance of the draft. Much of the information in the current version -- particularly the highly complex risk assessment calculations presented in Appendix A -- was not available for review in the earlier draft and is not based in published literature. The prior plans to defer the October 22 meeting further limited the Institute's efforts. The Institute has expert review of Appendix A underway and expects to submit further comments in the near future. Accordingly, the Institute requests extension of the comment period for a reasonable period after October 22 to allow further opportunity for expert review and comment.

Respectfully submitted,

John F. Murray
President

Enclosures

The Formaldehyde Institute

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BEFORE THE STATE OF CALIFORNIA AIR RESOURCES BOARD

COMMENTS REGARDING SEPTEMBER 1991 DRAFT DOCUMENT ON PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT

The Formaldehyde Institute, Inc. ("the Institute") offers the following comments on the September, 1991 "Draft SRP Version" of the "Proposed Identification of Formaldehyde as a Toxic Air Contaminant", issued by the California Air Resources Board ("CARB").

EXECUTIVE SUMMARY

In its March 26, 1991 opening comments, the Institute focussed on several flaws in CARB's February 1991 "Preliminary Draft" document:

(1) The Preliminary Draft does not properly incorporate all of the relevant mechanistic information regarding formaldehyde. EPA issued a revision to its formaldehyde risk assessment yielding a prediction of risk much lower -- by a factor of 10 to 100 -- than that provided in the Preliminary Draft. Further, cell proliferation data are available; incorporation of that data would further reduce the prediction of risk by over one order of magnitude. The Preliminary Draft should be revised to reflect EPA's updated analysis and the other available data.

(2) The Preliminary Draft uses an interspecies scaling factor which significantly overestimates the true risk of formaldehyde exposure.

(3) The Preliminary Draft does not provide a balanced discussion of the formaldehyde epidemiology data. In particular, the epidemiology data regarding lung cancer do not show excess risk attributable to formaldehyde.

(4) The Preliminary Draft improperly concludes that formaldehyde is genotoxic in vivo.

(5) The Preliminary Draft relies upon poorly-conducted studies in deriving a conclusion that formaldehyde is likely to be carcinogenic by the oral route.

(6) The Preliminary Draft incorrectly suggests that benign tumors are meaningful in assessing cancer risk of formaldehyde.

(7) The Preliminary Draft gives undue weight to a few poorly-controlled studies finding hyperplasia in exposed workers.

The September, 1991 Draft Document reflects some revisions from the earlier version, most notably in its recognition of some of the DNA cross-linking data developed by the Chemical Industry Institute of Toxicology ("CIIT"). Regrettably, however, the September, 1991 version continues many of the deficiencies of the earlier version:

(1) The CIIT monkey data are rejected in favor of use of rodent data which is unquestionably less relevant to humans.

(2) In contrast to EPA and other organizations that have considered incorporation of cell proliferation data in risk assessment, the Draft states that these data increase the risk prediction.

(3) The Draft totally ignores published studies indicating that while formaldehyde is weakly genotoxic in vitro it does not have the same effect in the live animal.

(4) The one-sided presentation of epidemiologic data continues and analysis relating to the conclusion that formaldehyde does not cause cancer in humans is ignored.

(5) The Draft fails to respond to the Institute's comments respecting the Edling and Holmstrum reports respecting hyperplasia.

(6) Erroneous reliance is placed on the ingestion study by Soffritti.

Each of these points is set forth in more detail below.

The short time for public review has precluded full comment on the new, highly complex risk assessment calculations presented in Appendix A of the Draft. The Institute shortly will be submitting technical comments respecting those calculations.

I. CARB SHOULD CORRECT ITS USE OF ANIMAL DATA FOR RISK ASSESSMENT PURPOSES

A. CARB Improperly Rejects the CIIT Monkey Data

It is both incontrovertible toxicology doctrine and a specific finding of the U.S. Environmental Protection Agency that primate data are more relevant to humans than rodent data. As EPA stated, the predicted risk level using the rat DNA cross-linking data is believed to overestimate true risk. EPA reiterated that the data showing lower DNA cross-linking in monkeys are more significant to the likely effects in humans:

> As stated before, nonlinear dose responses for nasal tumors in rats and [DNA cross link] formation as well as mucociliary clearance, cell proliferation, cytotoxicity, and nonneoplastic pathology in rats and monkeys argue for the true risk being well below that predicted by the upper bound. . . .
>
> Rat-based estimates may be too high at a given exposure concentration, due to differences in breathing patterns.

EPA 1990 Risk Assessment, Ex. 2, at 4, 70.[1] See also Monticello, et al., "Effects of Formaldehyde Gas on the

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[1] All exhibit references are to the Institute's March 26, 1991 filing. All exhibits discussed herein are appended again for CARB's convenience.

Respiratory Tract of Rhesus Monkeys: Pathology and Cell Proliferation," Am. J. Path. 134:515 (Mar. 1989).

EPA's conclusions were based in part on extensive research, published in 1990 by Drs. Heck, Casanova-Schmitz and Starr of CIIT,[2] based on ongoing primate studies following on their previous experiments with rodents. That research concluded that response to formaldehyde is highly species-specific and that the primate data should result in a reduction in the cancer risk estimates for formaldehyde:

> Inhaled formaldehyde does not impair pulmonary function and does not induce airway hyperactivity in humans at airborne concentrations as high as 3 ppm. In Rhesus monkeys, absorption occurs primarily in the nasal cavity, and very little penetrates to the lung, especially at low concentrations. The concentration of DNA-protein cross-links in nasal cavity tissues of Rhesus monkeys was about an order-of-magnitude lower than in the nasal mucosa of rats.
>
> . . . .
>
> By utilizing DNA-protein cross-links as an internal dosimeter, the Rhesus monkey is predicted to be at much lower risk of nasal cancer than the rat. [Citations omitted] Thus, assuming that the monkey is susceptible to formaldehyde-induced carcinogenesis, the upper bound estimate of risk to the nasal turbinates and anterior nasal mucosa is 13 to 20 times smaller between 1.0 and 0.1 ppm than that predicted for the rat based on the administered concentration (column 5; "DPC/Monkey"). The maximum-likelihood estimate of risk for the monkey is between four and five orders-of- magnitude lower than that predicted for the rat over the same concentration range.
>
> In Rhesus monkeys, absorption occurs primarily in the nasal cavity, and very little penetrates to the lung,

---

[2] Heck, Casanova-Schmitz & Starr, "Formaldehyde Toxicity -- New Understanding," Crit. Rev. Toxicol. 20:397-426 (1990).

especially at low concentrations. The concentration of DNA-protein cross-links in nasal cavity tissues of Rhesus monkeys was about an order-of-magnitude lower than in the nasal mucosa of rats.

Id. at 41, 43.

The current Draft fails to give proper recognition to the role of interspecies variability and to the uncontroverted fact that primates are considered to be much better models for humans than the rat. In partial recognition of the primate data, the revised version presents a metabolically-adjusted contact scaling factor that results in an 18-fold adjustment below the best value used in the draft document. However, as discussed in the Institute's March 26, 1991 comments, full incorporation of the CIIT monkey data would reduce the predicted risk by a factor of 54. CARB should adopt the full adjustment as the scaling factor that would yield the best prediction of risk.

The short time for comment has limited the Institute's opportunity for review of the complex scaling-factor calculations presented in Appendix A. However, preliminary review indicates:

- CARB is presenting a new approach to development of a scaling factor that is not based in the published literature.
- There are myriad assumptions that are simply stated without support. Two key examples are: (1) derivation of nasal penetration data for monkeys from the high exposure level, rather than from the lower exposure level which would be more analogous to the human experience; and (2) use of the upper bound for the nasal penetration data in the rat. Despite the numerous assumptions, there is no discussion of the effect of uncertainty.
- In many respects, CARB's approach does not reflect data specific to formaldehyde.

- The calculations in Appendix A make errors respecting the body weights of monkeys and rats.

- In view of the numerous unsupported assumptions that form the basis for the scaling factor calculations, CARB's support for its default scaling factor -- that it is an intermediate value between scaling factors using other approaches -- is entitled to no weight. The full adjustment using the monkey data would yield the best estimate of risk.

Other aspects of the calculations in Appendix A also appear to be in error. For example, the time-to-tumor calculations appear to vary significantly from the time-to-tumor conditions actually observed in the CIIT study.

The Institute expects to submit technical comments respecting Appendix A in the near future. Especially in view of the absence of precedent or published support for its approach, CARB should extend the comment period to enable review and consideration of those comments.

B. CARB Gave Insufficient Recognition to Cell Proliferation and Therefore to the Effect of Formaldehyde Concentration

CARB has failed to recognize, as did EPA, that airborne concentration is a more important exposure parameter than total dose:

> The combined results of several toxicologic studies further support the importance of airborne formaldehyde concentration in the induction of toxic effects. Inhalation exposure to a low level of formaldehyde for a long duration of daily exposure (1 ppm for 22 hours) over the course of 6 months does not cause lesions in the rat nose. In contrast, subchronic or chronic inhalation exposure to higher formaldehyde concentrations (2-4 ppm) but with a shorter duration of daily exposure (6 hours) produces varying degree of nasal damage in rats. . . .

> All these findings demonstrate that airborne formaldehyde concentration is an important exposure parameter and imply that the utilization of lifetime average daily concentrations for risk quantification purposes may overestimate risk potential by arbitrarily lowering the dose at which adverse effects are observed.

EPA Formaldehyde Risk Assessment Update -- Preliminary Analysis Discussion of Evidence, Sept. 28, 1990, Ex. 5, at 4; see Comments of Dr. James A. Swenberg, Mar. 25, 1991, at 4; Comments of Dr. Thomas B. Starr, Mar. 26, 1991, Attachment B, at 6.

EPA's findings were based in part on new research confirming earlier CIIT findings that formaldehyde dose response is highly non-linear; cell-proliferation caused by exposure to high cytotoxic doses appears to represent the mechanism of formaldehyde carcinogenicity. CIIT concludes that the new data demonstrates that the toxic effects induced by formaldehyde depend non-linearly on concentration. The "Conclusions" section of CIIT's article summarizes the major advances that have been made in recent years on the implications of mechanistic data:

> (1) Concentrations that are demonstrably carcinogenic are also cytotoxic and increase cell proliferation in the nose. Increased cell turnover is an extremely important, and possibly essential, component of the carcinogenic mechanism of formaldehyde. The rate of cell proliferation in the nasal mucosa of rats exposed to a constant total dose of formaldehyde increased with increasing concentrations.
>
> (2) Increased turnover resulting from a single infliction of severe tissue damage was insufficient by itself or when coupled with exposure to a low concentration of formaldehyde ($\leq$ 1.0 ppm) to induce nasal cancer in rats. A statistically significant tumor incidence was observed only when tissue damage took place in conjunction with exposure to a very high

concentration (e.g., 10, 15, or 20 ppm). The concentration of formaldehyde delivered to cells of the nasal mucosa increases nonlinearly with the airborne concentration, with rapid increases occurring at concentrations above 2 to 3 ppm. . . .

* * * *

(4) The nonlinear concentration dependence of DNA-protein cross-link formation and the predominant role of concentration in determining cell turnover and mutagenic efficiency strongly suggest that the intracellular concentration of formaldehyde is modulated by saturable defense mechanisms. . . .

(5) Lesions induced in the rate nose (squamous metaplasia and epithelial hyperplasia) by a subchronic exposure to 10 ppm of formaldehyde were reversible if exposure was discontinued before 8 weeks. Irreversible lesions were induced by exposures for longer times or to higher concentrations.

(6) Formaldehyde-induced lesions in the respiratory tract of monkeys exposed to 6 ppm for 6 weeks were similar in nature to those observed in rats. However, the lesions were more widespread in monkeys than in rats exposed under the same conditions, while the concentration of DNA-protein cross-links in the turbinates and anterior nose following a single exposure to [^{14}C] formaldehyde was significantly lower in monkeys than in rats. Cross-links were also detected in more distal regions of the respiratory tract of some monkeys exposed to 2 or 6 ppm, but not to 0.7 ppm.

(7) Formaldehyde failed to induce hepatotoxicity, immunotoxicity, or DNA-protein cross-linking at sites remote from the site of deposition following inhalation exposures, it failed to induce hepatotoxicity following oral exposures, and it failed to induce tumors in rats when administered at high concentrations in the drinking water. Formaldehyde concentrations in the blood of rats, monkeys, and humans were not significantly increased by inhalation exposure.

A report by V. Feron and R. Woutersen, "Role of Tissue Damage in Nasal Carcinogenesis" (TNO-CIVO) (presented to Toxicology and Nutrition Institute, Zeist, The Netherlands)

(Sept. 1988) (the "Feron Report"), concluded from the CIIT data that human exposure to non-cytotoxic levels of formaldehyde represents a negligible cancer risk. Feron found that malignant tumors occurred in rats exposed to 10 ppm, concentrations that were observed to cause severe tissue damage. The Feron Report provided examples of human cancers which develop in chronically injured tissue, such as skin cancer and colon cancer, and noted that "[c]ytotoxic effects and epithelial hyperproliferation appear to play an almost essential role in the development of nasal tumors in rats exposed to formaldehyde."

With respect to the Feron study and a more recent study by Woutersen,[3] CIIT recently stated:

> These results demonstrate that irreparable tissue damage and cancer can occur in rats exposed subchronically to formaldehyde, but that the induction of cancer appears to require very high concentrations of formaldehyde. . . .

The current Draft offers two arguments in support of its failure to consider the cell proliferation data. First, CARB asserts that incorporation of the cell proliferation data actually would increase the prediction of risk. In fact, incorporation of that data would further reduce the prediction of risk by over an order of magnitude. See Comments of Dr. James A. Swenberg, Mar. 25, 1991, Attachment A; Comments of Dr. Thomas B. Starr, Mar. 26, 1991, Attachment B, at 2, 6-7; Comments of CIIT

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[3] Woutersen, et al., "Nasal Tumors in Rats After Severe Injury to the Nasal Mucosa and Prolonged Exposure to 10 ppm Formaldehyde," J. Appl. Toxicol. 9:39 (1989).

to EPA, Oct. 25, 1990, Ex. 6; Comments of Dr. James A. Swenberg to EPA, Oct. 19, 1990, Ex. 7. Second, CARB asserts that cancer was observed in rats at 6 ppm, although there was no evidence of cell proliferation at that level. In fact, there was evidence of some cellular effects at 6 ppm; further, the tumors observed at 6 ppm were not statistically significant. These issues will be addressed in more detail in the Institute's forthcoming technical comments.

C. CARB Should Consider the CanTox Risk Assessment

CARB also ignored the CanTox report. As discussed in the Institute's March 26, 1991 comments, CanTox, Inc. conducted a comprehensive literature review of all formaldehyde health effects studies, including laboratory animal and human epidemiology studies. CanTox prepared a biological risk assessment utilizing data on respiration rate, respiratory tract physiology, mucociliary clearance mechanisms, cytotoxicity, and DNA repair. CanTox, Inc., "Biological Risk Assessment of the Potential Carcinogenesis from Exposure to Airborne Formaldehyde," (Oct. 27, 1988), Ex. 4. CanTox reached the following conclusion:

> the data demonstrate that the no effect level for carcinogenicity of formaldehyde is 1 ppm and an assessment of biological relevance of available formaldehyde data indicates that an exposure level of 1 ppm or less would eliminate the risk of developing cancer in humans.

Id. at viii.

CanTox reached the following findings with respect to specific aspects of the biological data:

Protective Mechanisms. The average human adult produces about 51 grams per day of formaldehyde as a metabolite for use in building essential body chemicals and in breaking down other chemicals. In contrast, a person continuously exposed to 1 ppm of formaldehyde for 24 hours would take in 24.6 milligrams, over 2,000 times less than that produced in the body. CanTox concluded that "[t]he addition of such a tiny fraction to the body pool would not be expected to add significantly to the risk of developing formaldehyde-induced systemic effects" and that "[a]t diminished delivered doses [less than 2 ppm], it is reasonable to expect that normal cellular metabolism and DNA repair would adequately protect cellular systems from adverse effects of formaldehyde. These mechanisms exist to protect against adverse effects from normal endogenous formaldehyde. . . ."[4]

Cell Proliferation and DNA repair. CanTox reached the following conclusions regarding the biological data that indicate a non-linear response to formaldehyde -- in other words, that the cancer observed in laboratory rats at 14.3 ppm results from

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[4] CanTox referred to studies by CIIT using rhesus monkeys that showed no significant increase in blood formaldehyde concentration following exposure to 6 ppm for four weeks and finding that, at an exposure of 6 ppm for one and six weeks, only effects on the nasal cavity, larynx, trachea and upper bronchi, and not in the lung or other organs, were observed. Id. at 31-32, 74 (citing Casanova-Schmitz, et al., "Formaldehyde (HCHO) Concentrations in the Blood of Rhesus Monkeys Exposed to HCHO by Inhalation" (1989); Monticello, et al., "Effects of Formaldehyde Gas on the Respiratory Tract of Rhesus Monkeys" (1988)).

persistent cytotoxicity at high doses and would not be expected to occur at lower levels:

> [A]bove 2 ppm . . .[n]ormal metabolism and repair functions would begin to become saturated and there would be a greater chance of formation of DNA-protein cross-links from formaldehyde. Increased cellular injury would produce a hyperproliferative response and the resulting increased cellular turnover would further increase the DNA-protein cross-linking with formaldehyde.[5]

Id. at vii.

Interspecies variation. CanTox noted that "[t]he occurrence of high local concentrations of formaldehyde in the rodent, as influenced by the unique geometry of the rat nasal cavity, leads to hyperproliferative responses that are critical to the development of cancer in that species." Applying the recent CIIT data, CanTox also concluded that there are substantial species differences which make humans less susceptible to the effects of formaldehyde than rats:

> The respiratory tract of humans more closely resembles that of the monkey than the rat. Therefore, based on species differences in breathing patterns, respiratory tract physiology and doses of formaldehyde delivered to nasal tissues, the linear extrapolation of formaldehyde

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[5] CanTox also described the recent results of an improved analytical method developed by CIIT to determine the extent of binding of formaldehyde to mucosal DNA. The data based on rats exposed to 0.3, 0.7, 2, 6 and 10 ppm formaldehyde confirmed the non-linearity of covalent binding: "(1) at the limit of inhaled formaldehyde concentration approximately 12% of absorbed formaldehyde is bound to DNA (88% is detoxified; (2) the detoxification pathway is half-saturated at an airborne concentration of 2.6 ppm; and (3) the limiting slope of the concentration-response curve for DNA-protein cross-linking at high concentrations." Id. at 86 (citing Casanova-Schmitz, et al., supra).

> data from rodents to humans would result in an overestimation of expected cancer incidence.

Id. at vii-viii.

> Based on review of these data, CanTox concluded:
>
> Assessment of the factors that affect tumor development, respiratory patterns, respiratory tract physiology, mucociliary clearance, rate of cell turnover, detoxification metabolism, DNA-binding and DNA repair, and lower delivered doses of formaldehyde to nasal tissues of primates compared with rats leads to the conclusion that at 1 ppm the operation of protective mechanisms would eliminate the risk of developing formaldehyde-induced cancer of the upper respiratory system.

Id. at 195.

II. PUBLISHED STUDIES SHOW FORMALDEHYDE IS NOT GENOTOXIC IN VIVO

The Draft Document's discussion of genotoxicity continues to be one-sided. While formaldehyde has been shown to be weakly genotoxic in vitro, the Draft ignores the thrust of the Institute's March 26, 1991 comments -- that as a result of protective mechanisms formaldehyde is not genotoxic in vivo. The Brusick study[6] showed formaldehyde is not mutagenic at levels up to 25 ppm in live animals repeatedly exposed through inhalation. In live animals, the presence of various defense mechanisms (such as metabolic deactivation of inhaled formaldehyde, cellular repair processes, and the protective action of mucus) affect the action of formaldehyde.

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[6] Brusick, "Genetic and Transforming Activity of Formaldehyde," in Formaldehyde Toxicity (Gibson, ed., 1983) at pp. 72-84.

A panel of scientists which reviewed the literature on genotoxicity in a report for the government of Ontario concluded:

> The genetic toxicity of formaldehyde has been studies extensively in both in vitro and in vivo test systems. . . .
>
> The results of in vivo studies of genetic toxicity are equivocal and positive results, when obtained, were generally marginal and occurred only at very high exposure rates (25 ppm) No consistent positive results have been reported in dominant lethal studies in rats and formaldehyde failed to induce micronuclei or chromosome aberrations in vivo.
>
> While formaldehyde has been shown to be weakly genotoxic in several test systems in vitro, there is no substantial evidence that it is mutagenic in mammalian systems in vivo. The nasal mucosal epithelium has not been studied in this regard. This lack of clear evidence of genotoxicity in vivo may be explained by the rapid metabolism of formaldehyde in intact animals.

I. Munro, E. Farber & L. Golberg, "Review of the Available Information on the Health Effects of Formaldehyde on Behalf of the Ontario Ministry of Labour" (Mar. 1985), Ex. 1. Genotoxicity studies are, of course, of less relevance given the extensive data base on animal carcinogenicity and mechanism research.

III. THE DISCUSSION OF THE EPIDEMIOLOGIC DATA IS ONE-SIDED

As the Institute pointed out at pages 21-42 of its March 26, 1991 comments, CARB's discussion of the epidemiologic data is one-sided, ignoring that there is no overall excess risk of cancer among formaldehyde workers. The Institute will not duplicate that discussion here, but finds it especially disappointing that CARB totally ignores the refutation of the Sterling data by Dr. Gary Marsh of the University of Pittsburgh

who performed a reanalysis of the NCI cohort data.[7] The reanalysis corrected several flaws in the Sterling work, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to the different measures of exposure.

Marsh first compared its data set, which was in "excellent agreement" with the Blair data, and the data set used by Sterling and Weinkam. Marsh found that Sterling and Weinkam apparently made several cohort data management decisions which were not typical of current epidemiological practice, including (1) exclusion of deaths with no death certificates, (2) exclusion of deaths with unknown vital statistics, (3) inclusion of unknown job types with hourly workers, and (4) for purposes of the observed death data, inclusion of unknown race with the non-white cohort. However, even after taking these data management decisions into account, Marsh found that Sterling and Weinkam apparently made a significant counting error in computing person years at risk. Marsh Report at pages 8-9.

Marsh then reanalyzed the data to correct several flaws in Sterling and Weinkam's analysis, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to different measures of exposure. Marsh stated:

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7 Marsh, et al., "A Reanalysis of the National Cancer Institute Study on Mortality Among Industrial Workers Exposed to Formaldehyde" (Mar. 1990), Ex. 15.

> We did not confirm Sterling and Weinkam's finding of an increased risk for lung cancer mortality as a function of cumulative formaldehyde exposure, adjusting for length of exposure. Lack of adjustment for length of exposure did not mask a positive association . . . . We found no evidence of a positive trend with cumulative exposure in the models we considered . . . . There was no evidence of confounding by calendar time. . . . Latency was the only statistically significant exposure measure among those we considered (cumulative exposure, average exposure, length of exposure, exposure with particulates, exposure without particulates, and latency).

Id. at 21. Marsh concluded that "[u]nlike Sterling and Weinkam, none of our estimates [relating to cumulative formaldehyde exposure] were statistically significantly elevated and the trend with cumulative exposure was not statistically significant." Id. at 22. CARB's statement at p. 170 that Sterling was unrefuted is flatly incorrect and its analysis does not seem objective.

Similarly, CARB has ignored the published findings of the distinguished panel chaired by Dr. John Higginson, the former chairman of the International Agency for Research on Cancer (IARC), which rejects the assertion that the epidemiologic data indicate formaldehyde presents cancer risk to humans.[8] Based on review of all of the human epidemiologic studies, including the

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[8] Also participating on the panel were Ole M. Jensen, M.D., Danish Cancer Registry; Leo Kinlen, M.D., F.R.C.P., University of Edinburgh; Werner H. Kirsten, M.D., University of Chicago Medical School; Brian MacMahon, M.D., Harvard School of Public Health; Genevieve M. Matanoski, M.D., Dr.P.H., The Johns Hopkins University; Thomas J. Smith, Ph.D., University of Massachusetts; Duncan C. Thomas, Ph.D., University of Southern California.

recent NCI data, the report concluded that there is no convincing evidence of human cancer risk:

> Two conclusions from this review that would have widespread agreement among epidemiologists are: (1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure; and (2) furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small.

UAREP, "Epidemiology of Chronic Occupational Exposure to Formaldehyde," Tox. Ind. Health 4:77 (1988). Respecting specific sites for cancer, UAREP found:

- "[N]either the presence nor the absence of an association between formaldehyde exposure and sinonasal cancer can be said to be firmly established. It should be noted that even a doubling of this rare form of cancer represents a very small absolute risk."

- Regarding nasopharyngeal cancer, "These shortcomings and inconsistencies [of the epidemiologic studies] indicate that the association of nasopharyngeal cancer with formaldehyde exposure must be regarded as weak. However, it is to be noted that despite extensive studies no definite evidence exists in humans that nasopharyngeal cancer can be produced by inhaled carcinogens."

- "More data are available about lung cancer and formaldehyde than for any other topical site . . . . Overall, the evidence is not indicative of an association between formaldehyde exposure and lung cancer risk."

Id. at 81-83. The report is cited by CARB, but its findings are not reflected in the Draft's discussion of the epidemiology data.

IV. CARB MISCHARACTERIZES THE INSTITUTE'S COMMENTS REGARDING THE EDLING AND HOLMSTRUM STUDIES

The Draft (at p. 171) mischaracterizes the Institute's comments on the Edling and Holmstrum studies. The Institute's comments addressed much more than the small size of those

studies. In particular, the Institute raised the following concerns:

- There is no statistically significant correlation between the observations and degree and duration of formaldehyde exposure.
- Alterations of the nasal mucosa have many possible causes, including smoking and passive smoking. There was insufficient examination of the confounders.
- The control group was too small to be representative of the population as a whole.
- There is insufficient characterization of the formaldehyde exposure levels.
- These results are inconsistent with other studies of the nasal mucosa of formaldehyde-exposed workers. Berke, et al., 29 J. Occup. Med. 681 (1987) (finding no associated of abnormal cytology and formaldehyde exposure when controlling for age).

See Comments provided in Ex. 20. CARB has failed to consider or respond to these points.

V. THE SOFFRITTI INGESTION STUDY HAS BEEN DISCREDITED

CARB also relies on the suspect Soffritti [ingestion study] in lieu of [a] well-conducted ingestion study[9] such as the Til [study] that find that formaldehyde is not tumorigenic even at high doses. As the Institute pointed out in its March 26, 1991 comments,

- The Soffritti study does not indicate the substance being ingested. Because the report mentions impurity by methanol, it is possible that the study used formalin rather than formaldehyde as the test material.
- Incidence of stomach tumors -- the observation on which the authors rely for their conclusions -- did not

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[9] Til, et al., "Two-Year Drinking Water Study of Formaldehyde in Rats," 27 Food Chem. Tox. (1989).

differ significantly from the background rate observed in historical controls. An increase in the embryo group appeared only by combining different stomach tumor types with various gastrointestinal tumors. The tumors did not exhibit a clear dose-response relationship.

- The report does not present statistical evaluation of the data or time-to-tumor information.
- The test animals were not sacrificed at designated intervals, but rather were allowed to live until spontaneous death, which would be expected to result in a higher cancer incidence rate.
- There was no analysis of clinical chemistry, urinalysis, hematology, or non-cancer pathological response. These gaps make interpretation of the study results difficult.

Detailed comments on the Soffritti study were provided in Exhibit 19.

In contrast to the Soffritti and Takahashi studies, the Til study was a state of the art study, more extensive, more fully analyzed, more carefully monitored, and more definitive.

The September 1991 Draft (at 182) states that CARB would be willing to consider any published rebuttal or critique of the Soffritti study but that no such publications are available. That is incorrect. Drs. Feron, Til and Wouterson, distinguished scientists with the independent TNO-CIVO Toxicology and Nutrition Institute in the Netherlands, have published a letter critiquing the study, including the absence of "crucial information on procedures and histopathology of non-neoplastic lesions . . . ." Feron, et al., "Letter to the Editor," Tox. Ind. Health 6:637-38 (1990), Attachment A. Further, it is important to note that Drs. Feron and Til have attempted to

contact Drs. Soffritti and Maltoni by letter and telephone on numerous occasions to seek to resolve the differences in results of the Til and Soffritti studies. No response has been received.[10] Under these circumstances, the Soffritti study should be accorded no weight.

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10 Dr. Feron could be contacted by the CARB staff if further information were needed.

CONCLUSION

Although the September 1991 Draft Document reflects some improvement over the earlier Preliminary Draft, many of the comments by the Institute and Drs. Starr and Swenberg have not been adequately addressed. Further, additional time is needed to address the new and highly complex calculations presented in Appendix A.

Extension of the comment period to enable consideration of the Institute's forthcoming technical comments, as well as further attention to the Institute's March 26, 1991 comments as discussed herein, could provide CARB with better scientific basis for a decision whether to list formaldehyde as a toxic air contaminant.

Respectfully submitted,

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October 18, 1991

ATTACHMENT A

Toxicology and Industrial Health, Vol. 6, No. 6, 1990 637

LETTER TO THE EDITOR

Sir—In their article on 104-week drinking water studies of formaldehyde in Sprague-Dawley rats Soffritti et al (1989) concluded that "formaldehyde must be considered a multipotential experimental carcinogen". The results of their studies, in combination with the well-known fact that prolonged inhalation exposure to high, cytotoxic concentrations of formaldehyde vapour may lead to nasal tumours in rats, formed the basis of this conclusion.

We disagree with this conclusion and we do not see that the *preliminary* results reported by Soffritti et al would justify such a bold conclusion. These authors reported increased incidences of leukemias and gastro-intestinal tumours in formaldehyde-treated rats. However, statistical analysis of the tumour data (Fisher's exact test; two-sided) showed that for leukemias there was in no case statistical significance when the incidences in test groups were compared with those in the methyl alcohol control group. Moreover, a search in the literature for historical control data on Sprague-Dawley rats of the colony used demonstrated that leukemia incidences in groups of untreated controls vary widely (Ciliberti et al., 1988; Conti et al., 1988; Cotti et al., 1988; Maltoni et al., 1988; 1989) and may be as high as 19% (males) or 14% (males + females) (Maltoni et al., 1988). This may also be valid for studies using other colonies of Sprague-Dawley rats (Arnold et al., 1985; Berger et al., 1985). Therefore, the somewhat high incidences of leukemias (at most 22% in males or 18% in males + females) in several test groups of the Soffritti et al-study may well be chance effects unrelated to formaldehyde ingestion.

The incidences of gastric and intestinal tumours were statistically significantly increased in formaldehyde-treated offsprings (but not in breeders), and when taken together as gastro-intestinal tumours also in the high dose group of rats 7 weeks old at the start of the study. Gastro-intestinal tumours were found in both breeders and their offspring, and in the groups of 7-week old rats receiving 10, 50, 1000 or 1500 mg/l, but not in rats receiving 100 or 500 mg formaldehyde/l. In addition to the striking distribution of the gastrointestinal tumours over the various groups i.e. the lack of a dose-response relationship, the strong heterogeneity of both the gastro-intestinal tumours (adenomas, adenocarcinomas, squamous cell carcinomas, papillomas, acanthomas, leiomyomas and leiomyosarcomas) and the leukemias (lymphoblastic leukemia, lymphoblastic sarcoma, immunoblastic lymphosarcoma and other types of leukemias and haemolymphoreticular sarcomas) is remarkable.

It is also striking that, apart from gastric papillomas, none of the tumour types

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mentioned has been observed in any of the other long-term oral (or inhalation) studies with formaldehyde in rats reported so far (Takahashi et al., 1986; Til et al., 1989; Tobe et al., 1989). It is surprising that none of these oral studies have been discussed by Soffritti et al (1989): Takahashi et al published their study in 1986, and preliminary results of the Til et al-study were already reported during international meetings in 1986 and 1988 (Feron, 1986; 1988; Clary et al., 1988). The results of these previous studies should have been discussed, particularly because they differ dramatically from the findings of Soffritti et al (1989).

As far as the statements of Soffritti et al (1989) regarding humans are concerned the authors considered from the many epidemiological studies published only the very few older ones included in a review by Nelson et al (1986). The numerous newer ones were omitted, as was a more recent review by an international Ad Hoc Panel on Health Aspects of Formaldehyde chaired by Professor J. Higginson, previous Director of the International Agency for Research on Cancer (Universities Associated for Research and Education in Pathology, Inc., 1988) concluding: "For no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure and furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small".

Since crucial information on procedures and histopathology of non-neoplastic lesions in the Soffritti et al-paper is lacking, the adequacy of the study and the relevance of the data obtained can hardly, if at all, be judged. We do hope that the *definitive* results will soon be published and will be discussed in the light of relevant findings of other investigators who published their studies in full detail.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 15 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
California Air Resources Board
Attention: Formaldehyde
1102 Q Street
Sacramento, CA 95814

Dear Ms. Shiroma:

We received the document, Proposed Identification of Formaldehyde as a Toxic Air Contaminant, but not until October 7, 1991, although the cover letter was dated September 20. Thus there has not been sufficient time to review the document thoroughly, especially the new sections concerning cell proliferation modelling and the third interspecies scaling factor. In an attempt to meet your October 15 deadline for comments, a preliminary list of remarks follows:

- The Summary (pp. 1-2,1-6) should indicate more clearly which UCL unit risk estimates incorporated cell proliferation modelling, and which did not. The discussion concerning scaling factors is not quite clear, either, as to which unit risk estimates incorporate which scaling factors. My understanding from Appendix A is that cell proliferation modelling was ultimately not used, and that the default scaling factor of 1.2 was considered most appropriate. These sections should coordinate better.

- The "best estimate" UCL on unit risk (p. 1-6) would be better described as your most plausible value, because "best estimate" has become statistical jargon which implies a different situation than the Summary describes. Incidentally, this value (7.0×10^{-3} ppm^{-1}) is close to the value EPA will be considering the upper value for its range of UCL values; EPA will not choose a single unit risk estimate at this time.

- Relationship of Predictions to Observed Human Cancer Risks, p. 2-20 - The use of lung cancer incidence and the

assumption of 2.0 ppm exposure associated with non-sedentary activity are not adequately justified. In relation to formaldehyde exposure, lung cancer was not as clearly in excess as was nasopharyngeal cancer in the Blair et al. study. Concerns were noted in the document explaining why the excess lung cancer may not be entirely due to formaldehyde exposure. In addition, it would probably be more realistic to halve the exposures in less active scenarios when trying to generalize to other situations, than to double the estimated exposures in the Blair study.

- p. 2-10, first sentence - The estimation method used for the dosimetric model appears to have involved a least-squares procedure to obtain a best fit between the observed rate of binding of formaldehyde to DNA (y) and the exposure concentration (X), instead of a fit between the predicted and observed values of y, which would probably be a straight line with a slope of unity.

- The discussion of the third scaling factor might be easier to follow if the dimensional units of the variables were included (p. A-14).

A more complete list of remarks on this document will follow in a few days from the Health and Environmental Review Division (Office of Toxic Substances).

Sincerely,

Karen A. Hogan

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OCT 16 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
California Air Resources Board
Attention: Formaldehyde
1102 Q Street
Sacramento, CA 95814

Dear Ms. Shiroma:

Thank you for providing the Office of Toxic Substances an opportunity to review the State of California Air Resources Board's draft documents, Proposed Identification of Formaldehyde as a Toxic Air Contaminant (September, 1991). Regrettably we did not receive these reports until October 7, 1991, although the cover letter was dated September 20. Thus, there has not been sufficient time to review the document thoroughly, especially the new sections concerning cell proliferation modelling and the third interspecies scaling factor. In an attempt to meet your October 15 deadline for comments, a preliminary list of remarks follows:

- The revised cancer risk assessment incorporates several different methodologies and assumptions (e.g. models, species scaling factors) and presents as a range of risks which are within two order of magnitude ($0.31-41.0 \times 10^{-3}$ ppm^{-1}) but endorses the use of the unit risk derived from a three-stage tissue-based (pharmacokinetics) model with a rat to human scaling factor of 1.2 as the **best estimate of Upper Confidence Limit (UCL) on unit risk** (i.e., 7.0×10^{-3} ppm^{-1}) . The Summary (pp. 1-2, 1-6) of Part B Health Assessment should indicate more clearly which UCL unit risk estimates incorporated cell proliferation modelling, and which did not. The discussion concerning scaling factors (Appendix A) is not quite clear, either, as to which unit risk estimates incorporate which scaling factors. These sections should coordinate better.

- The "best estimate" UCL on unit risk (p. 1-6) would be better described as the reference value, because "best estimate" has become statistical jargon which implies a different situation than the Summary describes. Reference value is a more neutral term and it should be accompanied with the appropriate qualifiers as to it being a current judgement in the midst of a number of possibilities.

- Relationship of Predictions to Observed Human Cancer Risks, (p. 2-20, Part B) - The use of lung cancer incidence and the assumption of 2.0 ppm exposure associated with non-sedentary activity are not adequately justified. In relation to formaldehyde exposure, lung cancer was not as clearly in excess as was nasopharyngeal cancer in the Blair et al. study. Concerns were noted in the document explaining why the excess lung cancer may not be entirely due to formaldehyde exposure. In addition, it would probably be more correct to halve the exposures in less active scenarios when trying to generalize to other situations, than to double the estimated exposures in the Blair study.

- p. 2-10, Part B, first sentence - The estimation method used for the dosimetric model appears to have involved a least-squares procedure to obtain a best fit between the observed rate of binding of formaldehyde to DNA (y) and the exposure concentration (X), instead of a fit between the predicted and observed values of y, which would probably be a straight line with a slope of unity.

- The discussion of the third scaling factor might be easier to follow if the dimensional units of the variables were included (p. A-14).

Please contact Dr. Vanessa Vu (202-260-1256) should you have any questions regarding these comments and suggestions.

Sincerely,

Joseph A. Cotruvo, Ph.D.
Director
Health and Environmental
Review Division (TS-796)

COMMENTS ON THE CALIFORNIA AIR RESOURCES BOARD PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT SEPTEMBER 1991 DRAFT SRP VERSION

Prepared for

The Formaldehyde Institute
Washington, DC

Prepared by

Thomas B. Starr, Ph.D. and Principal
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10 November 1991

COMMENTS ON THE CALIFORNIA AIR RESOURCES BOARD PROPOSED IDENTIFICATION OF FORMALDEHYDE AS A TOXIC AIR CONTAMINANT SEPTEMBER 1991 DRAFT SRP VERSION

1. Introduction

In a preliminary draft report dated February 1991, the California Air Resources Board (CARB) proposed that formaldehyde be identified as a toxic air contaminant. CARB based this proposal in part on the California Department of Health Services' (DHS) "best value of potency for unit risk" associated with airborne formaldehyde exposure, namely, 29×10^{-6} $ppbv^{-1}$ (i.e., 0.029, or approximately 3%, per ppm). Detailed comments on the February 1991 draft have been submitted to CARB previously (ENVIRON, 1991). An extensive verbal presentation describing concerns with the February draft document, as well as mechanistic issues that require full and proper consideration, was also made at the public workshop on formaldehyde risk assessment held by CARB in Sacramento in early April 1991.

The draft SRP Version dated September 1991, which is the subject of the present comments, has reduced CARB's previous unit risk estimate by over 4-fold, to 0.007, or 0.7%, per ppm. The reduction arises solely as a consequence of CARB's election to use California's default interspecies scaling factor of 1.2, rather than the 5.0-fold generic contact scaling factor that CARB derived and employed previously.

The current draft document does consider two mechanistic issues in much greater detail than did the earlier draft. First, the role of enhanced cell proliferation in formaldehyde's carcinogenicity at high airborne concentrations has been explored by CARB. In fact, twelve distinct dose-response models incorporating different kinds of cell proliferation effects on the cumulative hazard function for nasal tumors were fit to the CIIT bioassay data using specific cell proliferation data (in the form of ratios of labeling indices) and molecular dosimetry data (in the form of DNA-protein crosslink concentrations), rather than airborne formaldehyde concentration, as the independent variable. Five of these models were subsequently used by CARB to develop unit risk estimates, which ranged in value from 0.0011 to .0079 per ppm (without interspecies scaling). This range brackets the corresponding unit risk estimate of 0.0058 per ppm, which CARB obtained with a 3-stage version of the conventional multistage model.

CARB described this range as "informative", but elected to use the conventional 3-stage model estimate, after scaling by the 1.2-fold default interspecies factor, since "no single cell proliferation approach appears justified as a best estimate at this time."

Second, CARB examined the implications of its previously derived generic contact scaling factor (5-fold for rat-to-human extrapolation) by comparing the monkey-to-rat DNA-protein crosslink ratio predicted by this factor to the ratio that had actually been observed by Casanova et al. (1989) and Heck et al. (1989). CARB noted that their generic contact scaling factor (2.66 for rat-to-monkey extrapolation) overpredicted the observed ratio by more than 26-fold, and they commented that this large discrepancy merited investigation and reconciliation.

CARB therefore explored a third approach to interspecies scaling, the "local dosimetric approach." This approach attempted to account for the local pattern of formaldehyde deposition from the inhaled airstream along the upper respiratory tract walls. It yielded a rat-to-human scaling factor of 0.28, approximately 18-fold lower than CARB's generic contact scaling factor of 5.0, and 4.3-fold lower than its default scaling factor. CARB nevertheless finally elected to use its default scaling factor (1.2 for rat-to-human), stating that "conflicting evidence prevents making a clear case for using either form of contact scaling factor."

In the end, then, the revised quantitative risk estimate recommended in the September 1991 draft SRP version of CARB's formaldehyde document differs from the earlier estimate solely in CARB's election to use the default interspecies scaling factor of 1.2, rather than the generic contact scaling factor of 5. While data regarding cell proliferation in rats and DNA-protein cross-linking in monkeys that were considered point toward reduced human cancer risk, these data were not utilized at all in CARB's final risk computations.

In our previous comments regarding CARB's February 1991 draft document (ENVIRON, 1991), we expressed a firm conviction that "the best presently available scientific evidence provides a compelling basis for concluding that CARB and DHS have overstated the potential human cancer risks from formaldehyde exposure by a very substantial margin." That conclusion applies equally well to the September 1991 draft, because the critical cell proliferation and DNA-protein crosslink data have again been unjustifiably disregarded. Indeed, when only one component of this evidence, namely, the extent of formaldehyde-induced DNA-protein crosslinking in monkeys, is fully and properly taken into account, then CARB's new upper bound estimate of human cancer potency is reduced by a factor of approximately 13-fold.

CARB has also continued to assume that different temporal exposure patterns corresponding to a given continuous lifetime exposure all yield the same cancer risk.

Because this assumption stands in direct contradiction to the acknowledged amplifying effects of increased cell replication on the carcinogenic process at high, but not low, formaldehyde concentrations, it introduces additional conservative bias into CARB's upper bound estimates of human cancer risk, further exaggerating the risks associated with low exposure levels. CARB's own computations indicate that this bias may be as large as another 5.3-fold factor. Taken together, CARB's failure to fully and properly account for the currently available DNA-protein crosslink and cell proliferation data imply an overestimation of human cancer risk from formaldehyde exposure by as much as 69-fold. These and other flaws in the revised CARB formaldehyde health assessment are discussed in greater detail in subsequent sections of these comments.

2. DNA-Protein Crosslinking

The CARB cancer potency factor of 7×10^{-3} ppm^{-1} was derived from an analysis of nasal cancer incidence among rats exposed for up to two years to 0, 2, 5.6, or 14.3 ppm formaldehyde vapor for six hours per day, five days per week (Kerns et al., 1983). CARB employed a pharmacokinetic model of DNA-protein crosslink (DPX) formation nearly identical to one originally developed by Casanova et al. (1989) to describe the nonlinear dependence of DPX formation in the rat nasal mucosa upon airborne formaldehyde concentration. The predicted levels of DPX were then multiplied by two scaling factors, 1.2 ppm/(pmol/mg-hr) and 30 hr/wk/(168 hr/wk) to express the DPX levels in ppm units of "lifetime equivalent metabolic exposure." For example, 15.0 pmol/mg is the DPX level predicted to result from exposure of rats for 6 hours to 2 ppm formaldehyde, and also from 24 hour (i.e., continuous) exposure to 0.54 ppm. CARB then fit various dose-response models to the rat bioassay data with this scaled DPX level as the independent variable.

The CARB model of DPX provides a reasonably accurate description of the relationship between DPX and airborne formaldehyde concentration, but, as we have noted previously (ENVIRON, 1991), it also consistently overpredicts the DPX levels observed in rats exposed to low concentrations. For example, after 6 hours exposure to 0.3 ppm, while 1.4 pmol/mg DNA was actually measured by Casanova et al. (1989), CARB's equation (1), with the parameter values given in Table 1, predicts a DPX value of 1.59 pmol/mg DNA, about 14% higher than the observed value. Such overpredictions are expected to occur at all of the comparatively low airborne concentrations of concern to CARB. This conservative bias in DPX prediction at low airborne formaldehyde concentrations should be corrected, even though it is quite small when compared to the overpredictions resulting from CARB's interspecies extrapolation procedures and its failure to adequately account for formaldehyde's effects on cell replication in target

tissues.

3. Cell Replication

As we have already noted, the September 1991 draft document describes an extensive exploration of the potential impact of cell proliferation data on CARB's unit risk estimates. The model-fitting experiments utilized an approximate form of the two-stage growth model with time-invariant parameters proposed by Moolgavkar and Venzon (1979). They also employed certain proliferation data collected in rats following twelve months of formaldehyde exposure. In essence, CARB assumed that proliferation would have an effect on tumor response only in the highest bioassay dose group (14.3 ppm), where replication was taken to be constant (i.e., time-invariant), and approximately 10-fold greater than that occurring in control animals.

However, it is known that cell proliferation also increases dramatically, though in a transient fashion, in rats exposed to 6 ppm formaldehyde (Monticello, 1990). Specifically, cell proliferation was observed to be over 10-fold greater in animals exposed to 6 ppm for six weeks, yet by three months, turnover appeared to return to control levels. Nevertheless, CARB's assumption of no increased cell proliferation at all in this treatment group is certain to underestimate its true effect on tumor response. Furthermore, as CARB has noted, it is the 5.6 ppm group that is the most influential treatment group in determining the unit risk for formaldehyde. It would be very useful to explore the effect on the unit risk estimate of setting R > 1 for this group.

The fact that cell proliferation is not constant during chronic exposure conditions points up an additional shortcoming in CARB's exploratory proliferation approaches: they have all assumed that exposure will alter cell proliferation solely in a manner that is independent of the exposure duration. CARB's risk estimation should be modified so as to fully and properly account for the explicitly time-dependent effects on proliferation that are known to be present. Also, CARB has failed to take account of the detailed time-to-tumor information that is presently available regarding the 14.3 ppm dose group (Kaplan-Meier estimates of survival in this group were first reported by Starr et al. (1985)). These data provide an excellent additional opportunity to test the adequacy (or lack of it) of the cell proliferation models explored by CARB.

4. Interspecies Extrapolation

Appendix A of the draft health assessment document describes the approaches CARB has employed in extrapolating human cancer risks from the corresponding predicted rat risks. The first, denoted as the default approach, has apparently been employed in other cases "in the absence of decisive empirical evidence" for some other

scaling procedure. It is predicated on the assumption that "equal rates of intake of carcinogen per species body-surface area imply equal risks" in different species. After adjusting for the comparatively less efficient absorption of the human respiratory tract and accounting for interspecies differences in respiratory minute volume and body-surface area, CARB concluded that rats and humans would receive the same formaldehyde dose (intake rate per body-surface area) and hence experience the same cancer risk, if the rats were exposed to airborne concentrations 1.2 times higher than humans. This default scaling approach further implies that for a given airborne concentration, humans would experience about a 20% greater formaldehyde intake rate per body-surface area than rats and hence a 20% greater lifetime cancer risk.

CARB's second approach, termed the generic contact approach, purports to account for "the contact mechanism of carcinogenesis, in which the average concentration in the respiratory surface layer provides the measure of dose to characterize risk." CARB's resulting calculations lead to a scaling factor of 5.0. In other words, with this generic contact scaling assumption, CARB has concluded that rats and humans would receive the same formaldehyde dose at the target tissues in the respiratory tract if the rats were exposed to airborne concentrations five times higher than humans. This generic contact scaling approach thus also implies that for a given airborne concentration, humans would experience about a 5-fold greater formaldehyde dose at the target tissues and hence a 5-fold greater lifetime cancer risk.

CARB's third approach, termed the dosimetric contact approach, attempts to describe the longitudinal gradient in formaldehyde concentration that would obtain during stead-state inspiratory flow as it relates to depth of penetration, anterior airway surface area, and volumetric inflow rate. While this approach represents an improvement over CARB's generic scaling approaches, it is nevertheless very crude, and is not likely to provide accurate quantitative predictions of species differences in dosimetry. For example, CARB employed an approximate formula for penetration of a contaminant gas along an airway (equation A-16) in deriving its dosimetric contact scaling factor. This equation is really valid only for straight cylindrical passages of constant cross-section with unlimited and homogeneous absorptive capacity. It does not account for nasal airway curvature, the numerous flow bifurcations created by the presence of obstructing nasal turbinates, or the active countercurrent system of mucociliary flow. These physiologic and anatomic features induce locally complex turbulent flows and deposition "hot spots", where the airstream's boundary layer can become sharply compressed, the "deposition velocity" can peak, and the finite absorptive capacity of the respiratory tract surface layer can become overwhelmed. In addition, because the nasal passages are of highly variable cross-sectional area and perimeter, the

parameter k, which CARB has assumed to be a species-specific constant, will almost certainly be significantly dependent upon the depth of airway penetration.

Finally, CARB cites Heck et al. (1989) as providing the high dose binding data from which CARB's rat- and monkey-specific estimates of nasal penetration were obtained. First, it is not appropriate to use the high dose binding data to estimate the extent of airway penetration that occurs at lower concentrations because, as Heck et al. noted, airway penetration was demonstrably dose-dependent, with significantly less penetration occurring at low than at high formaldehyde concentrations.

Second, it is not clear how CARB derived its estimates of airway penetration for rats and monkeys (0.03 and 0.7 respectively, as presented in Table A-3) from the data provided in Heck et al. (1989). Those investigators only reported nasal "absorption efficiencies" of > 0.93 for rats and 0.7-0.9 for monkeys.

In our critique of CARB's February draft (ENVIRON, 1991), we demonstrated that CARB's default and generic contact scaling factors were both inconsistent with what is known regarding the molecular dosimetry of airborne formaldehyde in rodents and primates. In the September 1991 draft, CARB acknowledged this inconsistency with regard to its generic contact scaling factor, but not with regard to its default scaling factor. We therefore summarize our earlier analysis for the default scaling factor here.

The Rhesus monkeys employed by Heck et al. (1989) weighed approximately 7 kg, i.e., 1/10 the 70 kg human body weight employed by CARB. Assuming that the monkey respiratory tract absorption efficiency is comparable to that of the human (namely, 76% that of the rat), the default scaling factor for monkeys is readily calculated:

$$(a_m/a_r)(W_m/W_r)^{0.08} = (0.76)(7.0/0.25)^{0.08} = (0.76)(1.31) = 0.99.$$

Thus, the default scaling procedure predicts that monkeys and rats should receive practically identical target site doses when both are exposed to the same airborne formaldehyde concentration.

The measured values of DPX in monkey respiratory mucosa reported by Heck et al. (1989) are clearly inconsistent with these predictions. Indeed, at the lowest airborne formaldehyde concentration (0.7 ppm) for which DPX measurements were made in both rats and monkeys, the rat DPX value following 6 hours of exposure was 3.9 pmol/mg DNA, while the corresponding monkey DPX value was 0.36 pmol/mg DNA, i.e., 10.8-fold lower. Thus, when CARB's default scaling procedure is applied where DPX measurements exist for comparison, it overpredicts the observed DPX in monkeys by about a 10.7-fold factor. It should be noted that this default scaling procedure also predicts that DPX in humans under these conditions should be (1.2)(3.9 pmol/mg DNA) = 4.7 pmol/mg DNA, i.e., approximately 13-fold greater than was observed in the monkeys.

The findings of Heck et al. (1989) and Casanova et al. (1989) are described in considerable detail on pp. 2-8 and 2-9 of the CARB draft document. In particular, CARB noted that the "monkeys had much lower (up to 10-fold) concentrations of crosslinks in the nasal turbinates and anterior nose than did rats at a given formaldehyde concentration." However, the utility of these data was characterized as limited "because it is not known how susceptible monkeys are to formaldehyde-induced carcinogenesis." Despite this and other objections CARB has speculatively raised, the monkey DPX data can and should be used to estimate human cancer risk, as has been demonstrated and recommended by Starr (1990) and, subsequently, by the US EPA in its recent draft update (USEPA, 1990) and final draft update (USEPA, 1991) of its 1987 formaldehyde health assessment document. It should also be noted that in October 1990, the US EPA's Science Advisory Board concurred with this recommendation, and encouraged the Agency to complete its risk assessment for formaldehyde by making use of the monkey DPX data.

At the present time, it remains our firm conviction that the Rhesus monkey provides the best available animal model for DPX formation in humans exposed to formaldehyde. Heck et al. (1989), Starr (1989, 1990), USEPA (1990 and 1991), and CARB have all noted that the monkey is far closer to the human than the rat in terms of its respiratory anatomy, physiology, and breathing patterns. Until direct measurements of DPX in humans are available, the most plausible and scientifically defensible assumption is that humans develop DPX, and experience attendant cancer risk following formaldehyde exposure, to the same extent as do monkeys. CARB should not continue to disregard these data, as they provide the best available scientific information relevant to estimating a human cancer potency factor for formaldehyde.

5. References Not Already Cited in the September 1991 CARB Draft

Starr, T.B, J.E. Gibson, and J.A. Swenberg. 1985. An integrated approach to the study of formaldehyde toxicity in rats and mice. In Toxicological Risk Assessment, Vol. 2. Clayson D.B., Krewski D.R., Munro I.C., eds., pp. 195-210, CRC Press, Boca Raton.

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24th April, 1991

Genevieve Shiroma, Chief
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Air Resources Board
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Dear Madam

EPA Formaldehyde Risk Assessment Update of Sept 24th, 1990

Please find a copy of my comment report on the above review document attached. This is additional information to that sent in to you on 27th March, and which I have mentioned to Robert Krieger.

In dealing with the risk of cancer from human contact with individual chemicals it is reasonable as a first approximation to assume that there is no lower threshold limit in each one's cancer inducing mode. However, I now believe that in the case of formaldehyde, with the wealth of physico-chemical information becoming available and the additional positive information contained in my comments on why DPX is a valid indicator, the EPA's assumption of a "zero threshold" should be re-examined in this case. There is strong evidence in the EPA Revised Risk Assessment Report (1990) that such a positive threshold does indeed exist, and my report contains suggestions for a revised set of occupational and carcinogenic exposure limits.

If you have any queries, please feel free to contact me. From 29th April I will be at the new address/fax above - I am going up to read for an MBA at Wilfrid Laurier University in Waterloo, Ontario, lasting 1 year. If you wish to speak to me, either leave a message on (519) 884-1970 ext 2544, leave a fax, or write, and I will phone you as soon as possible.

Yours sincerely

PVL Barrett

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COMMENTS on, and SUGGESTIONS for, the

EPA FORMALDEHYDE RISK ASSESSMENT UPDATE

(External Review Draft of Sept 24th, 1990)

by

Dr P V L Barrett

24th April, 1991

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1 SUMMARY

The US EPA Formaldehyde Risk Assessment Update of Sept 24th, 1990, does an excellent job in pulling together all the latest information related to the health risk associated with exposure to formaldehyde.

However, the EPA report does not refer to the extensive experience base in the UK, and this report goes some way towards rectifying that situation. It provides additional support to the idea that the 1987 EPA report overstates the risk, and suggests a set of occupational and ambient exposure limits based on control of irritation and odor.

As a result of my extensive experience with formaldehyde, I am convinced that many complaints which have been ascribed to formaldehyde are more likely to be caused by reactions to excessive concentrations of fungal spores and mycotoxins. This therefore makes the analysis of the epidemiological surveys that much more difficult, particularly when the UAREP report commented that "the excess risk (of cancer from exposure to fomaldehyde vapour) must be small."

This report re-analyses the EPA DPX data and shows that both the rat and monkey data follow the same quadratic relationship with formaldehyde vapour concentrations, except for a 7.6 times larger nasal surface area in monkeys compared to rats. It is also shown that strong aqueous formaldehyde solutions follow a quadratic relationship with their vapour concentrations, and it is suggested that formaldehyde dissolved in the thick nasal mucosa behaves as if in a concentrated solution, and the DPX data are therefore following a normal vapour/liquid relationship. Since it is the liquid phase which is important in a study of carcinogenicity, it follows that DPX is a better indicator of potential risk, rather than the vapour concentration used directly. The EPA DPX interpolations need to be revised accordingly.

The EPA risk assessment of cancer from exposure to formaldehyde vapour is re-analysed, in particular the assumption of a zero threshold. This report concludes that such an assumption is no longer tenable. This report shows that using the unadjusted DPX data together with time adjusted risk factors from 4 long term rat studies, including 2 types of rat, a single straight line correlation is obtained with $R^2 = 0.9982$, and $P = 0.00003$. The zero threshold was found to be at a DPX value of 107 pmol/mg DNA/6 hours, equivalent to a formaldehyde vapour concentration of 5.7 ppm. The data standardisation procedure used in this report when comparing data and in making interpolations/extrapolations was confirmed by showing that Feron et al's short term data (4, 8 and 13 week exposures) agreed well with the long term data of 24 and 28 months.

A revised set of conservative cancer risk criteria are suggested, with vapour concentrations of 2 ppm and below being considered non-carcinogenic. Occupational criteria should therefore be based solely on control of the odor and irritancy of formaldehyde. A set of indoor and ambient criteria are also suggested.

NOTE: detailed technical references are only given in this report where they are not already in the EPA (1990) report.

2 UK EXPERIENCE WITH FORMALDEHYDE

In my opinion, the substantial UK experience with formaldehyde and the use of UFFI - a formaldehyde emitter - should be added to give a broader perspective to the EPA Review.

I have been involved with various aspects of formaldehyde since I joined ICI in the UK in 1974 as Technical Manager for their UFFI operation. I became Chairman of the British Standards working party which developed the Specification[1], Code of Practice[2] and Quality Assurance Scheme[3] for the installation of UFFI in masonry buildings. UFFI continues to be installed as an approved method under the UK Building Regulations when it is installed in compliance with the British Standards requirements. To date over 2.2 million buildings have been insulated with UFFI, and, taking a population of 52 million and a 19 million housing stock, this means that some 6 million people have lived in buildings at the time of the UFFI installation. When I left the company in 1981 to become a private consultant, I was personally responsible for over 300,000 UFFI installed buildings as Technical Director, which is more than the grand total insulated with UFFI in the US and Canada combined.

Long before formaldehyde became a health issue in the US, we always treated complaints of formaldehyde irritation subsequent to UFFI installation very seriously. I had to personally deal with all the more difficult cases for my Company, so I have had extensive direct experience.

According to the 1982 BSI Quality Assurance Programme Survey[4], copy attached as Table 1, there were only 0.2% complaints of formaldehyde irritation, and there were only 0.02% which had not been resolved by 8 weeks after the installation - usually the UFFI had penetrated into the building via a hole in the inner wythe of the outside wall. Note that in the period covered from Oct '80 to Sept '82, the survey covered a total of 176,486 installations. It should also be noted that with the tightening up in 1982 (after the St Thomas More School problem) of the BSI building survey requirements prior to installation and with the introduction of lower formaldehyde emitting resins subsequent to 1984, formaldehyde has virtually ceased to be a complaint issue in the UK with respect to UFFI. UFFI continues to be used in the UK.

Dr Lyn Everett of the UK Building Research Establishment presented a paper to the Formaldehyde Workshop in Arkansas in 1983[5] which described his measurements of indoor formaldehyde concentrations in UFFI homes in the year after installation. He found a peak of around 0.3 ppm 2 to 3 weeks after installation, which then decayed with a half-life of between 60 and 100 days to around 0.1 ppm at the end of the year. Subsequent decay has a much longer half-life; it appears to be a two stage process. The highest value which he measured was 1.6 ppm in a framed building. (From a

TABLE 1 BSI 1982 COMPLAINT SURVEY

UF FOAM INSTALLED IN BUILDINGS MEETING THE REQUIREMENTS OF CLAUSE 4. BS 5618: 1978 (Excluding Amendment No. 3)	1 Oct 1980 - 30 Sept 1982				1 June 1979 - 30 Sept 1980
	Domestic Buildings		Others		All Buildings
1. TOTAL NUMBER OF BUILDINGS FOAMED = 176,486					
a) Existing	153,185		8241		)
b) New (less than 1 year old)	5,433		359		) 151,309
c) Under construction	8,862		406		)
2. REPORTS OF WATER PENETRATION					
a) Existing	793	[52]*	1	[1]*	)
b) New	88	[162]	12	[334]	) 430 [28]*
c) Under construction	44	[50]	2	[49]	)
3. VERIFIED REPORTS OF PRESENCE OF FORMALDEHYDE					
a) Existing	408	[27]	47	[57]	)
b) New	9	[17]	2	[56]	) 337 [22]
c) Under construction	-		-		)
4. EXTENDED PRESENCE OF FORMALDEHYDE					
a) Total number of reports (3)	417	(100%)	49	(100%)	337(100%)
b) Lasting more than 14 days but less than 8 weeks	147	(35%)	36	(75%)	131 (39%)
c) Lasting longer than 8 weeks	36	(9%)	11	(22%)	64 (19%)
5. ROUTE BY WHICH FOAM/FORMALDEHYDE ENTERED BUILDING					
a) Reports of presence 14 days - 8 weeks	147		-		
(i) via gaps in inner leaf e.g. under bath/stairs	72		-		
(ii) via building/constructional faults	54		-		
b) Reports of presence longer than 8 weeks	36		-		
(i) via gaps in inner leaf e.g. under bath/stairs	12		-		
(ii) via building/constructional faults	12		-		
6. NUMBER OF INSTALLATIONS REPORTING PRESENCE OF FORMALDEHYDE WHICH REQUIRED ASSISTANCE FROM SYSTEM DESIGNER	36				

* [X] - representing X per 10,000 buildings foamed.

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general point of view these measured results are probably lower than typical because of the lower formaldehyde emissions from the Ufoam Plus UFFI system which was used in the test in the domestic homes (which had a citric acid catalyst rather than the more normal sulphuric/phosphoric system)). I would submit that before the new generation of low formaldehyde resins were introduced generally in the UK that normal peak values would have averaged closer to 0.5 to 0.6 ppm indoors 2 to 3 weeks after installation.

From my personal experience, most people cannot detect formaldehyde below 0.5 ppm, and it takes a very well trained person to recognise formaldehyde down to 0.3 ppm. At this level it is a transient irritation at the back of the throat, which rapidly disappears with acclimatisation. These odor threshold figures are supported by the low complaint level recorded in the BSI survey. The description of formaldehyde having a strong pungent odor is not really true until one experiences concentrations of 3 ppm and more. Below 1 ppm the pungency is relatively mild.

The unofficial, domestic indoor maximum in the UK remains at 0.5 ppm, as advised to the government by the BRE.

Whilst these odor threshold figures are mentioned in the EPA draft report, I would seriously disregard other claims of lower detection levels by people. It is extremely difficult to design an experiment which does not introduce a confounding factor, and I believe that the UK UFFI environment is relatively free from these factors and is a truer representation of the real situation. Such experimental confounding factors are cited in for example the report by Schuck et al.

The EPA report states that whilst one can acquire contact sensitisation by formaldehyde, there has been no convincing evidence that sensitisation can be induced by vapour inhalation alone. My experience would confirm this observation.

In 1982, a major formaldehyde problem arose in the St Thomas More School in Essex. Initial formaldehyde concentrations measured using a Draegar meter were as high as 2 ppm. Two staff claimed to be particularly "sensitised". The wall cavities of the steel frame building were between 6 and 10 inches wide, and were open in many places to the interior of the building. The British Standard was subsequently amended to ensure that such a building would be rejected at survey stage.

As a part of the remedial process I was asked to inject the UFFI in the school building with ammonia gas to neutralise the foam acidity and hence stop the formaldehyde evolution. Because of the unusual nature of the building I had to modify the ammonia gas injection technique and my first attempt was only partly successful, reducing the formaldehyde to an average of 0.3 ppm. However, the "sensitised" staff said that if anything the problem was then worse! I was requested to carry out a second injection and the formaldehyde was measured the next day by the Health & Safety Executive (a government agency) and was found to be on average only 0.03 ppm. Again the "sensitised" staff said that there was no

improvement. As a result, an intensive search was undertaken to find some other cause of their "sensitisation", see attached paper[6], and a survey was carried out to measure formaldehyde levels in all other buildings insulated with UFFI (137) under the same contract, some 4 to 10 months previously, as well as 17 uninsulated buildings and 14 insulated under previous contracts as controls - a total of 1,093 indoor measurements were made, mostly using chromatropic acid and some MBTH.

The results of the survey of the controls are given in the second attached paper[7], and the full results are shown on the attached graph, Fig 1, taken from the report to Essex County Council[8]. What this information shows is that the majority of the UK population has likely been exposed to indoor formaldehyde levels of 0.05 ppm and above, from UFFI and other sources, with many in UFFI insulated buildings having been exposed at up to 1 ppm, yet many were not aware even at this level. Note that at the time of the survey remedial action had already been taken at the worst sites, including the St Thomas More school.

When handling the problems in Essex, I did suggest that one of the best tests would be to take volunteers, of various claimed formaldehyde susceptibility, to various homes and buildings which had a range of measured formaldehyde concentrations, and to observe their responses, both on entry and up to 2 hours afterwards, in a proper double blind design. Unfortunately the medical officers thought I would be wasting their time as they did not take the problem that seriously.

In another case in which I treated a private home which had formaldehyde concentrations between 0.3 and 0.5 ppm a year after the installation of the UFFI, the complainants' problem disappeared with reduction of the formaldehyde off-gassing from the UFFI using the ammonia gas injection procedure[9].

3 OTHER CONFOUNDING ODOR/IRRITANT FACTORS

One has therefore to question why there is no major problem with formaldehyde in the UK, particularly with such a substantial installation base. By contrast, UFFI was banned in both the US and Canada in 1980/81 after far fewer installations. I believe that the most fundamental reason is that the majority of the American buildings insulated are of wood frame construction, whereas the majority of those in the UK are of masonry construction. Also the air-tightness of those in the UK is less because they do not experience the extreme cold of a continental climate in winter. As a result, in American homes insulated with UFFI and in mobile homes, there was often a higher initial formaldehyde concentration and hence more irritation. However, the building tightness does not account for the higher incidence of longer term complaints. One must therefore conclude that **there must be another factor involved** in the prolonged American complaints.

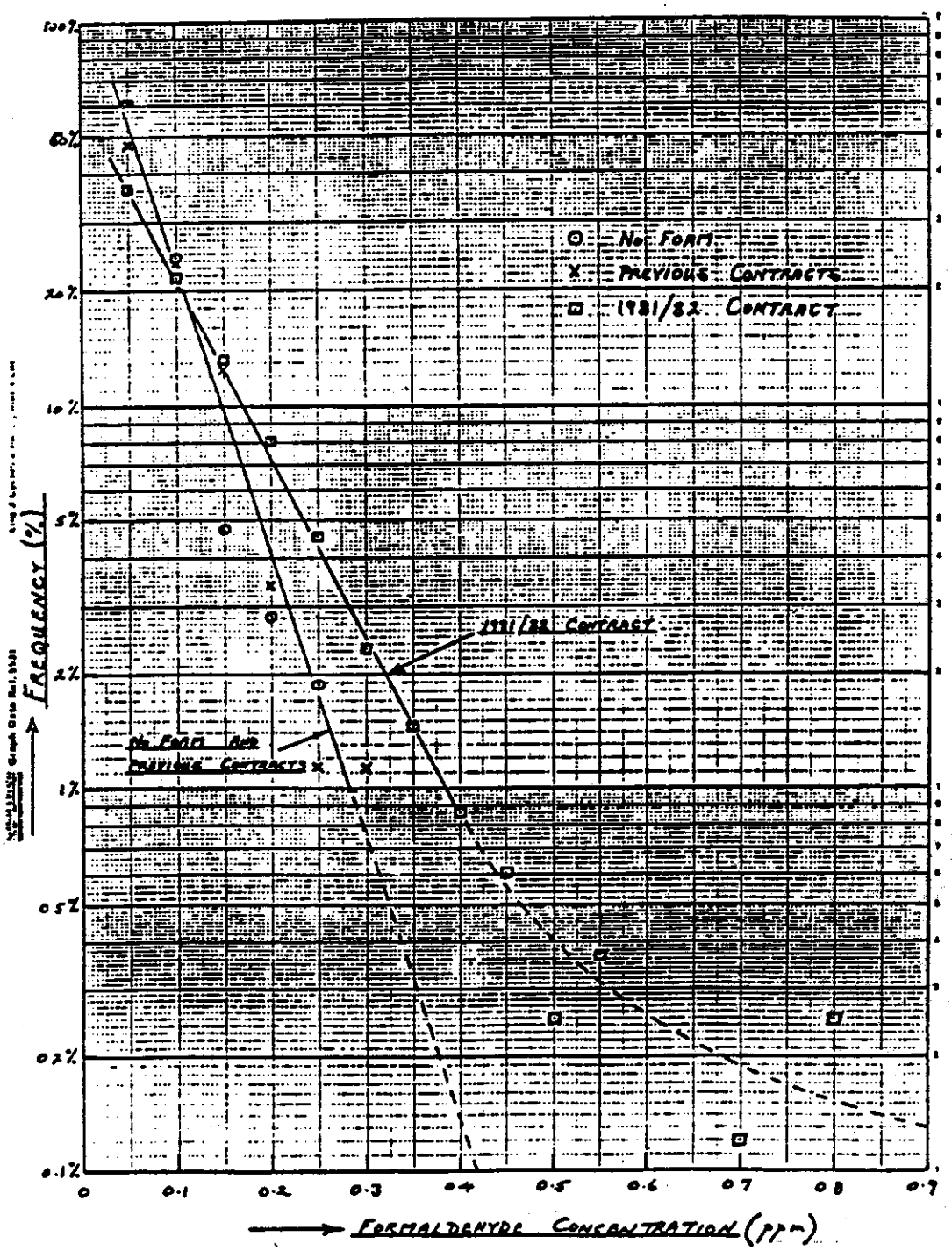

Fig 1 ESSEX FORMALDEHYDE SURVEY DATA

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Note that when developing the British Standard Code of Practice it was deliberately confined to use in masonry buildings. There was a fear that, by introducing an additional insulant into the external wall cavity, interstitial condensation would be encouraged under appropriate weather and internal conditions. This in turn could lead to rot developing in the frame structure. In the UK wood frame buildings often have an external masonry veneer, so creating a second cavity, with the frame sheathing covered in building paper, and the masonry tied to the frame by a bent flat tie. Unless great care is taken in the installation, it is easy to over-pressurise this cavity when installing UFFI, causing the flat ties to stretch and crack the outer masonry. Also the building paper can be pushed aside causing penetrating rain to lie against the wood sheathing, so inducing rot. For all these reasons wood framed buildings were deemed an unacceptable risk and so were excluded from the Code.

When one examines the huge amount of data collected by the Canadian Government in investigating the UFFI issue, formaldehyde does not come out as being an unambiguous cause. In fact the data is so conflicting that it is difficult to see how formaldehyde could be the unique cause. The analysis of some of the Canadian NRC technical data is contained in 2 reports which I prepared[10,11].

In one complaint which I investigated in the UK, they had a problem each spring. After a great deal of effort it was finally discovered that a bird had found a way into the eaves and regularly nested in the UFFI in the wall cavity. There were other cases where rats and mice nested in the UFFI.

In the St Thomas More School case described above, it is clear that the longe- complaint was not due to formaldehyde. It was afterward discovered, when the outer wall outer wythe had been pulled down, that, adjacent to the two critical rooms, there were urinals on the opposite sides of the walls leaking into the adjacent internal wall cavities. I believe that the installation of the UFFI blocked the normal cavity ventilation to the outside air and the spores from the more concentrated rotting residues came into the adjacent rooms via the open suspended ceilings.

In co-operation with the University of Victoria, Formtek Technologies Inc demonstrated that damp UFFI in contact with sterile sawdust would support the growth of stachybotris atra, a common wet rot fungus, and other fungii[12]. The test showed that this environment could provide the 3 key ingredients of moisture, cellulose and nitrogen for the fungii to grow. Stachybotris atra, in defending its territory against other fungii emits a mycotoxin which is the third most powerful poison known to man.

It is also important to realise that fungal spores and mycotoxins are ubiquitous, and that no animal or human could survive them unless they had built in defence mechanisms. It is only when these mechanisms are over-whelmed that we exhibit symptoms of ill-health. The existence of these biological thresholds is well accepted.

In investigating a seasonal complaint of induced heart problems related to sharp weather changes in Toronto, in a house insulated with UFFI, I discovered that the humidifier was full of a black mold which proved to be stachybotris atra. In another case in Chicago (which has been published, but I do not have the reference here) a family was hospitalised after growth of stachybotris atra in a heating duct in their home.

I persuaded the Canadian Federal Government in 1985 to conduct an initial investigation into the possible role of fungii in insulated buildings. Unfortunately they were unable to undertake a sufficiently comprehensive study to be able to come up with any definitive conclusion because of the sheer complexity of the issues involved.

3.1 Conclusion on Influence of Confounding Odor/Irritant Factors on Interpretation of Formaldehyde Epidemiological Studies

Barring the initial irritation effects, I believe that allergies and sensitisation to fungal spores and their mycotoxins are far more probable causes of the claimed adverse long-term health effects experienced in many buildings. They are also the probable cause of many intractable sick building syndrome problems.

The existance of ubiquitous confounding odor/irritant factors therefore makes the analysis of formaldehyde epidemiological data particularly difficult, particularly when "any excess risk must be small." (quoted in the EPA report from the UAREP (1988) evaluation of all the epidemiological data.).

4 CONCLUSION AND RECOMMENDATIONS BASED ON EXPERIENCE OF FORMALDEHYDE IN USE

Bearing in mind that:

a) formaldehyde used to have a ceiling limit of 8 ppm and high levels were experienced by large numbers of people, in many occupations, prior to the introduction of the 2 ppm ceiling limit,

b) prior to the introduction of low formaldehyde emitting resins, a substantial population had been exposed to significant formaldehyde concentrations from its wide-spread use in building products.

c) UFFI was first used in the UK in 1959. Since then over 6 million people have been exposed to the high initial formaldehyde concentrations experienced shortly after its installation without a major long term health problem becoming evident.

d) "Cancer of the nasal cavity and sinuses in humans is a very rare disease." Also, the UAREP (1988) review concluded that "a causal relationship has not been established for cancer at any site. In addition, the panel noted that if such a causal relationship exists, the excess risk must be small." The IARC review panal believed that they had been able to establish a "limited evidence of carcinogenicity to humans" ... "but chance, bias or confounding could not be ruled out with reasonable confidence." This report suggests that that confounding is likely to be much larger than had previously been considered, thus reducing the actual risk from formaldehyde even further.

We can therefore conclude that with such large and diverse populations having been exposed to significant levels of formaldehyde, over such extended periods of time, **there is no evidence that, at 1 ppm and below, that exposure to formaldehyde vapour alone causes serious adverse health effects, and any control should be based solely on control of the irritation and odor.**

1. Legislation on formaldehyde vapour concentrations should only be based on the minimisation of irritation, with criteria based on the classification of exposure, eg:

   0.4 ppm max 8h avg, for retirement homes and hospitals.

   0.5 ppm max 8h avg, for domestic and school environments.

   0.6 ppm max 8h avg, for office and shop type environments.

   1.0 ppm max 8h avg, for industrial environments.

2. For outside ambient air, I propose a total value of 0.1 ppm max 8h avg as a result of all local and natural sources of emission, on the basis that such an outdoor maximum should not substantially increase the risk that the above indoor figures should be exceeded.

   Since formaldehyde is at a natural equilibrium in the ambient environment, ie it is destroyed (half life of less than 12 hours) as well as being created naturally, and with normal atmospheric dilution and wash out, I believe that this maximum local figure provides an acceptable outdoor environmental criterion.

5 EVALUATION OF THE DPX DATA CONTAINED in the EPA DRAFT FORMALDEHYDE RISK ASSESSMENT (1990).

Chemical and biological process changes take place in a continuous manner rather than being disjointed, unless one is involved with competing processes. In my view, living creatures can be considered as being made up of a multiplicity of chemical reactors, some in series, some in parallel, some as pipe reactors etc. Therefore, the analytical processes used to solve conventional Chemical Engineering process problems are equally applicable to the resolution of complex life chemistry problems.

On reading the Draft Revised EPA Formaldehyde Risk Assessment Report (1990), I was immediately concerned by the way in which the DPX data had been analysed. Because they could find no underlying technical rational, the EPA resolved not to adopt any form of data correlation to smooth the data, but to take linear interpolations between adjacent data pairs, and where necessary use that linear interpolation to extrapolate outside the experimental range. This may eliminate bias by the statisticians, but certainly is no way to interpret scientific data.

I therefore investigated whether it was possible to fit a single equation to both the rat and the monkey data, the only difference being a 7.6 factor to account for the larger surface area of the monkey. If that were possible, then there must be a self-consistent underlying cause common to both species, and therefore this would greatly strengthen the validity of the DPX data as an indicator of potential carcinogenic changes in the nasal region and obviate the rational for the EPA linearised procedures.

One problem with conventional statistical routines is their implicit assumption that the errors are of equal size, independent of the magnitude of the particular data set. As a result, an undue weight is automatically given to the largest values. To resolve this problem one must normalise by dividing the differences between the predicted and measured values by the values themselves and then minimise the sum of their squares. **The objective was therefore to come up with a single equation in which these differences would lie within each data set's individual experimental range.**

As a first step the rat and monkey data were separately subjected to a polynomial regression analysis using the STATGRAPHICS program. In both cases a good second order fit was obtained, with the monkey data having a slightly steeper curve, ie a larger second order coefficient after allowing for the 7.6 area factor.

A manual iterative routine was then set up in LOTUS 123 so that the effect on each data set could be visually examined after a small change in one of the coefficients. The results are given in Table 2, showing that almost all the individual data sets can

Table 2 Formaldehyde and DPX Data

DPX vs form conc coefficien: 0.4 | r^2: 0.36 | AREA: 7.6

FORM CONC	MONKEY DATA: DPX (DIFF/MES)^	EXPTL LIMIT	DPX DIFF	DPX MEASURED	DPX PREDICT	RAT DATA: DPX PREDICT	DPX MEASURED	DPX DIFF	EXPTL LIMIT	DPX (DIFF/MES	FORM CONC
0		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		0
						1.25	1.40	0.15	0.60	0.0110	0.32
0.7	0.0717	0.10	-0.10	0.36	0.46	3.54	3.90	0.36	0.40	0.0086	0.71
2	0.0156	0.31	0.32	2.56	2.24	16.06	19.90	3.84	3.70	0.0373	1.93
6	0.0243	3.40	2.84	18.20	15.36	113.86	106.00	-7.86	6.00	0.0055	5.92
						296.54	266.00	-30.54	30.00	0.0132	9.87
	SUM: 0.1117								SUM:	0.0756	

DIFFERENCE SUM to be MINIMISED for RATS + MONKEYS: 0.187316

BIOASSAY EXPOSURE	MONKEYS TUMOR BEARING NO	TOTAL	%	DPX ADJ	DPX UNADJ	DPX UNADJ	DPX ADJ	RATS TUMOR BEARING NO	TOTAL	%	BIOASSAY EXPOSURE
0				0.0	0.0	0	0	0	156	0.0%	0
2				1.6	2.2	17	12	0	159	0.0%	2
5.6				9.7	13.5	103	73	2	153	1.3%	5.6
14.3				56.7	79.3	603	431	94	140	67.1%	14.3

FORM CONC	DPX Cont Daily	DPX 6 hrs dai	DPX 6 hrs daily	DPX Cont Daily	FORM CONC
0.1	0.17	0.04	0.33	1.39	0.1
0.5	1.16	0.29	2.20	8.82	0.5
1.0	3.04	0.76	5.78	23.10	1.0

REGRESSION ANALYSIS

FORMALDEHYDE VAPOUR PRESSURE DATA @ 35C (WALKER 3rd Ed)

MW = 30.03

g/L	M/L (liq)	mg/L (gas)	1000 ppm	predicted M/L (liq)
0	0	0	0	0
11	0.36	0.27	0.23	0.32
52	1.72	1.13	0.95	1.69
116	3.93	2.06	1.73	3.76
186	6.19	2.87	2.42	6.07
208	6.93	3.17	2.67	7.04
310	10.32	4.27	3.60	11.15
395	13.16	4.58	3.86	12.46

	a0	a1	a2	
Coefficient	0.000	1.302	0.800	
Std Error		0.321	0.098	
Student's t		4.060	8.119	
P value		0.0098	0.0037	
				P value
R^2 (adj)	0.9962	F ratio	785	0.0000
Std Error	0.4940	MAE =	0.2841	

	Sum of sq	DF	Mean Square
Model	383	2	192
Error	1.220	5	0.244

RISK vs (adj DPX)^2

ln(1-P)	(adj DPX)^2	PREDICTED ln(1-P)
0.000	0	0.007
0.000	148	0.006
-0.013	5364	-0.026
-1.113	185488	-1.113

Regression Output:

Constant		0.007
Std Err of Y Est		0.011
R Squared		1.000
No. of Observations		4
Degrees of Freedom		2
X Coefficient(s)	-6.03E-06	
Std Err of Coef.	6.88E-08	
Zero intercept	(adj DPX)^	1100
Zero risk formaldehyde		2.97 ppm

RISK vs adj DPX, 2 pt correlation

ln(1-P)	adj DPX	PREDICTED ln(1-P)
0.000	0.0	0.213
0.000	12.2	0.176
-0.013	73.4	-0.013
-1.113	430.7	-1.113

Regression Output:

Constant		0.213
Std Err of Y Est		0.000
R Squared		1.000
No. of Observations		2
Degrees of Freedom		0
X Coefficient(s)	-3.08E-03	
Std Err of Coef.	0.00E+00	
Zero intercept	adj DPX	69
Zero risk formaldehyde		4.50 ppm

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be fitted inside their own experimental error ranges and the equations were found to be:

$$DPX = 1.0*(0.4*F + 0.36*F^2) \text{ for the monkey data, and}$$

$$DPX = 7.6*(0.4*F + 0.36*F^2) \text{ for the rat data.}$$

where DPX = pmol/mg DNA/6 hours, and
F = formaldehyde vapour conc (ppm)

The original data and the curves computed from the above equations of fit are shown in Figs 2 and 3. Fig 3 is an expanded view of the lower portion of Fig 2. Fig 2 shows the importance of normalising the data since the large apparent discrepancy at the 9.9 ppm level for the rats is still just within the accuracy of the measured data. Note that corresponding experimental formaldehyde concentration ranges should also have been quoted, since I doubt they were controlled that precisely.

The question arises as to the meaning of such a quadratic effect. I then analysed the vapour pressure data presented in Table 43 of Walker's 3rd Ed "Formaldehyde"[13] from the original Ledbury and Blair data. Walker gives a logarithmic correlation for all the data in Table 43. The most complete data set is at 35°C, close to body temperature, albeit at much higher concentrations. To my surprise the data proved to be an almost perfect quadratic fit, see Table 2:

$$c_L = 1.3*c_G + 0.5*c_G^2$$

where c_L = Moles/L, and

c_G = 1,000 ppm

The results are shown on Fig 4. (In very dilute aqueous solutions this equation would appear to be almost linear, see Fig 5.) The reason for the quadratic form is that in these more concentrated solutions a proportion of the formaldehyde dimerises, and it is only the monomeric formaldehyde which is in direct equilibrium with the vapour.

The interpretation of the DPX data is that when low concentrations of formaldehyde are absorbed into viscous mucus, the formaldehyde solutions so created behave as if they were concentrated aqueous solutions with substantial dimerisation of the formaldehyde. However, when considering the subsequent reactions to cause the DNA protein cross-links (DPX), it is the total formaldehyde (monomer + dimer + higher polymer equilibrium) which is appropriate. Therefore, by measuring the DPX concentration one has a direct measure of the total active formaldehyde concentration dissolved in the mucous membrane, and hence of the driving force for potential carcinogenicity.

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Fig 2 NASAL DPX in R & M vs FORMALDEHYDE CONC

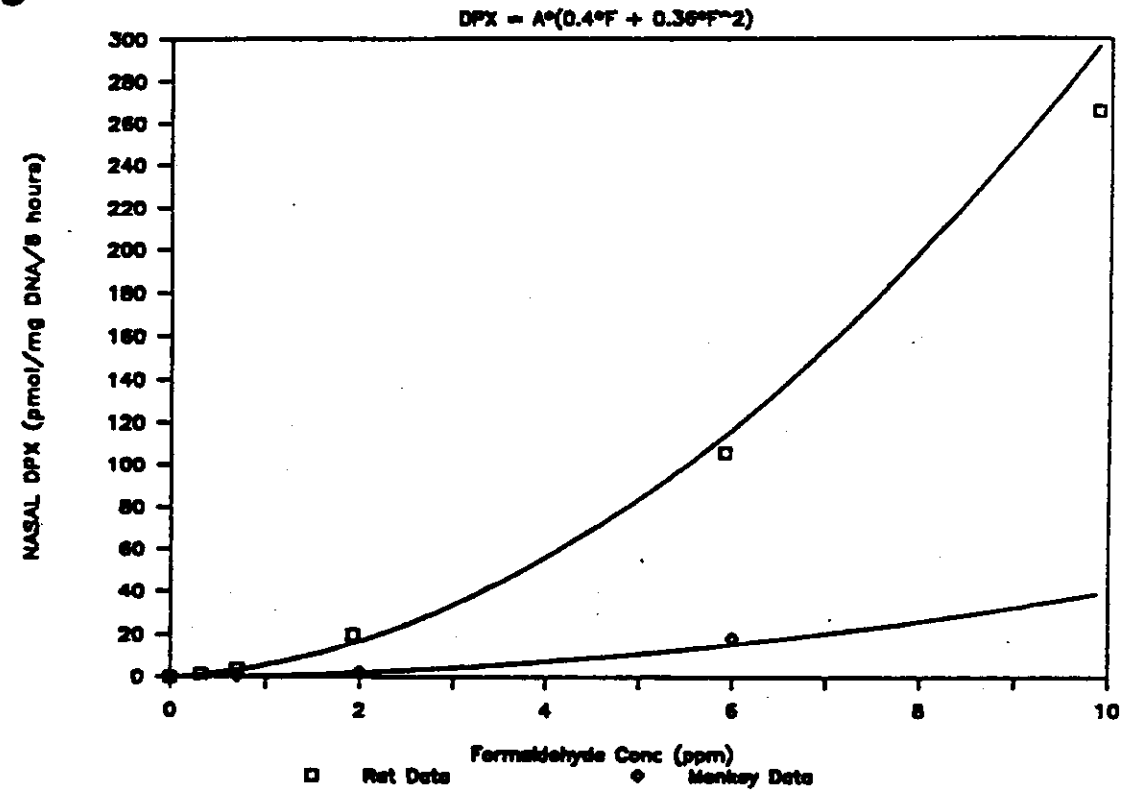

Fig 3 NASAL DPX in R & M vs FORMALDEHYDE CONC

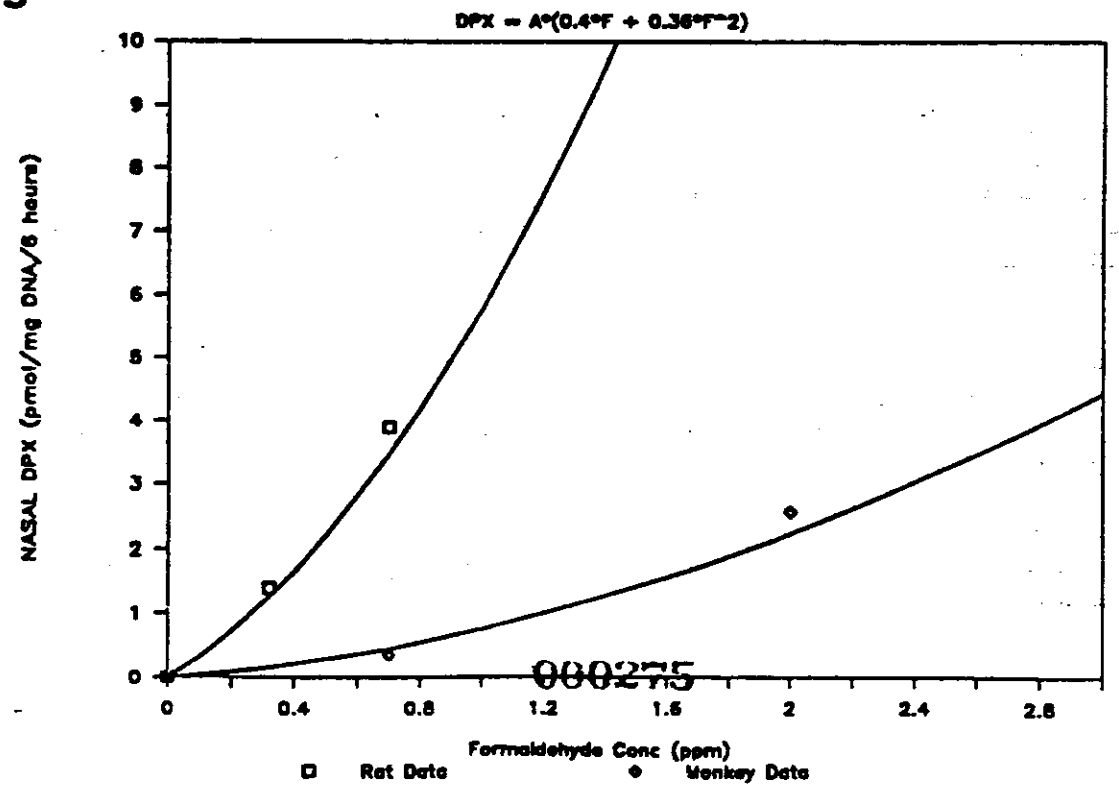

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Fig 4

FORMALDEHYDE VAPOUR PRESSURE DATA

WALKER, "FORMALDEHYDE" 3rd Ed, Table 43

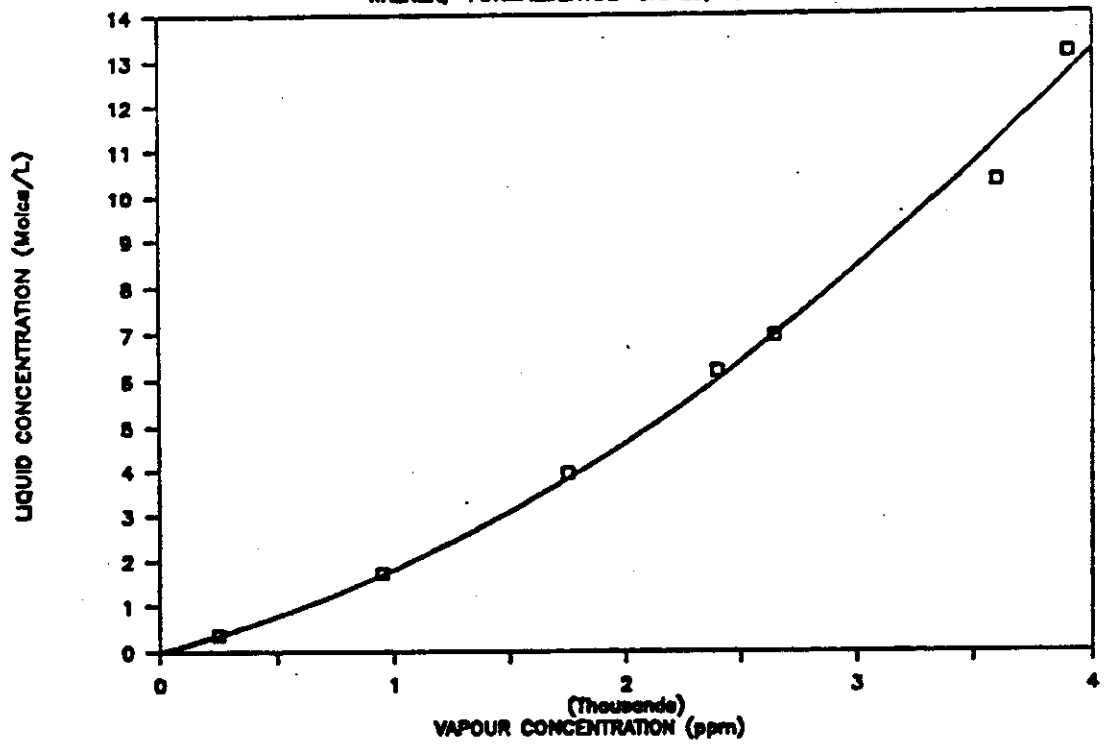
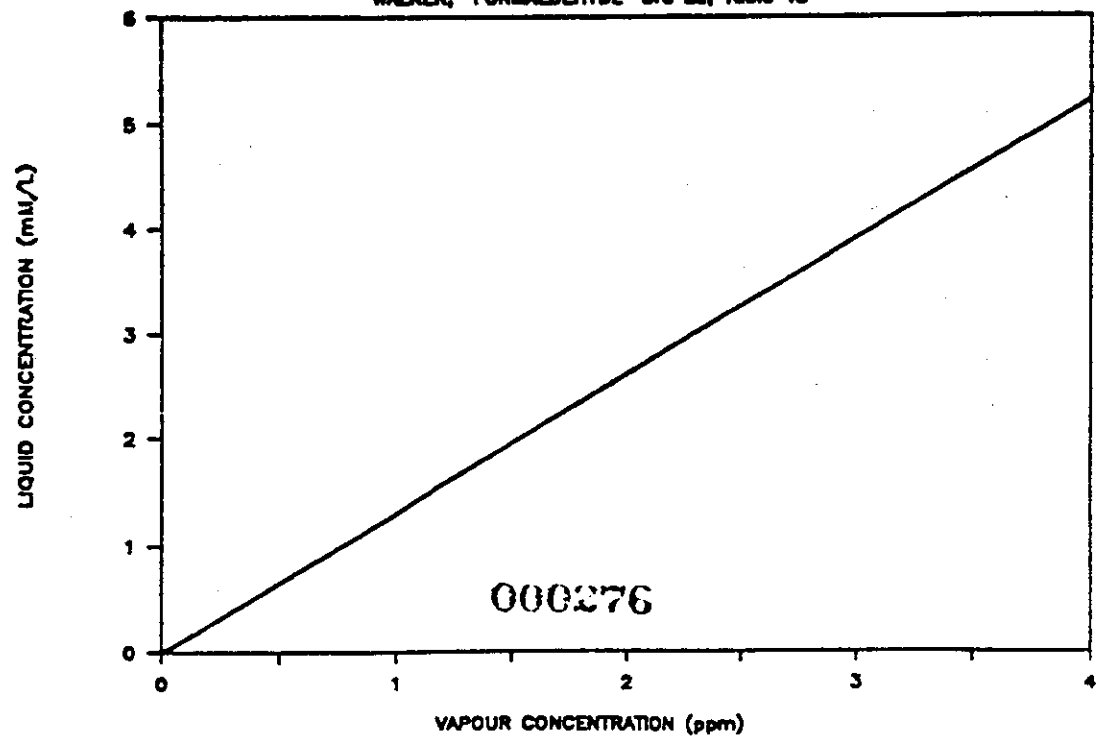


Fig 5

FORMALDEHYDE VAPOUR PRESSURE DATA

WALKER, "FORMALDEHYDE" 3rd Ed, Table 43



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5.1 Conclusion on the use of DPX as the proper indicator.

The following unique equation was fitted to both the rat and monkey DPX data:

$$DPX = A*(0.4*F + 0.36*F^2)$$

where DPX = pmol/mg DNA/6 hours
F = formaldehyde vapour conc (ppm), and
A = nasal area factor between monkeys and rats
= 1.0 for rats
= 7.6 for monkeys

From the above arguments it is therefore appropriate that this single interpretative equation should be used when interpolating the rat and monkey data and not the linear sets joining adjacent data points as used in the EPA Report. The EPA submission should be modified accordingly. It is also clear that the DPX data is the proper base from which to analyse the cancer data, since it properly relates to the liquid phase formaldehyde in the nasal mucosa, whose concentration in turn is directly related to the probability of subsequent cancer induction.

The interpolated and extrapolated DPX values for the required formaldehyde concentrations using the equations of fit are given below and in Table 2, and should be used in the EPA report:

formaldehyde vapour conc ppm	DPX pmol/mg DNA/6 hours in rats	in monkeys
0.1	0.33	0.04
0.3	1.25	0.16
0.5	2.20	0.29
0.7	3.47	0.46
1.0	5.78	0.76
2.0	17.	2.24
5.6	103.	13.5
5.7	106.	14.0
6.0	117.	15.4
10.0	304.	40.0
14.3	603.	79.
15.0	661.	87.0
20.0	1155.	152.

6 ANALYSIS OF THE CANCER DATA IN RATS CONTAINED in TABLE 5.3 of the 1990 EPA QUANTITATIVE RISK ASSESSMENT

The data in Table 2 shows the adjusted DPX levels corresponding to the CIIT rat tests (Kerns et al) as described in the EPA 1990 report (an adjustment factor of 5/7). EPA used the GLOBAL86 statistical analysis program to fit the probability, P, of the rats getting cancer (adjusted in accordance with the recommendations of the IRMC), **making the assumption that there is no threshold and that the risk curve must therefore pass through the origin**, as ln(1-P) against the DPX data, and they found that a second order (stage) polynomial gave a fit with a probability confidence of 0.07. Note that this is equivalent to a 4th order fit had the original formaldehyde data been used, which compares to the 5th order fit chosen in the 1987 report.

Now as a general principle, an equation can be fitted to any data, no matter how poor, by stretching the X-axis, which is achieved by choosing ever higher orders. To be justified, there must either be a lot of data, or some sound underlying rational to the use of higher orders. If neither is the case, then the hypothesis on which the modelling is based must be questioned.

In the present case we have only 2 positive cancer risk measurements given in Table 5.3 of the 1990 EPA report, adjusted in accord with the recommendations of the Interagency Risk Management Council (IRMC 1984), and 2 zero values. With so little information, the data cannot justify much manipulation. The problem the EPA faced was that at high vapour concentrations formaldehyde is unquestionably carcinogenic, yet both general cancer data and epidemiological data showed that "Cancer of the nasal cavity and sinuses in humans is a very rare disease," and, quoted from the UAREP report, "if such a causal relationship exists, the excess risk must be small." Therefore the only way to reconcile this conflicting information and maintain the assumption of a zero threshold was to use a high order fit.

Fig 6 shows a fifth order fit using the formaldehyde vapour concentration data as carried out in the 1987 EPA Risk Assessment Report. This technique basically locks the line of fit between the zero point and the high value point and squeezes the zero value data points together. Thus when "interpolating" the formaldehyde risk down to low concentrations, the computed risk values are not totally out of sync with the global low experience of risk.

Figs 7 and 8 show second and first order fits based on the adjusted DPX data (multiplied by the 5/7 factor see Section 5.3.3 of the 1990 EPA report), and a zero threshold assumption, together with the corresponding computed formaldehyde vapour concentration. The problem for the EPA can be seen in Fig 9, which shows a magnified view of the lower portion of Fig 8, which used a first order correlation. Because a zero threshold has been assumed, the first non-zero data point at an adjusted DPX of 73 pmol/mg is too close to zero to obtain a good fit, and the

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Fig 6

RAT CANCER IRMC RISK FACTOR vs F^5

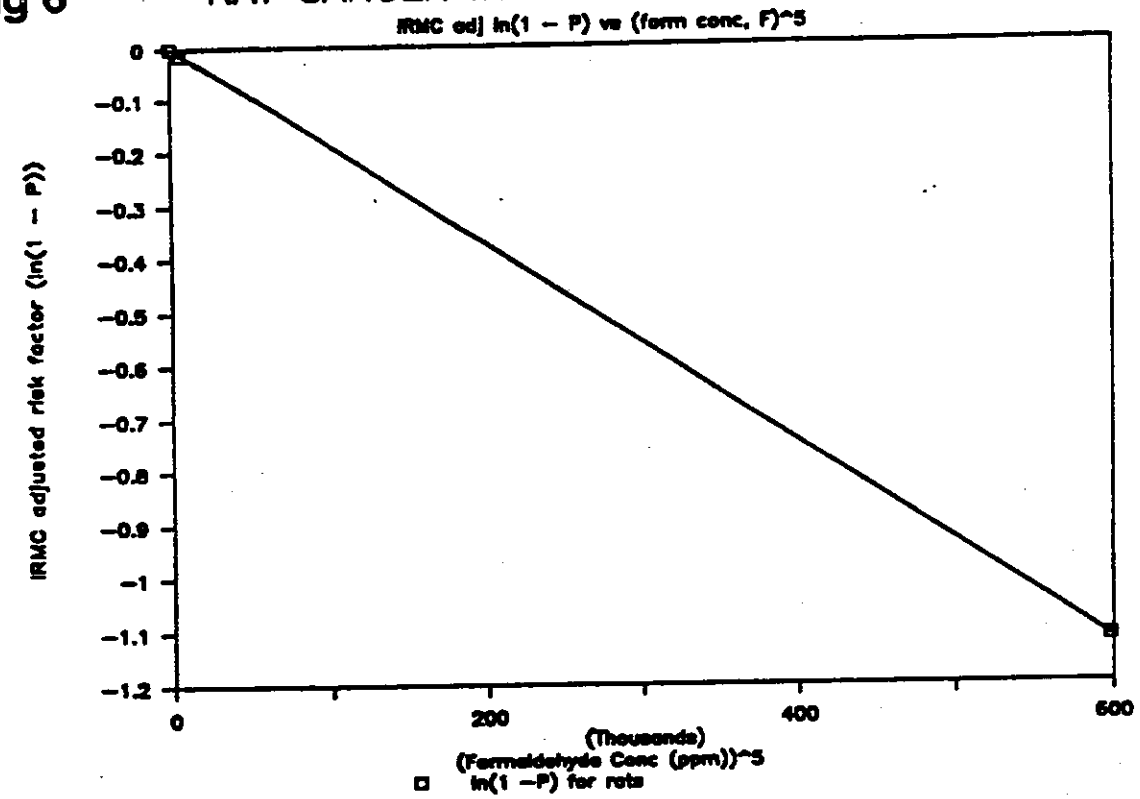

Fig 7

RAT CANCER IRMC RISK vs (adj DPX)^2

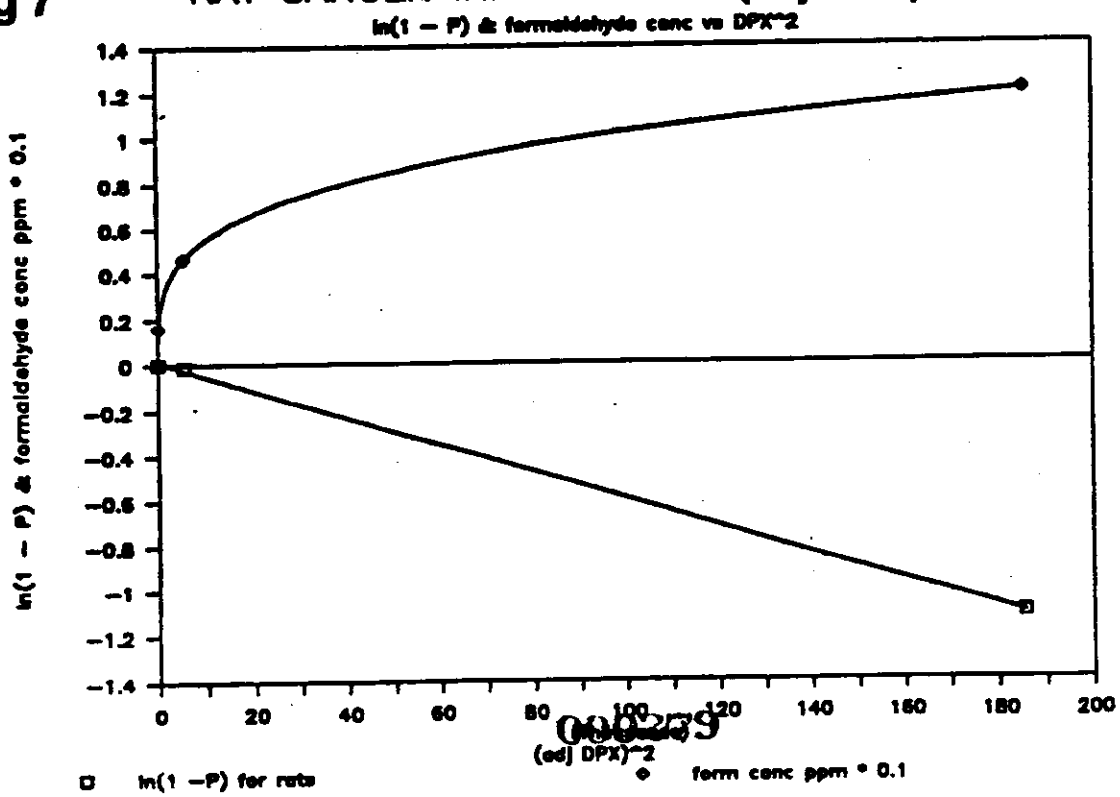

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Fig 8 RAT CANCER IRMC RISK FACTOR vs adj DPX

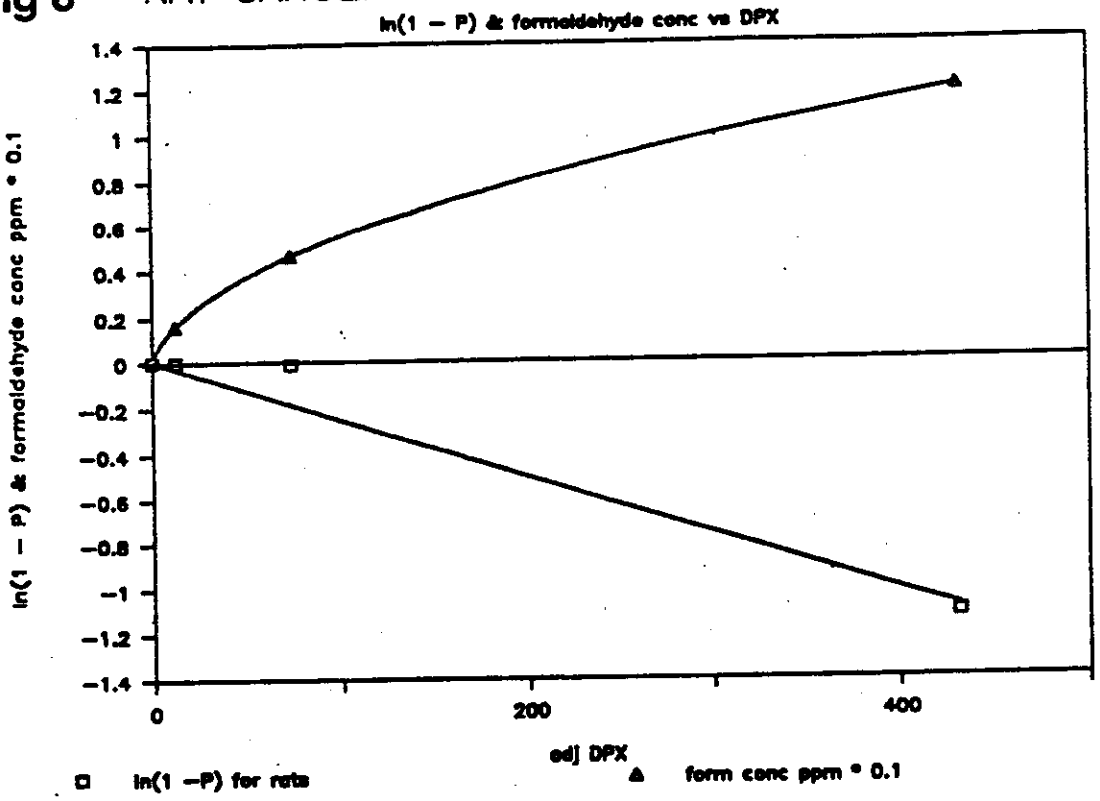
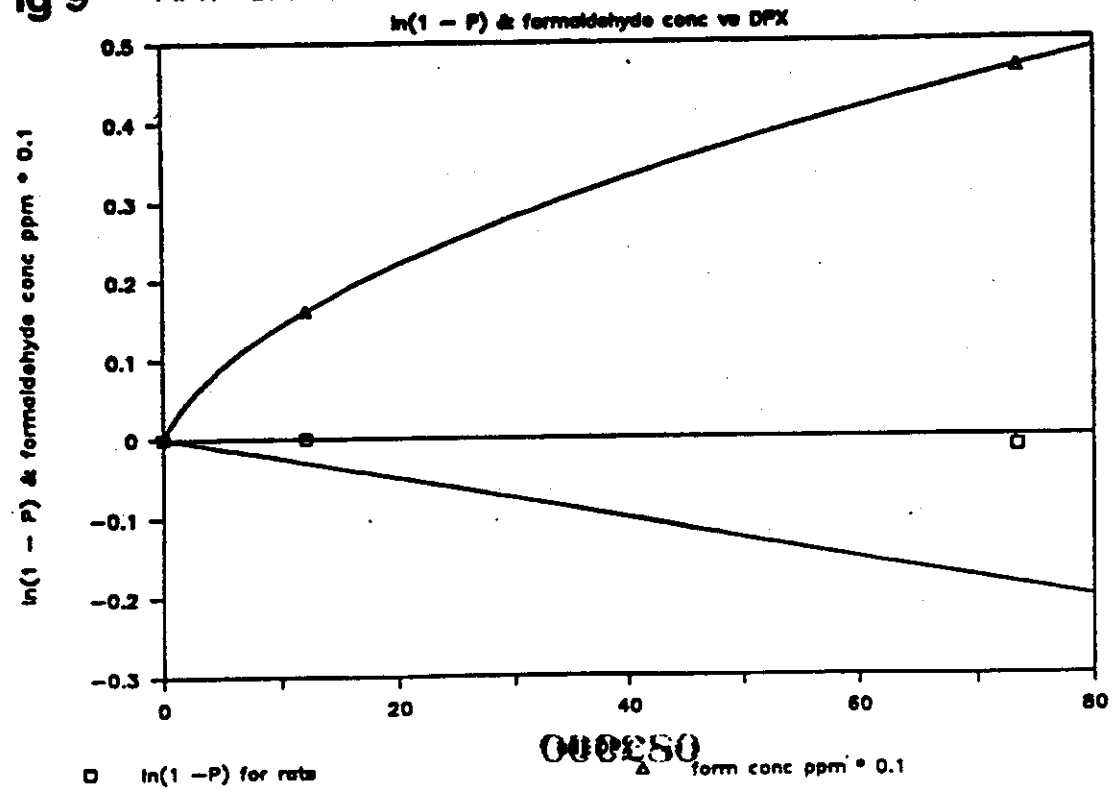


Fig 9 RAT CANCER IRMC RISK FACTOR vs adj DPX



computed low concentration risks are correspondingly too high. The problem is resolved by using a second order fit as shown in Fig 7.

The **alternative hypothesis is to assume that there is a threshold** and that the data are accurate and reasonably representative, see Figs 10 and 11. Fig 11 is a magnified portion of Fig 10 close to the zero probability region. In this correlation a straight line has been plotted between the 2 non-zero points. The line has a positive intercept on the X-axis at an adjusted DPX value of 69 which corresponds, see vertical line, to a formaldehyde concentration of 4.5 ppm. In other words, with this model, there is no cancer risk for rats if the 6 h/day 7 day/wk formaldehyde concentration is maintained below 4.5 ppm, see Table 2.

The likely positive threshold mechanism has been described in the 1990 EPA report (Section 4.5.3): "It has, therefore, been postulated that at low formaldehyde concentrations, the mucus layer of the rat nasal cavity may trap and remove much inhaled formaldehyde, thus preventing it from reaching underlying cells. If the mucus layer is saturated (at high concentrations), the mucociliary clearance system could be seriously compromised and may allow a greater amount of formaldehyde to reach the underlying respiratory epithelium."

7 OTHER SUPPORTING EVIDENCE IN THE 1990 EPA REPORT FOR A POSITIVE THRESHOLD IN RATS

The new information from Monticello at the CIIT (EPA Report, Section 4.1) "supports the results of the 1983 study in rats in that nasal tumours were found with formaldehyde exposures to 10 and 15 ppm. At 6 ppm, no tumours were observed." ... "other than fewer animals allotted to dose groups in Monticello (1990), reasons for the difference in these results at 6 ppm compared to those in Kerns et al (1983) are unclear." Note that the EPA report fails to mention the cancer fraction which Monticello found at 10 and 15 ppm.

Based on Fig 10, I believe the reason is quite clear. The EPA report states "The observed tumor incidence in these studies produces a very steep dose-response curve for the carcinogenic effect of formaldehyde." It was reported to the Appeal Hearing in 1982 which overturned the CPSC ban on UFFI that in the original CIIT study their ability to control the formaldehyde concentrations during the testing was not perfect. I am sure that, with the much better equipment now available, that Monticello was able to maintain a better degree of control. Fig 11 shows how critical this control must be, and why its experimental error should also be reported.

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Fig 10 RAT CANCER IRMC RISK FACTOR vs adj DPX

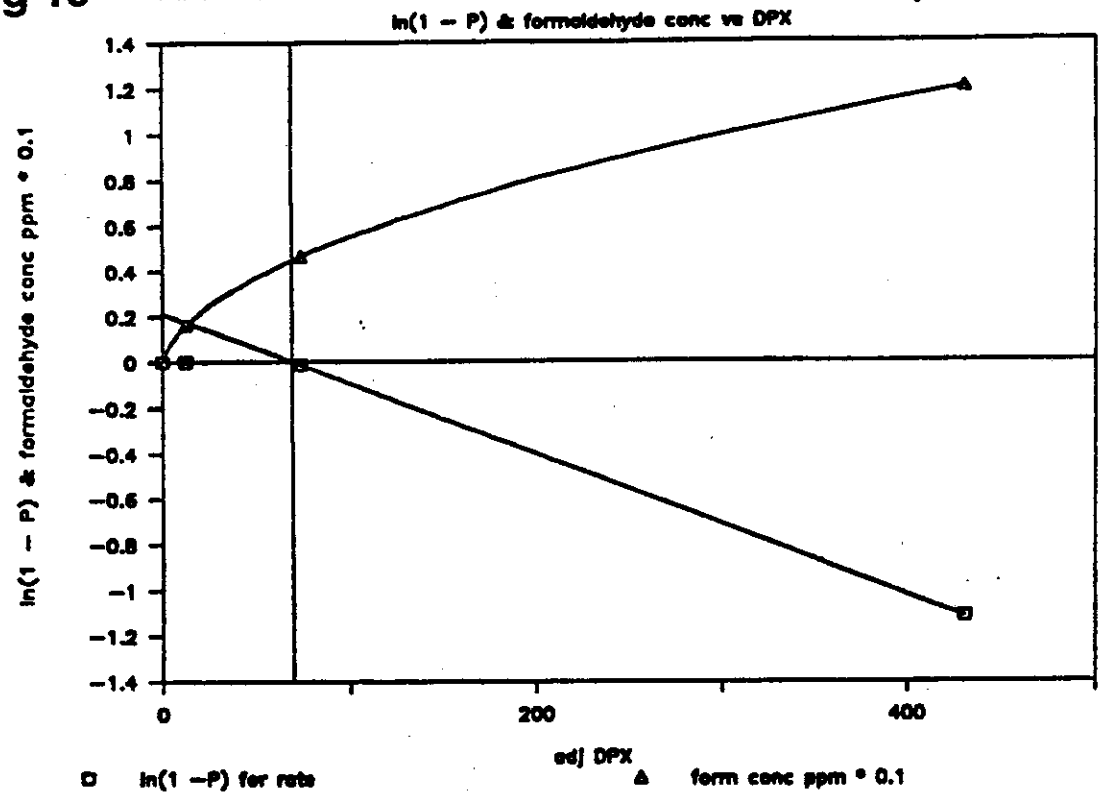
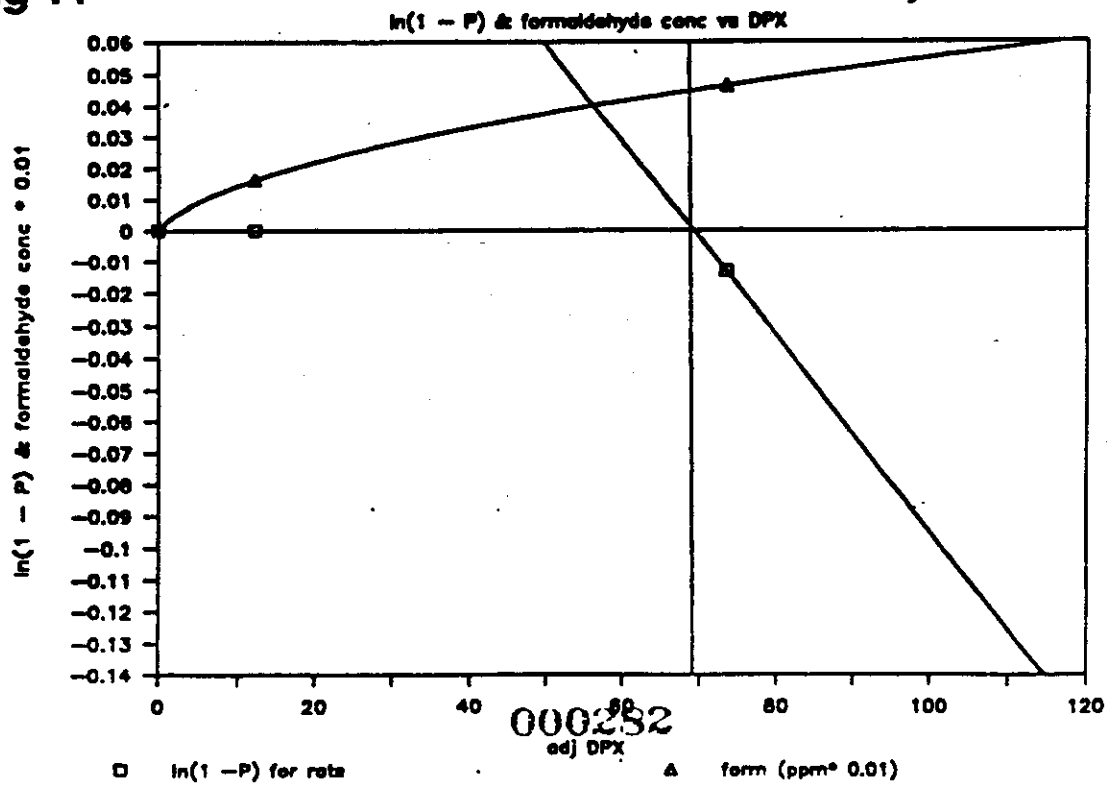


Fig 11 RAT CANCER IRMC RISK FACTOR vs adj DPX



In Tobe et al (1985)'s 28 month study, "squamous cell carcinomas of the nasal cavity were seen in 14/27 (52%) high-dose (15 ppm) rats surviving past 12 months; no such neoplasms were observed in the control or the low-dose groups (0.3 and 2.0 ppm)." Tobe's results are ploted on Fig 12 using unadjusted DPX data together with the data of Monticello and Kern. Tobe's data appear to show a much lower cancer incidence than Kern.

Albert et al (1982) and Sellakumar et al (1985) in lifetime studies "show that significant incidences (10-38%) of squamous cell carcinomas of the nasal cavity were induced in all rats exposed to formaldehyde (14-15 ppm) regardless of the concurrent exposure to HCl. No carcinogenic response was observed in the rats exposed to air (control) or to HCl alone." Even Albert's combined HCl and formaldehyde challenges at 14 - 15 ppm found a smaller proportion of cancers than apparently found by Kern, see Fig 12.

Woutersen et al's (1989) study reported on the deliberate damage to the rats' nasal mucosa in a portion of the rats prior to exposure. **Exposure for 28 months to 10 ppm showed no carcinomas in the undamaged rats**, but 15/58 (26%) in damaged rats. "no compound-related nasal neoplasms or cytotoxic effects were observed in rats (with either a damaged or undamaged nose) exposed to 0.1 or 1.0 ppm formaldehyde for 28 months." (Note that the important undamaged rat data has been omitted from EPA Table 4.1) Even Woutersen's damaged rats had a lower cancer incidence than apparently found by Kern, see Fig 12.

7.1 Re-analysis of the 1990 EPA adjustment factors

To reassess the adjusment factors, one must first consider the mode of carcinogenesis. A cancer cell is a fast-replicating, otherwise normal, mutant cell. It is treated by the body as a normal cell. Unlike many carcinogens, formaldehyde is one of the most reactive organic chemicals and can react with most types of amine or protein or DNA type molecules. Most mutant products are rejected by the body. It is therefore a matter of chance whether the formaldehyde molecule happens to hit the critical replication controlling entity to form the carcinogenic mutant. Most of the formaldehyde is absorbed in the thick nasal mucosa, particularly when below the threshold value, and it is the residual which is potentially carcinogenic. Because of the reactivity of formaldehyde, it will have reacted with some moiety within 24 hours of having been absorbed by the nasal mucosa. Therefore a day could be considered as the unit time frame in which it might form a carcinogenic mutant or not. The turn-over of the nasal mucosa is probably of the same order of time period. As far as the proportion of formaldehyde molecules available for this type of reaction is concerned, it would be proportional to the difference between the DPX value on the nasal mucosa and the threshold value. Therefore adjustments cannot be made to

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Fig 12 RAT CANCER RISK FACTOR vs adj DPX

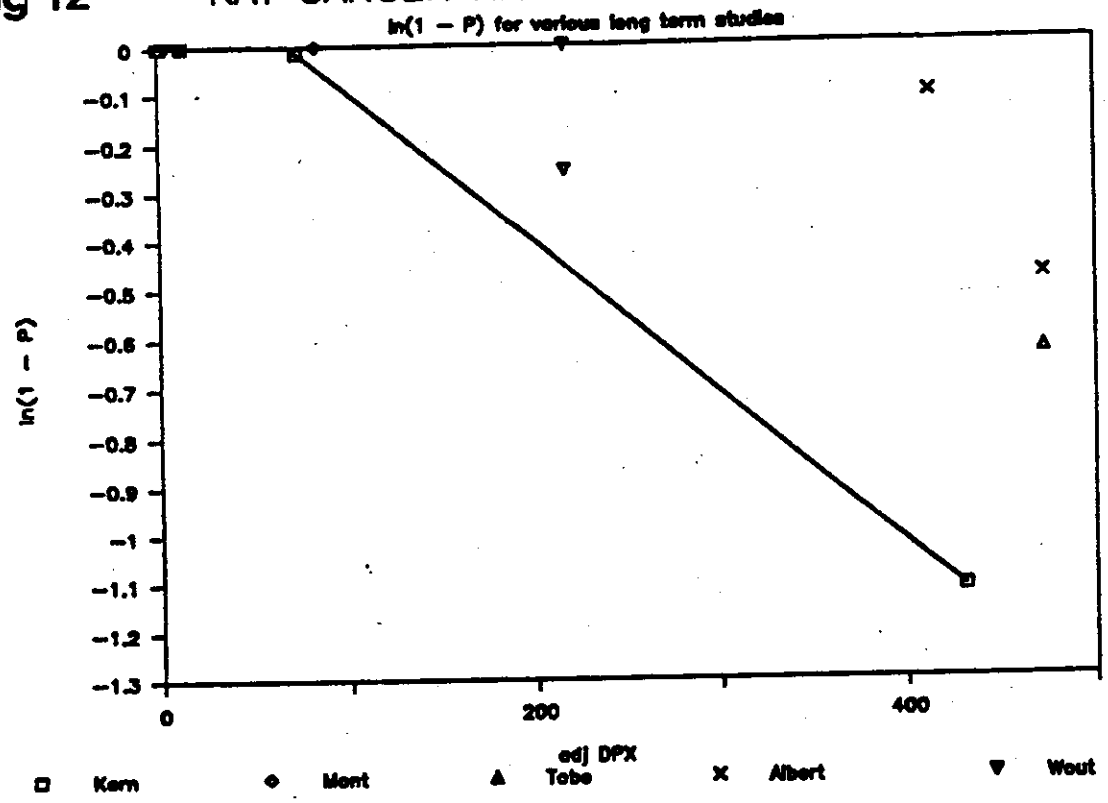
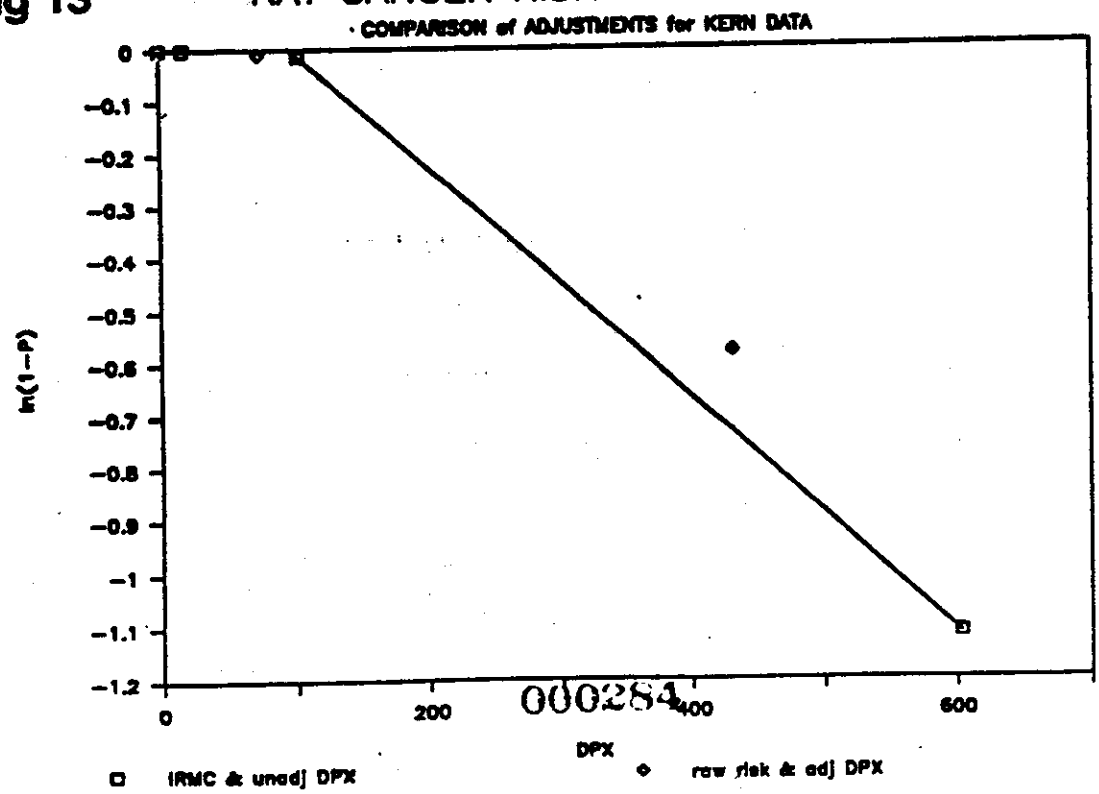


Fig 13 RAT CANCER RISK FACTOR vs DPX



the DPX value to account for exposure time differences, and all carcinogenic probabilities must be plotted against an unadjusted DPX.

It is seen from the above argument that all exposure corrections must be made on the carcinogenic risk data only. Because the unit time is around a day, any multiple unit is appropriate, such as a year, and would be in simple proportion - twice the exposure time at a given concentration would double the risk factor. Therefore, if some rats were sacrificed at the end of a year, one could double their measured risk factor to obtain the likely risk at the end of two years, for example.

The risk factor is given by ln(1-P), where P is the proportion of rats found to have cancer at any given time.

In examining Table 5.3 of the EPA report and comparing with the reported proportion of cancers found at the end of the 24 month study, one finds that the IRMC has increased the projected risk from 0.85% to 1.3% at 5.6 ppm, and from 44% to 67% at 14.3 ppm, based on the original group sizes. It would therefore appear that the EPA may have partly double-counted their corrections. Fig 13 shows the raw cancer proportion found in those rats which survived the 2 years plotted against the adjusted DPX and the IRMC adjusted figures plotted against the unadjusted DPX values.

In order to compare the various test data properly, one must use the raw cancer proportion of the survivors, corrected for time of exposure, against the unadjusted DPX value.

Of the 5 long term studies, 4 have the length of exposure reported. Albert et al are only quoted in the EPA review as a lifetime for their formaldehyde + HCl exposure. Of the remaining 4 long term studies with data available, 2 lasted 24 months, and 2 lasted 28 months. All used a 6 h/day, 5 days/wk schedule, so the risk factors for the 28 month studies were reduced by 24/28 to make them all compatible. A regression analysis was carried out and the results are plotted on Fig 14:

	Estimate	Std Error	t Value	Prob Level
Intercept	0.1229	0.0121	10.2	0.002
Slope:	-1.153E-03	2.80E-05	-41.2	0.00003

Analysis of Variance

Source	Sum of Sq	Df	Mean Sq	F ratio	Prob Level
Model	0.3668	1	0.3668	1698	0.00003
Error	0.0006	3	0.0002		
Total	0.3674				
Correlation coeff = -0.9991		**Std Error of est = 0.0147**		**R^2 = 0.9982**	

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Fig 14 RAT CANCER RISK FACTOR vs unadj DPX

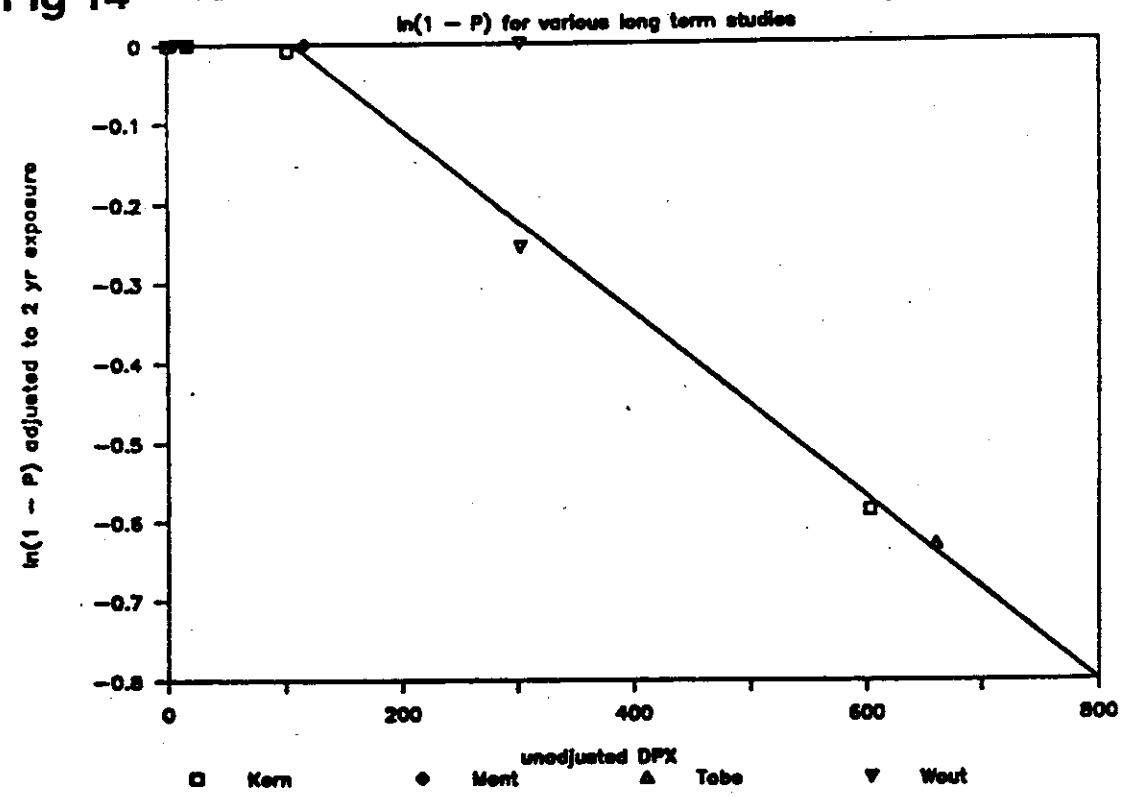
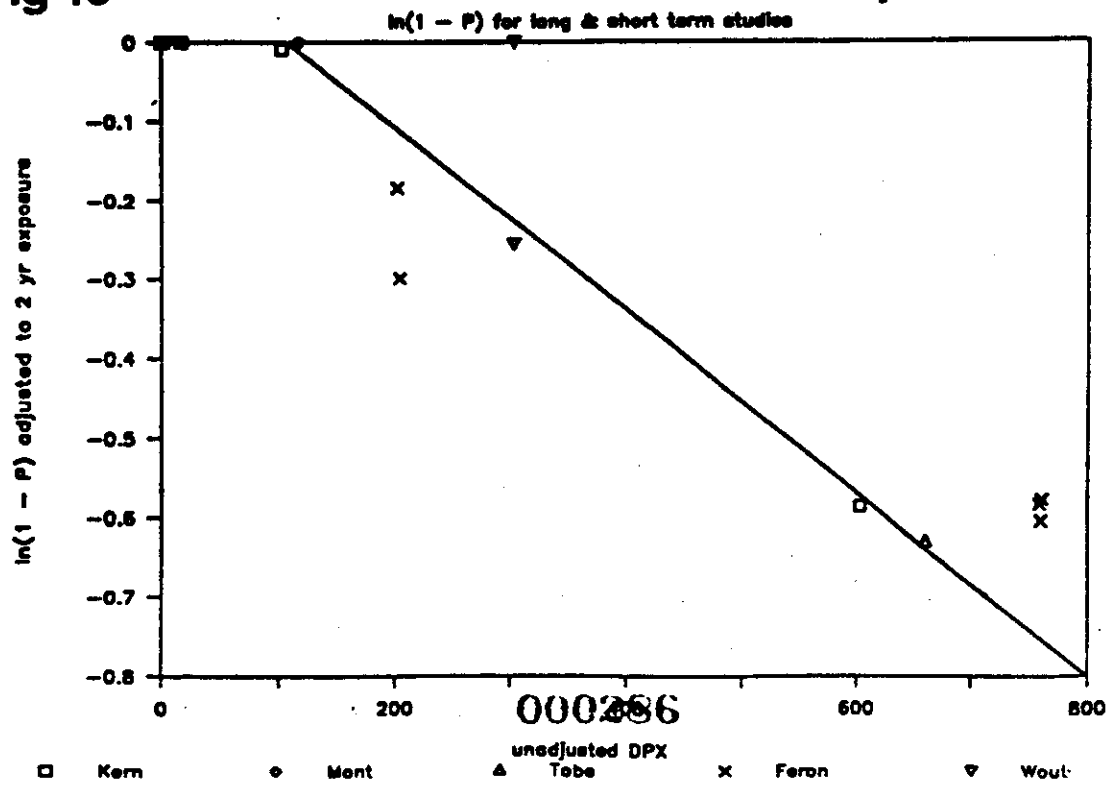


Fig 15 RAT CANCER RISK FACTOR vs unadj DPX



This very high degree of correlation of the data confirms the soundness of the underlying logic in analysing the data, and solidly confirms the concept of the threshold when considering the carcinogenicity of formaldehyde. A surprising observation is that Woutesen's damaged rats exactly fit the mean line, showing that the deliberate damage had no effect on their chances of developing cancers. Woutersen's zero cancers at 10 ppm in undamaged rats is therefore most surprising. Could it be that there was some error in the reporting?

The zero threshold is calculated to be at a DPX value of 107 pmol/mg DNA/6 hours, and an equivalent formaldehyde vapour concentration of 5.7 ppm. The low positive risk obtained by Kern at 5.6 ppm is now seen as being as good an estimate of the zero threshold value as the nul at 6 ppm found by Monticello.

Strictly speaking, the proportion of carcinomas found as a total number of neoplasms should be used in calculating the risk fraction, since at high exposure levels some rats will develop 2 or more separate neoplasms. For example, when Morgan (1986) re-examined the slides of 98 of the 103 tumour bearing rats in Kern's study, he found a total of 121 neoplasms. However, there is insufficient data to take this analysis further in this report.

In none of the long term studies were any carcinomas found in the controls (0 ppm) or at 0.1, 0.3, 0.7, 1 or 2 ppm. This is to be expected since "the spontaneous incidences of nasal neoplasia in these strains of rats and mice are extremely low. For example, though not statistically significant when compared to matched control mice, the nasal carcinomas observed in 2 (out of a total of 215) mice exposed to a concentration of 14.3 ppm were, therefore, regarded as related to formaldehyde exposure."

Albert et al's combined HCl and formaldehyde vapour exposure results, when plotted as raw risk factors against the unadjusted DPX values show lower risk factors than the other studies, which indicates that their lifetimes must have been shorter than 2 years.

7.2 Short Term Exposure Studies

Feron et al (1988) carried out a series of short term studies on a total of 465 male Wistar rats assigned to 9 different groups. 3 exposure levels (0, 10 and 20 ppm) and 3 durations (4, 8 and 13 weeks, each for 6 hours/day, 5 days/week) were used. Observation was continued on all the rats up to a total of 130 weeks from first test exposure. Strangely, out of all the studies reported in the EPA review, 2 carcinomas were found in the 8 week control group. In view of the fact that "the spontaneous incidences of nasal neoplasia ... are extremely low" the chances of finding 2 in a control group of 44 must be very low indeed. I therefore suspect that there may

have been a mix up and these should have been the 8 week, 20 ppm group, and the 1 reported in the 8 week, 20 ppm group should have been reported as the control group.

There is also confusion in the review over the group size at 20 ppm and 13 weeks exposure. Page 21 states 6 were found in 132 rats at 20 ppm, while page 36 states 5. Table 4.1 states 3 in 132 exposed to 20 ppm for 13 weeks, yet the design given on page 36 implies a final net of 43/44/45 in each group, after intermediate sacrifices. I therefore suspect that the total of the 3 groups at 20 ppm was 132, or the total of the 3 groups at 13 weeks was 132. In the latter case we know that there were 45 controls and 44 in the 10 ppm group, implying a total of 43 in the 20 ppm 13 week group. Assuming a mean group size of 44, and with the above, the group sizes are approximately:

Exposure	4 week	8 week	13 week
Control (0 ppm)	43	44	45
10 ppm	44	44	44
20 ppm	45	44	43
and from the details on page 36 we find:			
Control (0 ppm)	0	2	0
10 ppm	0	1	1
20 ppm	1	1	3
Swapping the 8 week contol with the 20 ppm gives:			
Control (0 ppm)	0	1	0
10 ppm	0	1	1
20 ppm	1	2	3

This now gives the total of 6 carcinomas as reported on page 21 at 20 ppm, and the 3/132 in Table 1 should read 3/43. The risk fraction pro-rated to 2 years can now be calculated, and compared to the expected values:

Exposure	4 week	8 week	13 week	Expected Risk
Control (0 ppm)	0	0	0	0
10 ppm	0.00	-0.30	-0.18	-0.23
20 ppm	-0.58	-0.60	-0.58	-1.21

Bearing in mind the small group size and the short exposure duration, the agreement of the 10 ppm data with the long term results is excellent. However, even with the above assignments, though the 20 ppm results are self-consistent, they are all much lower than expected; the results are more like those expected for 15 ppm, at which

the expected risk factor is -0.64. I suspect, therefore, that the original report used formaldehyde concentration factors of mg/m^3, rather than ppm. At 20°C the correction is 1.24, resulting in concentrations of 8.1 and 16.1 ppm, and the results are plotted on Fig 15, with expected risk factors of -0.125 and -0.75. Again bearing in mind the short exposure times and the corresponding small number of carcinomas found, these results are in excellent agreement with those of the long term studies, and we can conlude that the method of pro-rating the cancer risk factor used in this report is valid. **Would EPA please advise me, as soon as possible, on the validity of these deductions?**

7.3 Conclusions from Cancer Studies with Rats

A single, highly significant, correlation has been found to fit the rat cancer data from 4 different long term studies (24 to 28 months exposure to formaldehyde vapour) which were published in 1983, 1985, 1989 and 1990, as well as the data obtained in Feron's short term study (4, 8 and 13 weeks exposure).

This confirms:

1. that the DPX/formaldehyde vapour correlation as developed in this report is valid.

2. that the unadjusted DPX value is the correct correlating parameter.

3. that the raw risk factor, ln(1-P), adjusted for the time of exposure, is the appropriate correlating parameter when analysing cancer data, and the IRMC needs to revise its statistical standardisation procedures.

4. why no carcinomas were found at formaldehyde concentrations of 0.1, 0.3, 0.7, 1 or 2 ppm in any of the long term studies, with nuls also found at 6 and 10 ppm. Statistically, when the various experiments are considered together as an estimate of risk, these nuls reinforce the concept that certainly up to 2 ppm, the cancer incidence is truly zero. These nuls, together with the strong correlation above 6 ppm, confirms the existance of a cancer threshold in rats at around 6 ppm.

5. that damaging the nasal mucosa did not alter the risk of the Wistar rats contracting cancer when exposed to 10 ppm formaldehyde over 28 months.

Note that it was assumed in 7.1 above that the critical time period was a day or less. The problem is then how to correct if the exposure is, say, for 8 or 24 hours per day rather than 6. The key is the half-life of the active formaldehyde moieties in the nasal mucosa. If the half-life is less than an hour, then the times could be simply pro-rated, and this would provide a conservative estimate. Wilmer et al's (1989) experiment would need to be repeated at 10 ppm to get a better estimate.

8 OTHER CANCER DATA

Soffritti et al (1989) subjected groups of Sprague-Dawley rats of different ages to formaldehyde administered in their drinking water. "A low incidence (2-21%) of gastrointestinal neoplasms was observed in some treated animals. ... which were not seen in the matched controls." Note that some of the equivalent formaldehyde vapour concentrations are quite high (at a body heat of 35°C):

wt % formaldehyde	equiv ppm
0.001	0.26
0.005	1.28
0.010	2.56
0.100	25.4
0.150	37.9
0.250	62.5

Iversen's (1986) skin painting with 10% formalin solution is equivalent to a localised vapour concentration of 1,500 ppm.

Cosma and Marchok's (1987) study of rat tracheal transplants and challenge with 0.2% formaldehyde solution is equivalent to a vapour concentration of 50 ppm, yet this only resulted in a "weak" response.

Takahashi et al's (1986) study included rats drinking 0.2% formaldehyde in their drinking water for 32 weeks, after an initial period of 8 weeks drinking MNNG (100mg/L) and found an 88% incidence of papillomas in the forestomach. Again note the 50 ppm vapour equivalency. The prior MNNG challenge was found to amplify the effect of the formaldehyde.

8.1 Conclusion on Other Cancer Data

All these other tests show that formaldehyde, when sufficiently concentrated, is carcinogenic in rats, regardless of the route, but only at the local exposure site.

9 OTHER EFFECTS FROM EXPOSURE TO FORMALDEHYDE

Swenberg et al's (1983) investigation of cell proliferation showed a sharp increase from the controls at 6 and 15 ppm after 3 days exposure, and was substantially decreased after 10 days of exposure, ie the defence mechanisms had become sufficiently enhanced by the 10th day.

Monticello (1990) "following 3 to 18 months of exposure, no apparent increases in nasal cell proliferation and no treatment related lesions in the nasal passages occured with formaldehyde levels of 6 ppm as well as 2 and 0.7 ppm."

"Both in vitro and in vivo studies (Morgan et al (1983, 1986)) have shown that there is a clear dose-dependent effect of formaldehyde on the mucociliary apparatus of rats. At 15 ppm, there was significant inhibition of mucociliary activity, whereas at 2 or 6 ppm, only slight effects were noted." This therefore gives a physiological reason for the threshold existing at around 6 ppm.

9.1 Conclusion on Other Effects Data

These 3 studies would indicate that the zero risk formaldehyde concentration is around the 6 ppm value.

10 OTHER SPECIES

10.1 Mice

Both in Kerns et al (1983) (2/215 (0.93%) cancer incidence at 14.3 ppm) and Swenberg et al (1983) there are indications that a mouse's response to challenge by formaldehyde vapour at 15 ppm is equivalent to that of the rat at around 6 ppm. In DPX terms this represents a 6 fold lower degree of risk. What has not been proven is whether the rat DPX threshold value would be a good indicator for all species and could be used as a direct indicator of relative risk across species.

10.2 Hamsters

Though omitted from the 1990 EPA Report, I believe long term exposure challenge tests have been carried out with hamsters, and their cancer development proved to be similar to that of mice at around 14.3 ppm.

10.3 Monkeys

Heck et al (1989) measured the DPX levels in rhesus monkeys, and when combined with this report, their findings would indicate a 7.6 fold lower risk based on DPX. Though omitted from the 1990 EPA report, I believe long term exposure challenge tests have been carried out with monkeys, and their threshold was similar to that of the mice at around 15 ppm, which again would support the use of DPX as a direct carcinogenic indicator.

10.4 Man

Obviously no equivalent challenge tests have been carried out with human subjects. However, there has been substantial experience in times past of extended occupational exposures to formaldehyde concentrations in the 3 to 7 ppm range. If the threshold in man was equivalent to that in rats, with the orders of magnitude larger numbers of people having been exposed, a substantially increased risk of nasal carcinomas would have shown up in the epidemiological studies, whereas the UAREP Review of Epidemiological Studies (1988), quoted in the EPA review, states "the excess risk must be small."

11 CONCLUSIONS ON CANCER RISK IN MAN

We can therefore conclude that

1. There is extensive evidence that a threshold exists at around 6 ppm for rats exposed to formaldehyde, and that below that threshold the natural protective mechanisms built into their nasal systems are sufficient to suppress development of cancers.

2. The unadjusted DPX value appears to provide a direct indicator of carcinogenic risk.

3. The carcinogenic risk factor should be calculated from ln(1-P) and pro-rated to an appropriate standard time-frame, where P = cancer proportion found.

4. Fig 15, based on 4 long and 1 short term rat study, provides a good estimate of the risk of developing cancer in rats due to exposure to formaldehyde vapour.

5. Based on the 4 long term rat studies, the threshold unadjusted DPX level in rats is estimated as 107 pmol/mg DNA/6 hours, equivalent to a 6 h/day, 5 day/wk formaldehyde vapour concentration of 5.7 ppm.

6. Man's response to formaldehyde vapour is more like that of mice and monkeys, than of rats, with a threshold closer to 15 ppm, than 6 ppm. Therefore Fig 15 provides a conservative estimate of the carcinogenic risk in man.

7. On a very conservative basis, at 2 ppm and below, formaldehyde vapour should be removed from any of the carcinogenic safety classifications, and should be treated as having negligible carcinogenic potential. Based on conclusions 5 and 6, this provides a formaldehyde vapour concentration safety factor of 7 fold.

8. Intermediate classifications should be introduced:

   between 2 and 4.5 ppm as "possible",
   between 4.5 and 6 ppm as "probable", and
   above 6 ppm as "proven".

   The above criteria will provide an adequate margin of safety. These criteria can be relaxed further when the relationship between the cancer incidence in rats and that in man is better understood.

9. The epidemiological studies should be re-examined after separating out populations exposed to over 3 and over 6 ppm for extended periods of time and comparing their cancer incidence with those exposed to lower concentrations.

10. The exposure limits suggested in this report based on control of irritation and odor provide a sufficient factor of safety with regards to carcinogenic potential and should be adopted.

P V L Barrett

Dr P V L Barrett **24th April, 1991**

12 REFERENCES

1. British Standard, BS 5617:1985 (1st Ed 1978), "Specification for Urea Formaldehyde (UF) Foam Systems Suitable for Thermal Insulation of Cavity Walls with Masonry or Concrete Inner and Outer Leaves".

2. British Standard, BS 5618:1985 (1st Ed 1978), "Code of Practice for Thermal Insulation of Cavity Walls (with Masonry or Concrete Inner and Outer Leaves) by Filling with Urea-Formaldehyde (UF) Foam Systems".

3. "British Standards Institution Quality Assurance Scheme for Registration of Firms of Assessed Capability (Service Industries): relating to the Installation of Urea Formaldehyde Foam Cavity Wall Insulation", first registered in 1979.

4. British Standards Quality Assurance Division Scheme for the Assessment of Capability in the Installation of Urea Formaldehyde Foam, 1982 Complaint Survey, Milton Keynes, UK.

5. Everett L H, "Urea Formaldehyde Foam and Formaldehyde Emission; UK Experience with Cavity Wall Insulation", Formaldehyde Workshop, Little Rock, Arkansas, 1983.

6. Barrett P V L, "Formaldehyde and Urea Formaldehyde Cavity Insulation", Structural Survey, 1984, 2, 369.

7. Barrett P V L, "UF Foam - the Current Situation", Insulation Journal, 1982, Oct, 12.

8. Barrett P V L, Report on 1982 Formaldehyde Survey for Essex County Council, July 1983.

9. Barrett P V L, "Final Report on Formaldehyde Fumes in 3A Lake Road, Hamworthy", 7th Oct, 1983.

10. Barrett P V L, revised 1988, "How the Characteristics of, and Emissions from, Urea Formaldehyde Foam Insulation (UFFI) change with Age", Report prepared under NRC contract for the Canadian UFFI Centre.

11. Barrett P V L, "Experimental Investigations into Urea Formaldehyde Foam Insulation (UFFI), Part I", NRC Contract Nos: 041-1588/4049 and 042-938/1025, 1987.

12. Barrett P V L, Paryniuk M, Paden J W, and Giacometti L, "F6 series of Fungii Inoculation of UFFI Experiments", Formtek Technologies Inc report, 1985.

13. Walker, J F, "Formaldehyde", 3rd Ed, Robert E Krieger Publishing Company, 1964.

II.

ARB Staff Summary of Comments and Responses on the Draft SRP Version Part A

WRITTEN RESPONSES TO COMMENTS ON PART A

We have received comments from the Hardwood Plywood Manufacturers Association (HPMA) and the National Particleboard Association (NPA) on the draft formaldehyde report which are summarized and responded to below.

1. **Comment:** The HPMA and NPA comment that hardwood plywood is made of distinct layers of wood and is not classified as a reconstituted wood product.

Response: The classification in the text will be changed to pressed wood products.

2. **Comment:** They also comment that California home studies were conducted in homes built in the early 1980's and prior to that time. These studies included no information on the loading rates (usage) of wood products, materials containing formaldehyde, and sources of formaldehyde.

Response: The home studies used by the ARB provide the best and most recent data available on indoor formaldehyde concentrations. They included only randomly-selected homes; they could be expected to represent a realistic range of loading rates and presence of formaldehyde sources. They were used for estimating indoor concentrations only and not for source apportionment.

3. **Comment:** The reference to the UFFI ban on p. A-45 of the Part A report directly quotes "The ban was challenged on procedural grounds (but not on its technical merits)" is not correct. They say the actual findings of the Fifth Circuit Court of Appeals reveal that the Commissions rule banning UFFI is null and void based on procedural and technical merits.

Response: The reference to the UFFI ban on p. A-45 has been changed to read "The ban was challenged successfully in the U.S. Court of Appeals (1983) by UFFI and formaldehyde manufacturers."

4. **Comment:** In-home exposures are overstated relative to outdoor exposures. Further, if outdoor levels of formaldehyde have changed due to reductions in formaldehyde release from motor vehicles and other outside sources, then that reduction would be reflected indoors.

Response: While there have been decreases in motor vehicle emissions since 1965 due to emission controls, no correlation can be made at this time on the direct effect on indoor exposure levels. Because indoor levels are generally much higher than outdoor levels, any change due to changes in outdoor levels would be expected to be small.

5. **Comment:** The two Associations provided a number of comments regarding whether sufficient characterization had been provided regarding the impact of new UF-bonded wood products which contain less formaldehyde. They specifically indicated that the decay rate of these products had not been considered as well as their usage in homes, particularly new homes. The primary concern seems to stem from statements in the report that ascribe most indoor formaldehyde to pressed wood products.

Response: The data used for our indoor concentration estimates are the most recent and comprehensive available and are based on measurements of formaldehyde concentrations in homes of all ages. This takes into account new building materials in new (at the time of measurement) homes and older building materials in older homes where off-gassing of formaldehyde would have occurred. Because they are based on several studies of randomly-selected homes, we believe our indoor concentration estimates are representative of average homes. We do not have data at this time substantiating that indoor concentrations have decreased due to use of new, lower-emitting pressed wood products. However, we will add a discussion in the report indicating that concentrations in homes built recently may be lower (to an unknown extent) than in homes built before the early 1980s when they were new due to the use of lower-emitting products. Also, we will modify the statements regarding the contribution of pressed wood products to indoor formaldehyde concentrations to reflect the possibility that such products may not always make the largest contribution in all cases.

6. **Comment:** The principal California conventional home study (SAI) used by ARB states that the primary formaldehyde sources cited were homes where cigarettes were smoked and gas cooking fuel was used, with no mention of wood products. The Sexton study also made no mention of wood products as formaldehyde emitters.

Response: While the studies we used to estimate indoor concentrations did not measure all factors that could contribute to the formaldehyde levels measured in the homes (such as the use of pressed wood products or the presence of all other potential sources), we did not use those studies for source apportionment. This comment appears to reflect concerns about statements in the report which appear to ascribe most of the indoor formaldehyde to pressed wood products. These concerns should be addressed by the modifications to those statements as mentioned above. A more detailed discussion of the SAI study's results regarding the contribution of cigarette smoke to indoor formaldehyde concentrations will be added to the report.

III.

OEHHA Staff Summary of Comments and Responses on the Draft SRP Version Part B

Response to Formaldehyde Institute Comments of October 18, 1991

The Formaldehyde Institute comments on the revised version of the risk assessment are described and numbered as they appear on page 2 of the comments. The responses include an additional comment, identified as Comment 2A, which was stated on page 10 of the comments. *Those Formaldehyde Institute comments which quote EPA's Formaldehyde Risk Assessment Update quote only the incomplete September 1990 draft update rather than the draft update of June 1991. Often the differences are important, as pointed out in the responses below.*

(1) Comment: The CIIT monkey data are rejected in favor of use of rodent data which is unquestionably less relevant to humans.

Response: Staff very carefully reviewed all of the comments submitted during the first comment period regarding this topic. The articles referred to in the argument to support this comment were reviewed and were cited in the revised document. This current version of the health effects document has explicitly taken into account the monkey cross-linking data, and the range of risks incorporates this information. (as indicated on p. 167 of Part C). This information is reflected in Table 5 on p. 2-24 under column "contact, dosimetric." Although monkey cross-link data are incorporated into the range of risks, OEHHA staff concluded that the resulting risk estimate did not represent the best value because:

(i). It is unclear how the partitioning of the oral and nasal breathing in the monkey compares with the rats' nasal breathing or the typical human breathing patterns. The monkeys exposed to formaldehyde in the experiments may have breathed orally to a substantial degree, thus reducing the nasal exposure.

(ii). Rats may have more ability to detoxify formaldehyde than humans due to the rats' higher glutathione levels and enzymatic activities, compared to humans. Thus, humans may be more sensitive to formaldehyde. If the monkeys did not engage in substantial mouth breathing, the measured low DNA-binding in monkeys implies very high detoxification or other elimination of formaldehyde or a higher rate of DNA repair. The mechanism for this effect does not have a clear explanation.

(iii). The underlying cancer predisposition factors for lung in monkeys is unclear. Data are not available which indicate that respiratory cancer in monkeys correlates better with human respiratory cancer than rat respiratory cancer.

(iv). The available monkey data do not describe formaldehyde binding throughout the complete respiratory tract. Human data seem to indicate that the primary risk factor from formaldehyde exposure is lung cancer in particular and respiratory cancer in general. Elevated cancer rates have been reported in humans for the lung, nasal passages, nasopharynx and buccal cavity. Consequently, comparison of exposure between rats and monkeys, isolated to a small area of the respiratory tract does not consider the complete carcinogenic picture for humans.

(a) The argument that is offered to support the comment starts on p. 3 by asserting, "It is both incontrovertible toxicology doctrine and a specific finding of the U.S. Environmental Protection Agency that primate data are more

relevant to humans than rodent data." This generalization about toxicological doctrine can be misleading without some particulars. In the present circumstance, the issue is not a straight choice of cancer bioassays between rat and monkey. There is no cancer bioassay for monkeys. So the revised document chooses among three model results: (i) a standard default extrapolation of the rat bioassay, (ii) an extrapolation that takes the contact mechanism of carcinogenesis into account in a generic way without the use of any special data, and (iii) an extrapolation that takes the contact mechanism into account in a way that assumes that the monkey DPX data can be used in a straightford way to make an adjustment for non-allometric metabolism. While there is no citation for the specific finding, the lastest EPA draft update (June 1991) did state, "EPA favors (the risk estimate) based on DPX because monkey is considered a closer surrogate to humans than the rat." However, as indicated in the August 7, 1991 Environmental Policy Alert, the EPA Science Advisory Board's Health and Environmental Exposure Committee rejected the EPA draft analysis incorporating the monkey cross-linking data. The Committee indicated that it would not endorse the lower risk estimate based on the cross-linking data.

(b) The commenter's argument on p. 3 cites two quotations from the September 1990 incomplete EPA draft. The first quotation is highly questionable, especially as a summary of material in the test of the update.

> As stated before, nonlinear dose responses for nasal tumors in rats and [DNA cross link] formation as well as mucociliary clearance, cell proliferation, cytotoxicity, and nonneoplastic pathology in rats and monkeys argue for the true risk being well below that predicted by the upper bound....

While this assertion appeared in the summary of the incomplete draft of September 1990, it does not appear in the summary of the June 1991 draft of the update. A second quotation, "Rat-based estimates may be too high at a given exposure concentration, due to differences in breathing patterns.", also does not appear in the June 1990 update. In any case the statement is taken out of context because, further down, the original EPA paragraph states. "On the other hand, the monkey-based estimates may be too low because the DPX levels measured in the nasopharynx of monkeys, corresponding to a site having strong association of tumor incidence in humans, are not considered in the derivation of risk estimates." Section 5.5.1 on p. 80 of the 1991 draft EPA update has a more carefully worded version of the original paragraph containing both these statements.

> There are a number of uncertainties associated with risk estimates based on rat carcinogenicity data using dosimetry data, i.e. DPX, from the rat and monkey. Human risk estimates based on the rat dosimeter may be too high at a given exposure concentration, owing to differences in breathing patterns resulting in different exposure of the target tissue. The observed rat DPX concentrations best predict the rate of nasal tumors, albeit in rats. Since the DPX were lower in the monkey nasal mucosa, use of the rat dosimetry-based estimates may overestimate the probability of nasal tumors in primates. On the other hand, the monkey dosimetry-based estimates may be too low because the DPX levels measured in the nasopharynx of monkeys, corresponding to a site having a possible association of tumor incidence in humans, are not considered in the derivation of risk estimates. The dynamics of carcinogenesis in these different respiratory regions in different species have not been adequately examined.

A reference cited in connection with these statements, Monticello et al. (1989), provides data on the monkey for 1 or 6 weeks, but the discussion does not explain the significance of those data to the argument.

(c) The quotations on p.4 of the commenter's argument do not match the cited text of Heck et al. (1990). The second quotation does not appear in the original text at all, and the final sentence of that quotation is misleading for the quantitative risk assessment, "The maximum-likelihood estimate of risk for the monkey is between four and five orders-of magnitude lower than that predicted for the rat over the same concentration range." Maximum-likelihood estimates can, as in the present case, provide highly unstable predictions of risk at low exposures. See, for example, the 1991 EPA draft update, p. 80. Thus, though they can provide technically useful information in analyzing intermediate results, they should be avoided in ultimate statements of risk predictions at low exposures.

(d) The commenter's argument on p. 5 states that the 18-fold adjustment for the monkey cross-link data does not fully incorporate the monkey data and that a 54-fold adjustment is more appropriate. The 54-fold adjustment, which was relative to the allometrically derived dosimetric model, compares effects in only the nasal passages. Yet the monkey DNA-binding (DPX) data demonstrates that the potential risk of cancer goes well beyond the nasal passages. A complete comparison would compare the total DNA-bound dose in the rat to the total dose bound in the monkey. However, such a complete comparison of the relative cancer risk is not possible due to the incomplete data available on the distribution of formaldehyde throughout monkey respiratory tract. The analysis in the document used as much of the dose data as is available and found a best estimate that reduced the risk 18-fold, relative to the purely allometric analysis.

(e) Further, on p. 5 the commenter's argument asserts:

> There are myriad assumptions that are simply stated without support. Two key examples are: (1) derivation of nasal penetration data for monkeys from the high exposure level, rather than from the lower exposure level which would be more analogous to the human experience; and (2) use of the upper bound for the nasal penetration data in the rat. Despite the numerous assumptions, there is no discussion of the effect of uncertainty.

The three issues raised in this assertion are discussed in turn.

(i) Derivation of nasal penetration data. At lower applied concentrations Heck et al. (1989) clearly labelled the postnasal values as uncertain. The use of the highest exposure data for nasal penetration was to obtain the most numerically precise result. Response 4a to the T. Starr Comments of November 10, 1990 presents an account of the calculation and a discussion of the issues. The use of the highest exposure data does contribute to uncertainty of the result.

(ii) Use of upper bound. The use of the upper bound of 0.03 for rat nasal penetration was for convenience. Penetrations that are a few times lower would have little effect on the results, which depend on one minus the penetration -- thus at most a 3% error from this source -- and on the logarithm of the penetration, an insensitive function.

(iii) Effect of uncertainty. The OEHHA staff did consider how sensitive the results might be to the assumptions, with the idea that the document would point out any uncertainties found to have a major numerical effect.

(f) Remaining points. Further assertions in the commenter's argument on pp.5-6, not quoted here, lack specifics.

(2) Comment: In contrast to EPA and other organizations that have considered incorporation of cell proliferation data in risk assessment, the Draft states that these data increase the risk prediction.

Response: The EPA has not incorporated cell proliferation into their risk analysis. In response to the earlier comments of the FI this version of the California document developed predictions of the effect of cell proliferation on the basis of available data and a number of modeling assumptions. The results show that the use of a cell-proliferation model is likely to predict a somewhat increased risk, while there is a small chance that a lower risk would be predicted.

The commenter's argument does not provide new data indicating that the OEHHA data were incorrect.

(a) On p. 6 the argument to support the comment starts by asserting, "CARB has failed to recognize, as did EPA, that airborne concentration is a more important exposure parameter than total dose:". On the contrary, as pointed out in the previous reponse to comments (FI, 1d; Starr, 4a; Swenberg, 8a), the use of DPX in both versions of the document weights applied concentration more than time in the calculation of risk. In addition the cell proliferation models used in the revised version of the document heavily weight the applied concentration in the calculation of risk at high concentrations.

(b) On p. 7, the argument asserts , "cell proliferation caused by exposure to high cytotoxic doses appears to represent the mechanism of formaldehyde carcinogenicity." (emphasis added). The word "the" is entirely misleading. Cell proliferation is an enhancing mechanism, not the mechanism. Mutation is an essential mechanism in the Moolgavkar models advocated by the FI commenters, Starr and Swenberg. The Feron report, cited in the comments on p. 9, mentions several compounds which induce nasal cytotoxicity and hyperproliferation, but which do not cause nasal tumors. These compounds are either not mutagenic or weakly so.

In regard to this point, it is instructive to consider a model within the present understanding of the mechanisms of carcinogenesis, in which formaldehyde enhances the underlying background mutation rate, and therefore cancer rate, by virtue of increasing the net rate of cell replication due to cell proliferation. In order for this model to produce the high incidence of cancer observed in the bioassay at the high exposure (67%) it is necessary for the nasal cells to have a significant background cancer rate, even for the no exposure group. This background cancer rate would be determined by the rate of the no exposure group. A significant rate would be necessary because the risk of producing cancer depends on the product of the background cancer rate and the rate of cell proliferation. To produce the observed rate of cancer in the high exposure group of the bioassay requires a background cancer rate of

approximately 5 to 10% to get a hazard product of 50%, because the cell proliferation rate is 5 to 10 times the background rate. A 5 to 10% background cancer rate was not observed in the bioassay. Instead the background cancer rate observed in the control animals (as well as the 2 ppm exposure group) was zero, a result which is consistent with the very low incidence of nasal cancer in historical controls. The revised document did not include results of calculations for this cell proliferation model (0te0 in the notation of the revised version of the document, Appendix A) because the resulting predictions are contrary to the observations.

(c) On p. 9, the commenter states, "the Feron Report" concludes "from the CIIT data that human exposure to non-cytotoxic levels of formaldehyde represents a negligible cancer risk." Yet no quantitative estimates of risk are provided and term "negligible" is not clearly defined.

Also on p. 9, "With respect to the Feron study and a more recent study by Wouterson," the commenter cites CIIT as stating, "the induction of cancer appears to require very high concentrations of formaldehyde." No support for this asserted requirement is offered, and the unreferenced citation does not provide the necessary quantitative estimates for risk assessment.

(d) The commenter ends with a paragraph beginning, "The current Draft offers two arguments in support of its failure to consider the cell proliferation data." OEHHA staff strongly disagree with this statement. The revised version of the document provides the first thorough consideration of cell proliferation data for formaldehyde risk assessment and uses cell proliferation data, as outlined on p. 2-13 of the main text. In addition pp. A-3 through A-10 describe the process in some detail. OEHHA staff, however, believe that consideration of a model does not require acceptance of the model with all of its assumptions.

(2A) Comment: CARB should consider the CanTox risk assessment

Response: The OEHHA staff did review and consider the CanTox risk assessment, furnished by the Formaldehyde Institute. Page 2 of that assessment stated, "The primary objective of the biological risk assessment of formaldehyde prepared by CanTox is to update the EPA report with information either not considered, or not available in the April 1987 report." The CanTox assessment emphasized biological information, but the only quantitative risk assessment is in Appendix C. In striking contrast to the EPA risk assessments based on the multistage modelling, the principal conclusion of the CanTox assessment was that "the no effect level for carcinogensis is 1 ppm." This finding is based on the assertion "that at 1 ppm the operation of protective mechanisms would eliminate the risk of developing formaldehyde-induced cancer of the upper respiratory system." The CanTox assessment did not explore quantitative trends to reach this conclusion. Therefore, the conclusion does not meet the needs of the Toxic Air Contaminant Program. Furthermore, the detection of significant DNA binding of radiolabelled formaldehyde in the rat nasal passages for an applied exposure of 0.3 ppm and in the nasal passages of monkeys at 0.7 ppm greatly limits the finding that 1 ppm would protect humans, based on this protective mechanism hypothesis. The CanTox assessment was not discussed in the OEHHA document because it is one of many reviews of the formaldehyde literature but has not been published in the peer-reviewed literature.

(3) Comment: The draft totally ignores published studies indicating that while formaldehyde is weakly genotoxic in vitro it does not have the same effect in the live animal.

Response: The text of the 1987 IARC evaluation of genotoxicity of formaldehyde is as follows:

> In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings.
>
> No increase in the frequency of micronuclei or chromosomal aberrations was observed in rodents treated with formaldehyde in vivo; assays for dominant lethal mutations and DNA damage gave inconclusive results.
>
> Formaldehyde induced sperm-head anomalies in rats. It induced DNA-protein cross-links, unscheduled DNA synthesis, chromosomal aberrations, sister chromatid exchanges and mutation in human cells in vitro. It induced transformation of mouse C3H 10T1/2 cells and chromosomal aberrations, sister chromatid exchanges. DNA strand breaks and DNA-protein cross-links in rodent cell in vitro. In *Drosophila*, administration of formaldehyde in the diet induced lethal and visible mutations, deficiencies, duplications, inversions and translocations and crossing-over in spermatogonia. It induced mutation, gene conversion, DNA strand breaks and DNA-protein cross-links in fungi and mutation and DNA damage in bacteria.

Thus, IARC found in their official publication two years after the unpublished Ontario report cited by the commenter on p. 13 that formaldehyde has reportedly induced mutations in viruses, bacteria, yeast, fungi, drosophila, grasshoppers, and mammalian cells in culture. Also, formaldehyde has produced chromosome aberrations, sister chromatid exchange and single-strand breaks in DNA. The US EPA in their draft Risk Assessment of June 1991 cited the evidence for genotoxicity of formaldehyde and mentioned studies available subsequent to their 1987 document. They concluded, "The new studies corroborate previous findings of the genotoxicity of formaldehyde (EPA 1987)."

Although the SRP draft represents an expedited risk assessment focused on the carcinogenicity of formaldehyde, it does not ignore the in vivo data, much of which is negative, but in vivo assays tend to be insensitive. Page 1-1 of Part B states that "many in vivo studies have yielded negative or equivocal results." However, p. 1-1 also states that the presence of in vivo binding of radiolabelled formaldehyde to DNA in the rat and monkey following inhalation, in addition to in vitro studies, indicates that formaldehyde is genotoxic. While the commenter focuses on in vivo mutagenicity, staff have considered all data relevant to genotoxicity. Unanimity of test results is not required to consider an agent genotoxic. OEHHA staff believe that there is considerable evidence indicating that formaldehyde may act through a genotoxic mechanism to induce cancer. OEHHA staff have also considered the cell proliferation mechanism for formaldehyde carcinogenicity and concluded that the cell proliferation mechanism by itself cannot be responsible for the full extent of carcinogenicity observed in the rat.

(4) Comment: The one-sided presentation of epidemiologic data continues, and analysis relating to the conclusion that formaldehyde does not cause cancer in humans is ignored.

Response: Appendix C of the formaldehyde report contains an extensive review of the epidemiologic data. A section of the document on pp. 2-3 through 2-5 cites the studies that provide limited evidence of carcinogenicity and cites recent studies, both positive and negative. Some epidemiologic studies did not find an elevated rate for any form of cancer in formaldehyde-exposed workers. This outcome is consistent with formaldehyde having a carcinogenic potency in the range of the predictions in the document. Many of these non-positive studies, for example those cited on p. 59 of Part C, lacked the statistical power to detect such a small effect. Nevetheless, other studies cited in the document, studies with more subjects and therefore more statistical power, did detect excesses in various cancers. As pointed out on p. 2-3 of the document, seven studies reported statistially significant increases in upper respiratory tract cancer. In addition, "the three largest -- and therefore potentially most sensitive -- industrial cohort studies reported elevated rates of lung cancer."

On pp. 58-61, Part C, the commenter identified 10 studies that detected no nasal cancer in relation to formaldehyde exposure and 2 studies that did identify a statistically significant relationship (Olsen et al. 1984, Hayes et al. 1986). In regard to the two positive studies the commenter states on p.61, Part C, "the accuracy of the exposure assessments in the Olsen and Hayes studies is questionable, a problem of case-control studes, and wood dust may be a confounding factor." In response OSHA (1987, p. 46189) and others have pointed out that random misclassification of exposures tends to reduce the ability of a study to detect an effect. Also, OSHA in their final rule (1987, p.46184-5) reviewed these two studies along with the follow-up study of Olson et al. (1986) and reported that two industrial hygienists in each study developed retrospective exposure assessments that were blind to any workers history, an unbiased procedure. Thus, any inaccuracy would tend to reduce the magnitude of effects. In addition the OSHA review points out that these studies were able to separate out the effect of formaldehyde alone, finding " a consistent 2-fold relative risk of squamous cell carcinoma of the nasal cavity for formaldehyde exposure alone."

On pp. 63-69, Part C the commenter dicusses three studies (Stayner et al. 1986 at NIOSH, Blair et al. 1986 at NCI and Vaughan et al. 1986), two of which show excess nasopharyngeal cancer and one shows excess buccal (oral) cancer. The commenter asserts, "Careful review demonstrates that claims of an association beween formaldehyde exposure and nasopharyngeal cancer based on the NCI and Stayner cohort mortality studies and the Vaughan case control study are unsupported." We disagree with the commenter. OSHA in its final rule (1987, pp. 46193-7) addressed similar concerns and concluded that the concerns did not invalidate the association of excess cancers with formaldehyde exposure.

On p. 54, Part C, the commenter asserts, "in the discussion of lung and pharyngeal cancer, the Draft Document cites Blair, Vaughan and Acheson without giving full weight to the published conclusions of each of these well-credentialed investigators." The following responses discuss each of those

authors' conclusions, generally referring to the earlier discussion by the federal OSHA, one of the background sources for the risk analysis.

On p. 70, Part C, the commenter quotes Blair et al. 1986, "the data provide little evidence that mortality from cancer is associated with formaldehyde exposure at levels experienced by workers in this study." The OSHA final rule (1987, p. 46185-46191) deals extensively with this issue. That text cites (p. 46187) several experts who disagreed with this conclusion. Among the experts cited were five members of the Advisory Panel for the study. Much of the disagreement was with "the premise that the presence of rising trends for lung cancer risk and cumulative exposure was required to establish a finding that formaldehyde workers were at increased risk of lung cancer." The OSHA discussion also included considerable evidence concerning the probability of substantial exposure misclassification in the study and the effect of such misclassification on obscuring any trend which might be present. OSHA (p. 46191) went on to summarize reasons why Blair and his colleagues failed to find a dose-response relationship.

> First, exposure misclassifications will bias the results against finding a statistically significant dose-response relationship regardless of whether high exposures are classified too low or low exposures are classified too high.
>
> Second, there is some indication that persons who were exposed at the highest cumulative doses of formaldehyde may have been less likely to smoke cigarettes.

Finally OSHA (ibid.) stated,

> Based on the above discussion, OSHA is of the opinion that formaldehyde played a role in the excess risk of lung cancer observed in the workers studied by Blair *et al.* (Ex. 156-A4).

The commenter on pp. 68, Part C quoted Vaughan et al. (1986b) as finding "a strong association between a history of having lived in a manufactured home and NPC" with the caveat, "the association found with living in a mobile home must be interpreted with caution since it is based on a small number of cases and may be due to factors other than formaldehyde." The OEHHA staff agree with this caveat.

In the last paragraph (p.78, Part C) of the section on lung cancers, the commenter asserts, "there is no basis to predict a cancer risk to humans based on the epidemiology studies. EPA concluded that 'apparent elevations in lung cancer risk were not statistically significant' and that 'no statistically significant exposure trends were observed.'" The commenter, however, omitted the first sentence of the paragraph from which the EPA quote was taken. The first sentence states, "Increases in lung cancer were suggested in the newer studies, but the evidence is not as strong as that for sinonasal and nasopharyngeal cancer." Consequently, the EPA paragraph does not appear to agree with the statment by the commenter that "there is no basis to predict a cancer risk to humans based on the epidemiology studies."

Staff have not ignored the March 1991 comments by the Formaldehyde Institute regarding the epidemiologic data. Instead, the OEHHA staff have a different opinion of the weight of the human epidemiologic evidence. Like the USEPA and IARC, OEHHA staff have concluded that there is, at a minimum, limited evidence of carcinogenicity in humans. In their 1987 final rule, the federal OSHA concluded even more strongly (p. 46201),

> The evidence regarding human risk of exposure to formaldehyde has become substantial. Case control studies indicate an excess risk of developing nasal cancer which cannot be attributed to wood dust exposure. The type of tumor seen in humans is the same as that observed in the rodents. Oro- and nasopharyngeal cancers have been seen in more than one study. Finally, a study of the British formaldehyde industry (Acheson et al. 1984 a,b,c) suggesting a possible excess risk of lung cancer has been corroborated in the U.S. industry (Blair et al. 1986).

Consequently, OEHHA staff have considered all the available epidemiologic evidence. The staff concluded that there is limited evidence of carcinogenicity of formaldehyde in humans and that several tumor sites in the respiratory tract have been identified.

(b) The commenter asserts (p.14) that there is no overall risk of cancer among formaldehyde workers. Cancer evaluation in workers is made on a study-by-study basis. There is no comprehensive study which considers all workers exposed to formaldehyde. Because of the heterogeneity of such a group, any such effect would be very difficult to detect, even with exceptionally good data. Available data are entirely inadequate to make such a statement. Furthermore, as pointed out above and stated in Part B seven studies reported statistially significant increases in upper respiratory tract cancer. In addition, "the three largest -- and therefore potentially most sensitive -- industrial cohort studies reported elevated rates of lung cancer."

(c) The commenter expresses (p.14) special disappointment that the document "totally ignores the refutation" of the Sterling and Weinkam analysis in a report to the Formaldehyde Institute by Marsh et al. (March 1990). The executive summary of the Marsh et al. report begins,

> Following the 1988 publication of the Sterling and Weinkam reanalysis of the joint National Cancer Institute (NCI)/Formaldehyde Institute (FI) cohort study of formaldehyde exposed workers, the FI commissioned the University of Pittsburgh to perform an independent reanalysis to confirm Sterling and Weinkam's finding of an increased risk for lung cancer mortality as a function of cumulative formaldehyde exposure, adjusting for length of exposure.

The summary ends,

> We did not confirm Sterling and Weinkam's finding of a positive trend for lung cancer with cumulative formaldehyde exposure adjusting for length of exposure. Both length of exposure and cumulative exposure were noninsignifcant predictors in the Sterling and Weinkam model. Like Sterling and Weinkam, our risk ratio estimates for lung cancer were elevated for the higher categories of cumulative formaldehyde exposure relative to the baseline category. Unlike Sterling and Weinkam, none of our estimates were statistically significantly elevated. There was also no evidence of confounding by calendar time but a significant plant effect was found that warrants further investigation. Latency period was the only statistically significant formaldehyde exposure measure. For all cancer and all cause mortality workers in the second category of cumulative exposure (.1-.5 ppm-yrs) were at elevated risk relative to the baseline; this risk was significantly elevated for all cause mortality. The discrepancies between our findings and Sterling and Weinkam's cannot be explained by the data management decisions or by the

choice of statistical modeling algorithm. Recommendations are given for areas of additional investigation.

Thus, for lung cancer, Marsh et al. reported finding elevated risk ratio estimates but their values were not statistically significant. Furthermore, Marsh et al. reported that consideration of latency did have a statistically significant effect on the explanation of lung cancer. While some of the conclusions of Marsh et al. differ from those of Sterling and Weinkam, the staff do not believe that the Marsh et al. report constitutes "the refutation of the Sterling data."

The commenter's argument on p. 15 asserts,

> The reanalysis corrected several flaws in the Sterling work, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to the different measures of exposure.

Yet, nowhere in the report of Marsh et al. do the words, "flaws" or "failure" appear. Instead the report speaks of "discrepancies" and "difference." Also a statement on p. 3 of Marsh et al. acknowledges Sterling and Weikam's use of a trend test in their letter to the Journal of Occupational Medicine in early 1989, which furnished the data ultimately used as a basis for the 1990 comparisons of Marsh et al.

Also on p. 15 the commenter states, "Marsh found that Sterling and Weinkam apparently make a significant counting error in computing person years at risk." An informal inquiry by OEHHA staff on the telephone has obtained an acknowledgement from Sterling and Weinkam that their person-year values were about 10% higher overall than Marsh et al. because of reliance on nominal factory starting dates instead of actual starting dates. They also reported on the telephone that a recalculation of risks with the more accurate starting dates had a negligible effect on the ultimate risks.

At the end of p. 15 the commenter's argument again mischaracterizes the report of Marsh et al.

> Marsh then reanalyzed the data to correct several flaws in Sterling and Weinkam's analysis, including failure to properly classify exposures and failure to statistically evaluate trends in the results relative to different measures of exposure.

This appears to be the opinion of the commenter because the Marsh et al. report contains no statement like that in substance or in tone.

At the top of p. 16, the commenter quotes the Marsh et al.report in a way that leaves out an important qualification. The citation includes only the first clause of the key sentence, which reads in full,

> We found no evidence of a positive trend with cumulative exposure in the models we considered, *but the estimated risk ratios were elevated in Table 33 for the three categories of cumulative exposure relative to the baseline of less than .1 ppm-yrs*. (Emphasis added to the clause omitted by commenter.)

The next citation by the commenter on p.16 takes a sentence out of context on the same issue. The commenter quotes the Marsh report, "Unlike Sterling and Weinkam, none of our estimates were statistically significantly elevated and the trend with cumulative exposure was not statistically significant." The preceding sentence in the report stated, "Like Sterling and Weinkam, our risk

ratio estimates for lung cancer were elevated for the higher categories of cumulative formaldehyde exposure relative to the baseline category."

Finally on p. 16, this part of the commenter's argument concludes with the assertion, "CARB's statement at p. 170 that Sterling was unrefuted is flatly incorrect and its analysis does not seem objective." Contrary to the comment, the OEHHA staff conclude that the Sterling and Weinkam results are unrefuted and believe that this is a straightforward conclusion. The major issue between the two reanalyses is whether or not there was a significant trend of lung cancer with increased formaldehyde exposure in the NCI/FI study (Blair et al., 1986). Certainly there is disagreement between the two reanalyses of the original data, and the issue has become controversial. A refutation would require a much closer look which indicated that the cause for the difference is due to errors on the part of Sterling and Weinkam.

(d) The final section of the argument on epidemiology asserts (p.16), "CARB has ignored the published findings of the distinguished panel chaired by Dr. John Higginson, the former chairman of the International Agency for Research on Cancer (IARC), which rejects the assertion that the epidemiologic data indicate formaldehyde presents cancer risk to humans." This assertion is incorrect. Neither the document nor the staff ignored this published work. The commenter's characterization that the panel "rejects the assertion that the epidemiologic data indicate formaldehyde presents cancer risk to humans" overstates the actual conclusions of Dr. Higginson's panel:

> Two conclusions from this review that would have widespread agreement among epidemiologists are: 1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure and 2) furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small. It is between these positions that more specific conclusions are less certain.

A further conclusion of the panel's report, not referred to by the commenter, gives added perspective:

> Topical sites have a plausibility that is lacking in the case of non-topical sites, but with the exception of lung cancer, these topical sites are rare and there is a paucity of studies of them. The recognition of weaknesses in studies that have reported an association between potential formaldehyde exposure and cancer of the nasal sinuses or nasopharynx is not the same as explaining away their findings. Although individual studies of cancer of the nasal sinuses, pharynx and lung have shown significant association with formaldehyde exposure, overall, there is no consistency among studies from any of these sites.

The Part B document did not provide a discussion of the panel's report because of reliance on three reports by official bodies (EPA, OSHA, IARC) in the same year (1987) the panel issued its report. The OEHHA staff, nevertheless, considered the report of this distinguished panel in reaching the conclusion of limited evidence of carcinogenicity in human studies. Generally, the staff found the panel's report did not conflict with the conclusion of "limited evidence of carcinogenicity in humans." It is the OEHHA staff's belief that if consistency were demonstrated, that would consitute sufficient evidence of cancer in humans. However, due to lack of consistency the evidence can only be considered limited. A later study of garment workers (Stayner, 1988) adds to

the evidence for formaldehyde carcinogenicity in humans. A still later review (Blair et al. 1990b) adds to the case for carcinogenicity in humans.

(5) Comment: The draft fails to respond to the Institute's comments respecting the Edling and Holmstrum reports respecting hyperplasia.

Response: The commenter's argument starts on p. 17 by claiming that the Draft (at p. 171) mischaracterizes the original comment. The claim has no basis. The characterization of the comment relied on direct quotation of the commenter, using the full citation in the commenter's executive summary p. 36, Part C, and the first sentence of the supporting paragraph, p. 86 Part C. It was the OEHHA staff response which argued for concern because these human studies found marked cellular effects even though the numbers participating were quite small, from 74 to 206 persons in the individual studies, including controls.

The commenter's concern on p. 18 appears to be that indications of a positive relationship of histological findings with formaldehyde exposure may be due to bias. Responses to the commenter's concerns expressed on p. 18 follow:

(i). "There is no statistically significant correlation between the observations and degree and duration of formaldehyde exposure." None would be expected for such small numbers of subjects.
(ii). "Alterations of the nasal mucosa have many possible causes, including smoking and passive smoking. There was insufficient examination of the confounders." All of these studies addressed the question of confounding due to smoking, but the documentation of smoking habits was sketchy in the positive studies.
(iii). "The control group was too small to be representative of the population as a whole." The commenter furnishes no analysis to define or support this statement.
(iv). "There is insufficient characterization of the formaldehyde exposure levels." All of the studies reported estimates of exposure. The commenter in Ex. 20 does, however, raise doubts about the precision of estimates in the study which apparently took the most care in estimating exposures (Holstrom et al. 1988).
(v). "These results are inconsistent with other studies of the nasal mucosa of formaldehyde-exposed workers. Berke, et al., 29 J. Occup. Med. 681 (1987) (finding no associated of abnormal cytology and formaldehyde exposure when controlling for age)." The positive studies performed nasal biopsies on all of the subjects examined., In contrast the negative study of Berke et al., now proposed to be cited in Part B, performed a biopsy on only a single subject.

In their draft update of June, 1991, the US EPA concluded,

> In summary, results of the newer studies indicate that formaldehyde exposure along with other exposures encountered in the studied occupational settings may enhance the severity of cellular damage. The major cellular changes in the nasal epithelium of formaldehyde-exposed workers were loss of cilia, squamous metaplasia, and mild or moderate dysplasia. The magnitude of the squamous metaplastic changes was more pronounced among exposed than among the referent populations. A low

prevalence of dysplasia also existed among exposed workers which were absent among referents.
These findings are based upon few individuals, and this limits the conclusions. In addition, the prevalent design of these studies may over- or under-estimate the effects. The lack of exposure-response relationships in these studies may also be a reflection of the prevalent study design; the studied populations could be considered survivor populations. In addition, exposure misclassification may also be present, thus, limiting the ability to detect exposure-response relationships.

In overall response to the comment, the OEHHA staff proposes to add the following to the existing paragraph in the revised version p. 2-5.

Edling (1988) found significant histological differences in the nasal mucosa of formaldehyde workers compared to unexposed workers but found no histological differences between those exposed to formaldehyde and those exposed to formaldehyde and wood dust. Berke (1987) found no statistical relationship between exfoliated nasal cells in formaldehyde-exposed workers and control groups. The results of these four studies are varied, the studies all use small numbers of subjects and the study designs are not sufficiently definitive. Thus, the studies, even taken together, do not establish a relationship, but they do provide some indication of possible histologic change due to formaldehyde exposure in humans, consistent with results in animals.

Essentially all human studies have flaws. That is one reason why animal studies are conducted. Staff of OEHHA have reported the available human evidence and have considered them in totality.

(6) Comment: Erroneous reliance is placed on the ingestion study by Soffritti.

Response: Part B does not rely on the Soffritti et al. study or any oral study in determining the carcinogenicity of formaldehyde. Rather Part B on p. 2-3 reflects the investigator's reports of the principal studies of formaldehyde carcinogenicity of animals. Response to detailed points on pp. 18-19 follow.

(i). "The Soffritti study does not indicate the substance being ingested. Because the report mentions impurity by methanol, it is possible that the study used formalin rather than formaldehyde as the test material." Soffritti et al. clearly specify a 0.3% methanol impurity as a stabilizer in the test compound. The dominant pathway for metabolism of methanol produces formaldehyde in its first step; so any additional carcinogenicity would still be just as attributable to formaldehyde.
(ii). "Incidence of stomach tumors -- the observation on which the authors rely for their conclusions -- did not differ significantly from the background rate observed in historical controls. An increase in the embryo group appeared only by combining difference stomach tumor types with various gastrointestinal tumors. The tumors did not exhibit a clear dose-response

relationship." The commenter does not specify how the combining of tumors invalidates any of the study's conclusions and does not provide a statistical analysis to document the assertion of the lack of dose-response relationship.
(iii). "The report does not present statistical evaluation of the data or time-to-tumor information." Statistical evaluation of the data would certainly be useful, as would the time-to-tumor information.
(iv). "The test animals were not sacrificed at designated intervals, but rather were allowed to live until spontaneous death, which would be expected to result in a higher cancer incidence rate." In the ending clause the commenter's meaning is unclear. True lifetime cancer rates would usually be best estimated by using the actual lifetime.
(v). "There was no analysis of clinical chemistry, urinalysis, hematology, or non-cancer pathological response. These gaps make interpretation of the study results difficult." Such data might be useful, especially to check on the animals condition, but they are not often available in cancer bioassays.

(a). As the commenter points out on p. 19, the study of Til et al. (1989) appears to be excellent. Nevertheless, it was conducted in a different strain of rat with different responsiveness.

(b). The Feron et al. (1990) "Letter to the Editor" provides a useful addition to the evaluation of that study. Those writers report that their own statistical analysis of the leukemia data gives a nonsignificant result and go on to suggest how the leukemia results might be simply due to chance. In addition they point out unusual patterns of tumors, a lack of crucial information in the paper, and some oversights in the literature review. Those writers do not claim, however, to discredit the Soffritti et al. study. It is unfortunate that the two groups have not been able to get in touch in order to satisfy the Feron group about the conduct of the study, but that does not necessarily minimize the validity of the Soffritti et al. study.
The OEHHA staff propose adding the following sentence to the end of the first full paragraph on p 2-3 of Part B: "In a letter to the editor, Feron et al (1990) questioned the conclusions and some methods of Soffritti et al (1989)."

(c). The US EPA in the update of June 1991 stated, "Collectively, the findings of these drinking water studies with formaldehyde (Takahashi et al., 1986; Til et al., 1989; Tobe et al., 1989; Soffritti et al., 1989) provide only suggestive evidence for the carcinogenicity of formaldehyde in the rat by oral route."

(d). In conclusion, the commenter's argument does not support the assertions, "The Soffritti study has been discredited" or "the Soffritti study should be accorded no weight."

In Part B the Soffritti et al. study is cited along with the Til et al. and Tobe et al. and the Takahashi et al. studies. OEHHA staff disagree with the commenter and believe that the present reference to the Soffritti et al. study is appropriate in the document.

Response to USEPA Comments of October 16, 1991

The US Environmental Protection Agency sent two sets of comments that were very similar in substance. At the Science Review Panel meeting of October 22, the OEHHA staff responded orally to the first set, signed by K. Hogan and dated October 15. The present responses are to the second set, signed by J. A. Cotruvo and dated October 16.

(1) Comment: The revised cancer risk assessment incorporates several different methodologies and assumptions (e.g. models, species scaling factors) and presents as a range of risks which are within two order of magnitude ($0.31-41.0 \times 10^{-3}$ ppm^{-1}) but endorses the use of the unit risk derived from a three-stage tissue-based (pharmacokinetics) model with a rat to human scaling factor of 1.2 as the best estimate of Upper Confidence Limit (UCL) on unit risk (i.e., 7.0×10^{-3} ppm^{-1}). The summary (pp. 1-2, 1-6) of Part B Health Assessment should indicate more clearly which UCL unit risk estimates incorporated cell proliferation modelling, and which did not. The discussion concerning scaling factors (Appendix A) is not quite clear, either, as to which unit risk estimates incorporate which scaling factors. These sections should coordinate better.

Response: The OEHHA staff propose to edit the report to provide more clarity and coordination, in the manner suggested by the commenter.

(2) Comment: The "best estimate" UCL on unit risk (p. 1-6) would be better described as the reference value, because "best estimate" has become statistical jargon which implies a different situation than the Summary describes. Reference value is a more neutral term and it should be accompanied with the appropriate qualifiers as to it being a current judgement in the midst of a number of possibilities.

Response: The OEHHA staff propose to replace the term, "best estimate", throughout the text with the term, "best value". An explanation in the text would emphasize that this "best value" is selected by the OEHHA staff as a judgement from a number of possible values.

(3) Comment: Relationship of Predictions to Observed Human Cancer Risks, (p. 2-20, Part B) - The use of lung cancer incidence and the assumption of 2.0 ppm exposure associated with non-sedentary activity are not adequately justified. In relation to formaldehyde exposure, lung cancer was not as clearly in excess as was nasopharyngeal cancer in the Blair et al. study. Concerns were noted in the document explaining why the excess lung cancer may not be entirely due to formaldehyde exposure. In addition, it would probably be more correct to halve the exposures in less active scenarios when trying to generalize to other situations, than to double the estimated exposures in the Blair study.

Response: (a) The assessment extrapolates risk from rats to humans on the basis that the rates of cancer in the rat's nose are essentially spread out over the entire respiratory tract of the human, following the expected distributions of concentration in both cases. Thus, the comparison in Part

B is for lung cancer, which is nearly equivalent to total respiratory cancer, but the observations may be elevated above the pure formaldehyde risk because of accompanying exposure to particles. The OEHHA staff propose to add such an explanation at this point in the text (p. 2-20).

(b) The assessment provides a basic lifetime unit risk based on rats in a sedentary state, during their daytime exposure. So the extrapolation of rat incidence to human risk implies a sedentary state. Thus, the rat equivalent exposure for humans needs to be doubled to take into account the doubling of human ventilation rate of the physically active factory worker relative to the more typical worker -- $20m^3$ compared to $10m^3$ breathed during the 8-hour workday.

(4) Comment: p. 2-10, Part B, first sentence - The estimation method used for the dosimetric model appears to have involved a least-squares procedure to obtain a best fit between the observed rate of binding of formaldehyde to DNA (y) and the exposure concentration (X), instead of a fit between the predicted and observed values of y, which would probably be a straight line with a slope of unity.

Response: The OEHHA staff propose a change in terminology in that sentence: "The estimation method was to obtain an algebraic expression predicting y and then to determine the parameters a_1, b_1, c_1 by minimizing the summed, squared deviations between predictions and observations, using inverse variance weights on the squared deviations".

(5) Comment: The discussion of the third scaling factor might be easier to follow if the dimensional units of the variables were included (p. A-14).

Response: The OEHHA staff propose to add dimensional units as indicated on p. A-14.

Response to T. Starr Comments of November 10, 1991

Each of the four sections of comments is characterized by a single quoted sentence representing the central concern of that portion needing a response.

1. Comment: "While data regarding cell proliferation in rats and DNA-protein cross-linking in monkeys that were considered point toward reduced human cancer risk, these data were not utilized at all in CARB's final risk computations." (p. 2, below middle)

Response: The Draft SRP Version uses both the cell proliferation data in rats and the DNA-protein crosslinking data in monkeys in models to compute cancer risks. The resulting values appear in the range of risks, but the OEHHA staff did not select either of those results as the best value because of a lack of assurance on the scientific merit of either calculation with its set of assumptions.

(a) On p.2 the commenter asserts, "Indeed, when only one component of this evidence, namely, the extent of formaldehyde-induced DNA-protein crosslinking in monkeys, is fully and properly taken into account, then CARB's new upper bound estimate of human cancer potency is reduced by a factor of approximately 13-fold." This statement would be correct only if the monkey data could be interpreted in the manner that the commenter has suggested. That interpretation depends upon the assumption that the monkey breathes essentially through the nose and that virtually all the formaldehyde that could lead to cancer is absorbed there and that the nose is the only locus of cancer risk, as in the rat. But that assumption is contrary to the observations of DNA-protein cross links distributed well past the nose in monkeys (Heck et al.,1989). See response to Comment 2, below.

(b) On pp. 2 and 3 the commenter asserts,

> CARB has also continued to assume that different temporal exposure patterns corresponding to a given continuous lifetime exposure all yield the same cancer risk. Because this assumption stands in direct contradiction to the acknowledged amplifying effects of increased cell replication on the carcinogenic process at high, but not low, formaldehyde concentrations, it introduces additional conservative bias into CARB's upper bound estimates of human cancer risk, further exaggerating the risks associated with low exposure levels.

In the risk calculations The draft SRP version does use the simplifying assumption of the rate of cell proliferation remaining constant at the level of the 12-month data. This simplification contributes to the uncertainty of the resulting predictions. The risk predicted at low concentrations might be smaller in some cell proliferation models if they incorporated a rate of cell proliferation larger than background, as observed within the first 3 months for an exposure of 6 ppm. Nevertheless, whether this incorporation would increase or decrease unit risk is uncertain.

The section at the top of p. 3 goes on to assert, "CARB's own computations indicate that this bias may be as large as another 5.3-fold factor." The mention of the possibility of bias in only one direction appears to assume that the model predicting the lowest risk will provide the best predictor.

The ratio of UCL for unit risk of the three-stage tissue-based model (3t), selected to give the best value, to the UCL for unit risk of the cell proliferation model (ltn2) giving the lowest unit risk is 5.8/1.1 = 5.3, the factor mentioned in the comment. The ratio is a measure of uncertainty of the models. This cell proliferation model (ltn2) is statistically marginal and is difficult to justify biologically because the model requires formaldehyde to increase mutation rates of both normal cells and premalignant cells with no increase in numbers of premalignant cells due to formaldehyde. All the other cell proliferation models, some of which provide an excellent statistical fit of the data, increase the estimates of risk.

Attached is a figure, proposed as Fig. A-1 for Part B. The figure shows the assumptions about the mechanistic role of cell proliferation in each of the cell proliferation models reported in the Draft SRP Version.

2. Comment: "This conservative bias in DPX prediction at low airborne formaldehyde concentrations should be corrected, even though it is quite small when compared to (other overpredictions)." (p. 3, bottom)

Response: The comment, which points out that the metabolic model in Part B predicts DPX values that are greater than the (two) measured values at low concentrations, is essentially a reiteration of the commenter's previous comment on pp. 95-96 of Part C. The comment here does not specify a relationship to obtain coincidence of the predictions with these measured value, although the commenter has published (Starr, 1990) a risk model using linear interpolation between adjacent data points to obtain predictions of DPX. On p. 172 of Part C the previous response to this comment points out that the method used to predict DPX in Part B on pp. 2-9 and 2-10, which is that of Casanova et al. (1989), gives a central tendency of the relationship between DPX and applied concentration of formaldehyde. Thus, the commenter's published use of a particular measured value of DPX rather than the predicted central tendency would be more likely to lead to bias than would the use of the model in the risk assessment.

3. Comment: "CARB's risk estimation should be modified so as to fully and properly account for the explicitly time-dependent effects on (cell) proliferation that are known to be present." (p. 4, third paragraph)

Response: The cell proliferation modeling did not try to take the time dependence of the cell turnover into account explicitly, even though, as the commenter pointed out, at times much shorter than 3 months investigators have reported substantial cell proliferation at the key concentration of 6 ppm. The commenter suggested the very useful test of setting R greater than one for this exposure group to get an idea of the effect of the initial cell proliferation.
Also the analysis did not take account of time-to-tumor information. As the commenter pointed out, these data might provide a way to check the cell proliferation modeling. Such an approach does not appear to have been published in the scientific literature. It is unclear if the approach would have a significant impact on estimates of unit risk.

4. Comment: "Until direct measurements of DPX in humans are available, the most plausible and scientifically defensible asssumption is that humans

develop DPX, and experience attendant cancer risk following formaldehyde exposure, to the same extent as do monkeys." (p. 7, final paragraph)

Response: Page 1 of the Response to Formaldehyde Institute Comments of October 18, 1991, contains a general response to this assertion. The general response, which extends down to heading "(a)" on the cited p. 1, explains that the monkey dat may not be appropriate for the desired dosimetry because, among other reasons, the monkeys may have engaged in substantial mouth breathing and no oral measurements were reported. Specific responses to the argument follow:

(a) On p. 5 of the comments, the paragraph that begins below the middle of the page assserts that the approach used for the dosimetric contact scaling factor is "very crude and is not likely to provide accurate quantitative prediction of species diffences in dosimetry." For example, the formula for penetration of contaminant gas along an airway (equation A-16) is "really only valid for straight cylindrical passages of constant cross-section with unlimited and homogeneous absorptive capacity." The commenter's assertion is too restrictive. The equation will be approximately correct in an average sense in a number of configurations that can be approximated by flow in a simple tube. Significant variability of concentrations occurring in the actual configuration, such as "hot spots" mentioned in the commenter' argument, would tend to make the results imprecise but not invalid.

The commenter asserts that the parameter, k, will almost certainly be significantly dependent upon the "depth of airway penetration." The parameter may vary as a function of distance along the airway, but the commenter has given no evidence that the variation is enough to invalidate the results, which are only expected to be approximate in this complex biological situation.

In the first paragraph on p. 6 the commenter asserts that less penetration occurs at low exposures of formaldehyde than at high exposures. The commenter offers no support for this statement, and measurements accurate enough to establish this statement would be difficult to make because measurements of penetration at low concentrations are difficult to make accurately. Use of the penetration value calculated for the highest exposure appears to be the only feasible alternative. It avoids reliance on the uncertain values of the lower exposures, but it does contribute to uncertainty of the result.

On p. 6 the commenter asserts that the derivation of the estimates of airway penetration for rats and monkeys in Table A-3 of the draft SRP version is unclear. OEHHA staff propose to provide further explanation, as indicated below. In the parameter estimation for the monkey the OEHHA analysis used Table 1 of Heck et al. (1989) to obtain the value of 0.7 for nasal penetration from the binding data, as indicated in footnote "b" of Table A-3 of the draft SRP version. The following should be added to that footnote:

> (6.0 ppm) to avoid the uncertainty of binding data obtained at lower exposures. The calculation of penetration used the local concentration of DNA-protein cross-links (DPX), 9.4 pmol/mg DNA, in the larynx-trachea-carina region to infer the airway formaldehyde concentration in that region. This DPX value is about half the 18.2 pmol/mg DNA in the turbinates and anterior nose, associated with the applied exposure of 6

ppm. Figure 5 of Casanova et al. (1991) provided the interpolation curve to obtain the airway concentration of approximately 4 ppm at that location for half the binding of the 6 ppm exposure. Thus, penetration is 4 ppm / 6 ppm = 0.7.

The Draft SRP Version used this value, rather than relying on the unsupported range of absorption of 0.7-0.9 in Table 2 of Heck et al (1989), which gives a range of penetration of 0.1-0.3. Note also the rationale of the previous paragraph in this response. In the parameter estimation for the rat the OEHHA analysis used the Dallas et al. (1985) data referred to on p. A-11. That citation should be added to Table A-3. Footnote "a", specifying the upper-bound value of 0.03, includes the range of penetration of 0 to 0.02 that Dallas et al. reported. The OEHHA analysis used these data in preference to the upper bound of 0.07 from the unreviewed abstract cited in Table 2 of Heck et al. (1989). The preliminary study by Patterson et al. (1986), may have given the high penetration cited by Heck et al (1989) because the experimental design, which was not documented, may have used an atypical flow through the nasal passages.

(b) On p. 6 the commenter asserts that the default scaling factor is "inconsistent with what is known regarding the molecular dosimetry of airbore formaldehyde in rodents and monkeys." This assertion is an overstatement. The pattern of formaldehyde distribution of deposition is not the same in rats and monkeys. The commenter's approach, outlined on page 6, appears to assume that all the deposition (of concern) in both species occurred in the nasal passages. But the data from Casanova et al. (1991) show that the distributions are very different, and potential mouth breathing by the monkeys complicates distribution patterns further. Thus, the commenter's assertion appears to be based on a hypothesis which is unlikely to be correct.

(c) On p. 7 the commenter asserts that "the monkey DPX data can and should be used to estimate human cancer risk, as has been demonstrated and recommended by Starr (1990) and, subsequently, by the US EPA in its recent draft update (USEPA, 1990) and final (draft) update (USEPA, 1991) of its 1987 formaldehyde health assessment document." The draft SRP version considered such estimates in defining the range of risk, but the OEHHA staff do not agree that these data lead to the best value.

The commenter goes on to point out that "in October, 1990, the US EPA's Science Advisory Board concurred with this recommendation." In July, 1991, the Science Advisory Board has been characterized (Environmental Policy Alert, August 7, 1991) as not being prepared to endorse the lower risk estimate based on the (monkey) cross-linking data. Thus, the initial endorsement in 1990 by the USEPA's Science Advisory Board appears to have been reversed.

Response to P. Barrett Comments of April 24, 1991

Comment: The commenter forwarded a copy of his "comment report" on the EPA Formaldehyde Risk Assessment Update of September, 1990. In his cover letter he stated that the assumption of zero threshold should be re-examined in the case of formaldehyde. He asserted that the EPA document contains strong evidence that a positive threshold exists.

Response: The relevant part of the "comment report" starts on page 12 with a section that develops a fit of the DPX data to formaldehyde exposures in rats and monkeys. The commenter finds the EPA's segmented linear fit unacceptable, as did Part B of the present document. The commenter develops his own quadratic fit. His analysis arrives at this fit by polynomial regression and justifies it in retrospect by noting that the concentration in a pure aqueous solution of formaldehyde is also quadratic in the partial pressure of the formaldehyde vapor above it. However, he does not explain why the two quadratic relationships, aqueous and mucosal, have different shapes. The commenter asserts without supporting information that the dimerization of formaldehyde in solution at high concentrations causes the quadratic effect. The commenter does not mention the metabolic mechanisms presented by Heck et al. (1989) and in Part B, which justify the relationship developed in Part B. That relationship has a very different form, a linear asymptote at high exposure, compared to the quadratic form of the commenter's relationship. The commenter's unpublished analysis would require considerably more support and justification before inclusion in the analysis of Part B.

The remainder of the "comment report", starting on page 18, develops a prediction of risk using the foregoing quadratic relationship between DPX and exposure. So all that follows contains any shortcomings of that analysis. The commenter's risk prediction results from a numerical exploration of the relationship between the quadratically defined DPX and the risk factor, ln(1-P), obtained from the rodent cancer bioassays. The commenter points out that the EPA document, in effect, selected the model with the risk factor proportional to the square of the DPX and obtained a very poor fit. However, instead of considering a form of risk that is a general cubic in DPX, as in the three-stage model of Part B, to obtain a good fit, the commenter only considers a hockey-stick threshold shape to obtain a good fit of risk factor to DPX, without quantitative consideration of the mechanism that could produce such an abrupt change of slope in the risk relationship. Such an abrupt change, although convenient mathematically, is not likely to be mechanistically plausible.

The commenter's analysis has several other unconventional features that are insufficiently justified. The analysis does not use maximum likelihood estimates, which do provide valuable measures of uncertainty. The commenter also uses a completely new adjustment on risk to account for the time of the experiment, instead of the adjustment on dose used by toxicologists.

On the basis of this discussion, the OEHHA staff conclude that the commenter has not established a basis for a positive threshold for formaldehyde and that his suggestions are not appropriate for inclusion in Part B.