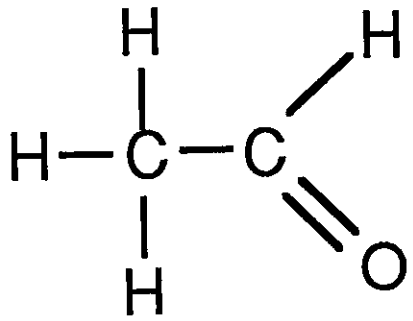
California Environmental Protection Agency

Air Resources Board

Acetaldehyde

as a Toxic Air Contaminant



Part C

Public Comments and ARB/OEHHA Staff Responses

Stationary Source Division

November 1993

PART C

PUBLIC COMMENTS AND ARB/OEHHA STAFF RESPONSES ON THE PRELIMINARY DRAFT OF THE ACETALDEHYDE IDENTIFICATION REPORT

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

April 1993

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Comment Letters Received on the August 1992 Preliminary Draft of the Acetaldehyde Report

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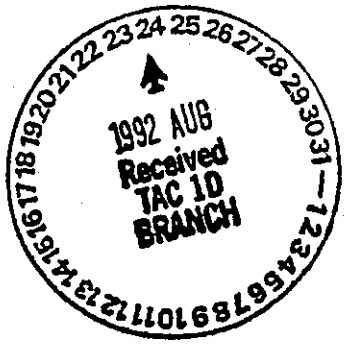
August 20, 1992

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



Dear Genevieve;

I read the preliminary draft of the acetaldehyde report with considerable interest. I suggest the conversion of ethanol to acetaldehyde which can occur in air at moderate temperatures is an additional source worth consideration.

Based on my own experience, when alcohol-containing solvents are evaporated in air at temperatures between 100 and 250 degrees Celsius, alcohols are converted to aldehydes. I have seen concentrations of aldehydes near percent levels(v/v) in stack emissions into the ambient air from such a source.

When ethanol is added to food prior to cooking, or produced by yeast during fermentation prior to baking, it is released into the air during cooking. The ethanol released can be converted to acetaldehyde by air oxidation at normal oven temperatures.

I hope you find these comments of some assistance. Please call me if you have any questions.

Sincerely,

John

John A. Wood
Senior Consultant
Arthur D. Little, Inc.
Acorn Park
Cambridge, MA 02140-2390
(617) 864-5770 ex.3036

Others whom I know + to whom I have mentioned this include Bob Barham, Beth Schwake, Dean Saito (+ Hunt), Dean Simonth + Janette Brooks.

John

Chevron

Chevron Research and Technology Company
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Environmental Group

September 28, 1992

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

Dear Ms. Shiroma:

We would like to offer the following comments for your consideration on the preliminary draft report, "Proposed Identification of Acetaldehyde as a Toxic Air Contaminant."

We recommend that the Executive Summary be considered the ARB's "risk characterization" document in the Toxic Air Contaminant listing process. To that end, the Executive Summary should attempt to answer the following question, "What do other risk-assessors, decision-makers, and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment?"[1] In order to do this the following items should be addressed.

The primary conclusions from page five of the Executive Summary are that "acetaldehyde can be detected in the ambient air throughout California." "... at ambient concentrations, acetaldehyde may cause or contribute to an increase in mortality or serious illness ...".

We agree that measurable quantities of acetaldehyde are found in the ambient air, but recommend that the executive summary expand on the uncertainties in the available exposure data. It should be made clear to the reader that exposure to acetaldehyde comes from outdoor air, indoor air, through the diet, and through metabolism of endogenous substrates. For each avenue of exposure the quality and impact of the data are different. We recommend that the executive summary indicate;

1) Data from the ARB toxics monitoring network is sufficient to estimate ambient air concentration of acetaldehyde. However, there is no quantitative information on near source exposures available at this time. The assertion that air concentrations near oil refineries (for instance) may be elevated is not supported by any measurement data. Data of this type are essential to estimate individual risk and the population risk distribution.

Telex: Domestic – WU 176967/ Foreign – ITT 470074 • Fax (510) 242-1380 or 5947

2) While available data indicate that indoor air concentrations are typically higher than outdoor concentrations, lack of quality data limits the staff's ability to apportion the resulting risk between indoor and outdoor exposure. Because people spend a majority of their time indoors, exposure to acetaldehyde may be dominated by indoor sources. Additional data on indoor concentrations are critical to estimate the "high end" of the risk distribution as well as other population exposure statistics.

3) Dietary sources are likely to be the major contributor to an individual's daily dose of acetaldehyde. Lack of quality data in this area is not critical because OEHHA has identified the respiratory epithelium (and inhalation exposure) as the only target tissue of concern.

4) Acetaldehyde is formed within cell from metabolism of endogenous materials.[2] Exogenous materials like ethyl alcohol are also metabolized to acetaldehyde. Acetaldehyde is ultimately used as an energy source by the body. Ambient air concentrations found in California may not change the internal concentration of acetaldehyde within the cells of the respiratory epithelium. Techniques to accurately measure acetaldehyde within the cell are needed to better address this issue.

The conclusion that ambient concentrations of acetaldehyde may contribute to mortality or serious illness is based on the cancer potency value determined by OEHHA. We believe the Executive Summary does not adequately address the assumptions used or uncertainty within the health risk assessment. We recommend the following information be included;

1) Include the maximum likelihood estimate (MLE) as well as the upper 95% confidence value for the "best" estimate of cancer potency. This additional statistic would give the reader a sense of the range of uncertainly associated with the cancer potency modeling.

2) Amend Table I to include the MLE for each material listed as a Toxic Air Contaminant by ARB.

3) More of the underlying assumptions used in the quantitative risk assessment should be presented in the Executive Summary (model type used, results of alternative models, scaling factors used, etc.).

4) Add a short discussion of the likely mechanism of action for acetaldehyde's genotoxic and carcinogenic effects (Schiff base formation[3]).

5) The reader should be made aware that the doses of acetaldehyde that caused cancer also caused significant cell death in the respiratory epithelium. Chronic injury at this site may have contributed to the development of the tumors.

In addition to changes in the risk characterization outlined above, we recommend that OEHHA and the Scientific Review Panel also carefully consider

two specific issues associated with the quantitative risk assessment.

1) Is the linearized multistage model appropriate for an endogenous cellular product? Other chemicals for which the GLOBAL86 model was developed are not normally found in the body. Acetaldehyde and formaldehyde are exceptions to the rule.

2) Is a metabolic scaling factor the correct method to estimate cancer risk to the respiratory epithelium between rat and man? The metabolic scaling factor (using body surface areas of rats and man) was chosen because it is the OEHHA default value. Clearly a better choice for acetaldehyde is the contact scaling method using respiratory epithelium surface area. While several "generic" assumptions for rat and man must be used (because of the limited data for acetaldehyde) this method at least begins to address the target tissue of concern. Using a metabolic scaling factor (or assuming equivalence between species) appears unjustified.

[1]Habicht, F. H., Guidance on Risk Characterization for Risk Managers and Risk Assessors. USEPA, February 26, 1992.

[2]Metzler, D. E., Biochemistry: The Chemical Reactions of Living Cells. p. 413, Academic Press, 1977.

[3]Ibid, p. 488

Please contact me at (510) 242-7038 if there are any questions about these comments.

Sincerely,

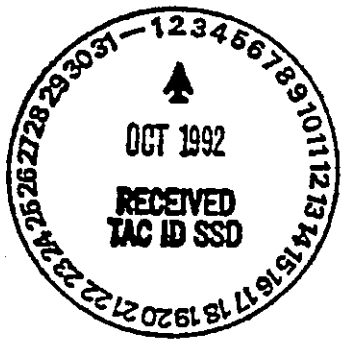
Russell D. White

RDW: jm

Motor Vehicle Manufacturers Association
of the United States, Inc.

Thomas H. Hanna
President and Chief Executive Officer

September 29, 1992



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

Dear Ms. Shiroma:

The Motor Vehicle Manufacturers Association of the U.S., Inc. (MVMA) is the trade association for domestic producers of car, trucks, and buses. MVMA members produce more than 90 percent of the motor vehicles manufactured in the U.S. MVMA has reviewed the preliminary draft report on the Proposed Identification of Acetaldehyde as a Toxic Air Contaminant (TAC) prepared by the staffs of the California Air Resources Board (ARB) and Office of Environmental Health Hazard Assessment.

Mr. Richard Paul of MVMA staff participated in the September 17 workshop to discuss the Technical Support Documents. Although Mr. Paul explained MVMA's concerns at the workshop, we now submit our comments in writing. There are several issues contained in preliminary draft reports which concern MVMA, including emission estimates, exposure data and calculations, animal toxicity testing results interpretation; and risk assessment assumptions and methods.

The exposure assessment in Part A of the Technical Support Document focuses on acetaldehyde emissions to ambient outdoor concentrations, yet acetaldehyde's natural occurrence and use as a food preservative literally dwarfs the exposure in air. In ARB's Executive Summary acetaldehyde is reported to be used in food preservation and as a flavor adjuvant at approximately 0.047 percent, which is 470,000 parts per billion volume (ppbv). Yet, the exposure assessment in Part A concludes that the mean annual acetaldehyde exposure level in air for California residents is 2.33 ppbv. This represents a major inconsistency in calculating risk when ARB staff concludes that acetaldehyde exposure, as a toxic air contaminant, represents a significant health risk and that "at ambient concentrations, acetaldehyde may cause or contribute to an increase in mortality or serious illness."

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Exposure through ingestion routes is many hundreds of thousands times higher and no adverse health effects are anticipated. In fact, as a food preservative, acetaldehyde is expected to decrease adverse public health effects from food contamination. This is particularly important because in Part B, Health Assessment, the calculation assumes the metabolism of acetaldehyde throughout the body for the interspecies scaling factor rather than the respiratory tract. MVMA recommends that ARB staff reconsider the significant sources of exposure to acetaldehyde from diet compared to the infinitesimal exposure of acetaldehyde from ambient air.

Other exposure related concerns include the emissions estimates used for mobile source contribution to total ambient concentrations of acetaldehyde. Appendix B details the information sources for these estimates as being from 1987 inventories. Emissions levels are significantly lower now based on fleet turnover, newer vehicle technology and changes in vehicle fuel composition. To best estimate likely future emissions and levels from mobile sources, MVMA recommends ARB consider the most recent data obtained in the auto/oil air quality research study sponsored by major auto manufacturers and oil companies. The methods and materials used in this research effort address the issues mentioned above. Use of this data will also address inaccuracies of the in-vehicle exposure estimates to acetaldehyde in Table IV-6 of the Part A report on exposure. In-vehicle exposures are directly a function of tailpipe emissions from vehicles in front of the exposed vehicle, and as such, should be based on the best emissions data.

There are several fundamental issues of toxicology which the preliminary report fails to consider. For example, in the chronic bioassay, rats were exposed to acetaldehyde for six hours a day, five days a week at 1,438 parts per million (ppm). The ARB staff assumed that Haber's law applies to the biological effects of acetaldehyde and calculated continuous exposure at 256.8 ppm, 24 hours a day for seven days a week. Haber's law states that the product of the concentration of a chemical and the duration of exposures produces a toxic effect and is used in extrapolation of high concentration to low concentration. However, significant criticism has been raised in toxicology that most chemicals are in fact, not subject to Haber's law and that high concentrations of exposure to a chemical do not have the same effect at low concentrations. For example, high concentrations of acetaldehyde will be much more irritating to nasal tissue than low concentrations and cause significant hyperplasia, cell death and regeneration. Consequently, tumors produced by the acetaldehyde cancer bioassay, can be caused by this mechanism of irritation, hyperplasia, death and regeneration with subsequent, exaggerated "cell proliferation."

At low doses, the toxicological impact of acetaldehyde is much different. Furthermore, the water solubility of acetaldehyde is such that this chemical would be easily

metabolized in the upper airway, especially at the low ambient levels predicted by ARB staff. Acetaldehyde is also a naturally occurring, essential chemical in human metabolism used in the synthesis and production of other biologically important compounds and also is present in humans as an intermediate in the Kreb's cycle. Accordingly, MVMA recommends ARB not assume the validity of Haber's law with acetaldehyde.

Another toxicity testing issue of concern is that rats are obligate nose breathers, and humans breathe through both their nose and mouth. Therefore, rats are a poor model for inhalation carcinogenicity studies when the only site of tumors is the nasal tissue. The gross anatomy of the rat nasal passage and humans is sufficiently different such that other rodent models should be used in quantitative risk assessment. Although hamsters breathe through both their mouth and nose they were exposed to only one fluctuating dose of acetaldehyde and therefore the data should not be used for quantitative risk assessment. MVMA considers the animal data discussed in Part B of the preliminary report, for the reasons discussed above, inadequate for quantitative cancer risk assessment and should be used only to qualitatively evaluate the carcinogenicity of acetaldehyde.

The acetaldehyde risk assessment also does not separate the calculated risk of indoor versus outdoor exposures to acetaldehyde. Although it was pointed out at the September 17 workshop that insufficient data exists for calculating indoor exposures confidently, CARB staff should pursue studies to more accurately determine indoor exposures. This is an important distinction in risk management for the ARB staff to make. In previous evaluations of other chemicals (e.g., formaldehyde) under consideration as Toxic Air Contaminants the ARB made this distinction. MVMA recommends that the differences in calculated risk be explicitly and clearly stated in the Executive Summary as well as the Technical Support Document. It is important to identify/account for the relative differences of risk from different sources, situations and activities, both voluntary and involuntary.

In addition, MVMA recommends ARB staff consider the results of a workshop organized by the Health Effects Institute on research needs to reduce uncertainty in risk assessment for several mobile source air toxics including acetaldehyde. The HEI workshop scheduled for December 4,5 and 6, 1992 in Monterey, California, will undoubtedly identify several key concerns with the existing data base for acetaldehyde and outline a comprehensive program to better understand the potential adverse health effects and estimation of risk from acetaldehyde. There may also be broader implications for risk assessment procedures, techniques, assumptions, etc., as a result of the HEI workshop. ARB staff should consider possible changes to their risk assessment procedures which are more scientifically defensible.

There is significant uncertainty in the public health evaluation and calculation of risk from acetaldehyde. The Technical Support Documents and particularly the Executive Summary should explicitly recognize this uncertainty throughout the text and clearly state the scientific limitations of the risk assessment process, both methodologically and in particular for acetaldehyde.

In conclusion, MVMA has identified technical and practical issues associated with the proposed identification of acetaldehyde as a toxic air contaminant. In addition, there are several additional information sources to be considered before the preliminary report is finalized. MVMA urges the ARB staff and Scientific Review Panel to reconsider the wholesale adoption of the assumptions and impractical implications of the identification of acetaldehyde as a Toxic Air Contaminant.

Thank you for your consideration in this matter. Please contact Richard T. Paul at 313/872-4311 should you have any questions.

Sincerely,

Lawrence E. Slimak for

Thomas J. Carr
Vice President
Technical Affairs

September 24, 1992

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

RE: Comments Regarding the Proposed Identification of Acetaldehyde as a California Toxic Air Contaminant

Dear Ms. Shiroma:

The Earth Technology Corporation (TETC) appreciates the opportunity to provide the following written comments to the California Environmental Protection Agency, Air Resources Board (CEPA-ARB) regarding the proposed identification of acetaldehyde as a California toxic air contaminant (TAC). In order to prepare these comments, TETC reviewed three preliminary draft documents--Part A Exposure Assessment, Part B Health Assessment and the Executive Summary. Comments are presented in this order and relate to technical critiques, interpretational questions, and general comments. If requested, TETC is available to provide additional detailed information related to each item.

PART A EXPOSURE ASSESSMENT

It is generally noted that the tone and presentation of the information in Part A suggests that the CEPA-ARB has already concluded that acetaldehyde should be classified as a TAC. Our understanding of the classification process requires the CEPA-ARB staff and Office of Environmental Health Hazard Assessment (OEHHA) to review and respond to public comments and prepare a Response to Public Comments (Part C). Subsequently, the CEPA-ARB will determine if acetaldehyde should be identified as a TAC and, if so, whether there is evidence of a threshold exposure below which adverse effects are not expected to occur.

However, the CEPA-ARB staff states on page A-44,

> "These values are based on emission estimates and the sources will be prioritized in the control phase when the Board identifies acetaldehyde as a toxic air contaminant" (emphasis added).

The CEPA-ARB staff used when the Board identifies rather than if the Board identifies. It therefore appears that the CEPA-ARB staff has already concluded that acetaldehyde is a TAC without following

the due process defined by the California Code of Regulations. TETC recommends that the CEPA-ARB considers all public comments prior to determining whether acetaldehyde should be identified as a TAC.

Also of concern in identifying acetaldehyde as a TAC, is the limited ambient air monitoring data collected over a very compressed time schedule. As noted in Part A, the study period (sampling time) occurred from September 1988 through August 1989 at only 19 monitoring stations. When the extensiveness of California (≈ 156,000 square miles) and the population (≈ 30,000,000 residents) is considered, the utilization of only 19 monitoring stations becomes most problematic. Confounding the concern regarding the limited monitoring stations is the lack of description of the location of these stations. Since there are limited direct emitters of acetaldehyde in California, the concerns regarding the secondary formation of acetaldehyde are profound. As stated on page A-55, considering that

> "secondary acetaldehyde formation from the degradation of organic pollutants frequently dominates direct emissions by contributing 41 to 67% of the total atmospheric acetaldehyde,"

the location of the monitoring stations is paramount.

TETC requests that the data assimilated from the individual monitoring stations is evaluated, including correlation of the data, with designated/identified acetaldehyde emitters. The evaluation should also include data from additional monitoring that was concurrently and/or subsequently collected but not utilized in the study. This evaluation should also include whether control devices/methodologies have proven effective in reducing the initial study period (September 1983-August 1989) airborne concentrations. TETC also strongly requests that the sampling and analysis protocol is critically reviewed to confirm the validity of the data. This critical review must include the analytical methods used for acetaldehyde including equipment, procedures, detection limits and chain-of-custody.

Further, the evaluation and analyses of the data is confusing. In general, such short-term measurements are generally lognormally distributed allowing the utilization of geometric as opposed to arithmetic calculations. The measure of central tendency (mean) in a lognormal description is the antilog of the mean logarithm of the sample values. The distribution is skewed, and the geometric mean is always smaller than the arithmetic mean by an amount which depends on the geometric standard deviation. Therefore, a complete definition on the analyses of the data is requested, including the rationale utilized in selecting the application of the arithmetic mean.

Based on this information, a critical review of the analytical data is recommended. This critical review must include:

- The limited monitoring stations.
- The locations of the monitoring stations.
- The restricted sampling duration and data set.
- The sampling and analysis protocol.
- The statistical analyses of the monitoring results.

PART B HEALTH ASSESSMENT

This part presents a variety of toxicological data associated with acetaldehyde while determining the toxicological endpoints. Several concerns were noted during TETC's review. These concerns and appropriate comments and questions will be presented in the following text.

Section 2.0

Section 2.0--Metabolism and Pharmacokinetics provides an overview of the relevant literature. However, it should be emphasized that the conclusions presented in the section are based on only three (3) inhalation studies that were based on elevated exposure concentrations (0.4 to 0.6 micrograms of acetaldehyde per liter of air--ug/l). (Note: The basin-specific mean annual acetaldehyde concentration of 0.0029 ug/l, which was established in Part A, Exposure Assessment, is 2 orders of magnitude lower than the inhalation study's elevated concentrations.) Further, this section has a major conflict where on page 2-7, Subsection 2.4--Metabolism Part B states:

> "Only 5% leaves the liver unchanged"

and on page 2-13, Subsection 2.5--Excretion Part B states:

> "Acetaldehyde can be excreted unchanged in urine, expired air and skin."

While TETC agrees that the liver provides effective enzymes to metabolize acetaldehyde, TETC is concerned that the second reference will confuse many and inflate the risk that could be considered from acetaldehyde exposure. TETC does agree with the statement on page 2-13, Subsection 2.5--Excretions:

> "The data on the disposition and elimination kinetics of acetaldehyde are scarce."

Finally, TETC also concurs with the CEPA staff's statement on page 2-14, Subsection 2-6--Conclusion, that

> ". . . , more complete studies are needed to examine the detailed pharmacokinetics of acetaldehyde metabolism, particularly via the inhalation route."

Section 3.0

In Section 3.0--Acute Toxicity, the primary acute effects of acetaldehyde are reviewed. As stated on page 3-1, Subsection 3.1--Human Health Effects:

> "The major effects of human exposure to acetaldehyde vapors consist of irritation to the eyes, skin and respiratory tract."

In general, there is scant literature reporting acute effects, therefore additional research is required.

Section 4.0

Section 4.0--Subchronic Toxicity, presents the limited subchronic toxicity results. Only four (4) animal studies (3 rats and 1 hamster) are discussed. Considering the few subchronic studies and the similarities in the toxicity between acute and subchronic, minimal information was obtained from the studies.

Section 5.0

Considering the long-term exposure concerns of a TAC, the rigorous evaluation of the literature presented in Section 5.0--Chronic Toxicity, is paramount. This section presents the sparse information (two inhalation and two intratracheal instillation carcinogenic studies in rats) for the chronic toxicity studies.

As evidenced by the scant literature, few meaningful studies are available regarding the chronic toxicity of acetaldehyde.

Section 6.0

In Section 6.0--Developmental and Reproductive Effects, the development and reproductive effects of acetaldehyde is presented. Of great concern is the presentation of selected articles related to the toxicity of acetaldehyde, the primary metabolic of ethyl alcohol, which results following exposure (often ingestion) to ethyl alcohol. While the presentation of these studies is of interest to selected toxicologists, it is not relevant when the primary objective is to determine acetaldehyde developmental and reproductive toxicity as related to a potential TAC. Of additional concern is that studies were not found in which acetaldehyde was administered via the inhalation or oral route of entry.

Rather, this section relies heavily on the presentation of in vivo and in vitro studies. Unfortunately, in vivo studies are limited to intraperitoneal and intravenous routes of exposure. In fact, only one reproductive toxicology study was located. The in vitro studies that were found are based on mouse and rat embryo culture systems for detecting developmental effects and testicular cell culture systems for detecting effects on male hormone production.

As stated on page 6-4, Subsection 6.4--Conclusions:

> "Because of their study design, the in vivo studies do not permit specific conclusions about the developmental toxicity of acetaldehyde and its mode of action."

Further, there is considerable concern regarding the scant literature, the design and conduct of the studies included in the literature, and the data assimilated from the research. Thusly, TETC concurs with the concerns of the CEPA-ARB staff when they state on page 6-5:

> "It is, therefore, not possible at present to determine if acetaldehyde possess a reproductive or developmental hazard to humans. It is desirable that studies relevant to hazard identification for possible reproductive and developmental toxicity of acetaldehyde to humans be performed."

Section 7.0

The genotoxicity literature is presented in Section 7.0--Genotoxicity. While the quality and quantity of this literature appears superior to other toxicity classifications, conflicting results were obtained in selected studies. In some studies it is difficult to ascertain the exposure (dose) loading, sample size and study design. Thus, TETC does not concur with the CEPA-ARB staff's statement on page 7-9, Section 7.7--Conclusions:

> "In summary, the available data indicates that acetaldehyde poses a mutagenic risk for somatic cells. Thus, acetaldehyde should be classified as a genotoxic."

Rather, TETC suggests that acetaldehyde may pose a somatic cell risk and could therefore be classified as a genotoxic.

Section 8.0

Section 8.0--Carcinogenicity presents the studies associated with acetaldehyde cancer concerns. As stated in Subsection 8.1--Introduction:

> "Only one epidemiologic study has investigated the carcinogenic potential of acetaldehyde. Major methodological limitations prevent the use of that study in determining acetaldehyde carcinogenicity. The determination of carcinogenicity rests on four studies using either rats or hamsters."

These four studies utilized a variety of acetaldehyde dosages resulting in various neoplasms at various sites. It should also be noted that two of these studies dosed the test animals with additional compounds not exclusively acetaldehyde. Further, the routes of entry were also variable.

While others have classified acetaldehyde as an animal carcinogen, TETC concurs with the International Agency for Research on Cancer (IARC) conclusion that there is inadequate evidence in humans for acetaldehyde to be classified as a human carcinogen.

Section 9.0

The final section of Part B, 9.0--Quantitative Risk Analysis, details quantitative risk analysis performed by the United States Environmental Protection Agency (U. S. EPA) and the refinements/adjustments to the risk analysis by the CEPA-ARB OEHHA staff.

This section is bifracted into noncarcinogenic and carcinogenic risks. TETC is most confused regarding the premise of the noncarcinogenic risk. Subsection 9.1--Noncarcinogenic Risks, states:

> "The United States Environmental Protection Agency (USEPA) has determined a Reference Concentration (RfC) for acetaldehyde of 0.04 mg/m^3 (20 ppb)."

In conversations with the U. S. EPA and in reviewing the latest U. S. EPA Integrated Risk Information System (IRIS) data package, (Attachment A) for acetaldehyde, an RfC of 0.009 mg/m^3 is listed,not the

0.04 mg/m^3 as listed in Part B. Additionally, Part B also provides an uncertainty factor of 3,000 while the IRIS data package reflects an uncertainty factor of 1,000.

Since the IRIS process is rather new, TETC contacted the U. S. EPA listed acetaldehyde contact person to ascertain whether the CEPA-ARB had utilized an RfC that was initially established. The U. S. EPA contact person stated that the 0.009 mg/m^3 RfC had been established approximately one year ago. Based on this confusion, it is essential that the noncarcinogenic risk associated with acetaldehyde is reevaluated and re-presented.

While evaluating the acetaldehyde carcinogenic risk, the OEHHA reviewed the 1987 acetaldehyde risk assessment for cancer based on animal studies and the IRIS risk assessment. The OEHHA then performed a quantitative risk assessment as follows:

> "OEHHA staff used the most sensitive sex, site and species for risk assessment (CDHS, 1985) unless other data appear to be more appropriate. In this case, OEHHA staff have used the rat nasal tumor data from the Woutersen et al. (1986) inhalation study (Table 8-3) and hamster laryngeal tumor data from the Feron et al. (1982) inhalation study (Table 8-4) to assess the cancer potency with the multistage model. Cancer risk at ambient levels was estimated by extrapolating downward 5 orders of magnitude from these data by means of the best fitting linearized multistage model. This model provides a reasonably health-protective risk estimate due in part to its property of furnishing a linear extrapolation of the 95% UCL on risk at low doses (CDHS, 1985; Howe et al., 1986)."

OEHHA attempted to select the most conservation variables (sex, cancer site and dosage) and to utilize a conservative model. TETC is unclear of the rationale utilized in selecting these variables and the model and requests additional data for review. Provided more realistic variables were utilized in a different linear model, the resulting risk would be modified.

TETC is concerned that the CEPA-ARB selected a whole body exposure rationale for an inhalation hazard. Nextly, this data was expanded to ascertain respiratory tract toxicological endpoints (cancer) through the application of a potential full body dose loading. The selection of a target (receiver) organ toxicity predicated on a body multifaceted exposure (inhalation, absorption, ingestion and endogenous production) is of great concern. Thusly, TETC requests additional data and the rationale for the use of the whole body exposure approach.

Additionally, TETC remains confused regarding the lack of discussion and evaluation of endogenously produced acetaldehyde in the risk assessment. Since acetaldehyde is formed during the normal biochemical functioning of the body and is also formed through the metabolism of other materials, TETC requests that this source of acetaldehyde is considered and compared to exogenous acetaldehyde exposure, which was determined in the conduct of CEPA-ARB's quantitative risk assessment. In view of acetaldehyde's endogenous nature within human systems, TETC suggests it is inappropriate to utilize the same methodology and approach for acetaldehyde as for compounds, such as benzene and chromium VI, previously designated as TACs.

TETC noted the absence of an evaluation of the uncertainty associated with the utilization of conservative assumptions, when data were lacking, to quantitate the carcinogenic risk. While it is

1traditional to make conservative assumptions in the absence of data, such assumptions must be reasonable and the assessment results must be interpreted with caution. Use of reasonably conservative assumptions at each step may produce cumulative assessment results that are overly conservative and thus unreasonable. TETC believes that it is critical that the CEPA-ARB evaluate and present for review the uncertainties in the health assessment. This evaluation should be both quantitative and qualitative in nature.

It is TETC's understanding that the guidelines utilized by the CEPA are currently being revised. If the proposed guidelines revise the methodology or approach or any of the variables utilized to quantitate risk, the evaluation of acetaldehyde as a TAC would be impacted. Consequently, it is requested that the pending revisions to the California risk assessment methodology are evaluated relative to the acetaldehyde health assessment and presented for review prior to finalizing the identification of acetaldehyde as a TAC.

EXECUTIVE SUMMARY

In general, the CEPA-ARB has reiterated information contained in Parts A and B in this document. However, the concerns specified regarding Parts A and B remain unchanged.

To reiterate, TETC appreciates the opportunity to provide this information. Please feel free to contact TETC if clarification or additional information is required.

Sincerely,

THE EARTH TECHNOLOGY CORPORATION (Milwaukee)

K.S.

Kim E. Anderson, Ph.D.
Principal
Senior Vice President

KEA:jlh
82-2811-02\comment.ltr

II.

Air Resources Board Staff Responses to Summarized Comments on the Preliminary Draft Part A and the Executive Summary

Air Resources Board Staff Responses to Summarized Comments on the Preliminary Draft Part A and the Executive Summary

o **Arthur D. Little, Inc., August 20, 1992**

Comment 1: The commenter suggested that the conversion of ethanol to acetaldehyde can occur in air at moderate temperatures and is an additional source of acetaldehyde worth consideration. When ethanol containing solvents are evaporated in air at temperatures between 100 and 250 degrees Celsius, alcohols are converted to aldehydes. The commenter has observed acetaldehyde stack emissions from such a source.

Response: The ARB staff was not aware that the conversion of ethanol at moderate temperatures could be a potential source of acetaldehyde. Under the ARB's AB 2588 Air Toxics "Hot Spots" program, stationary sources are required to report the type and quantity of certain substances their facilities routinely release into the air. As the emission inventory data is reported, we will be looking at sources of ethanol as possible emitters of acetaldehyde.

o **Chevron Research and Technology Company, September 28, 1992**

Comment 1: The commenter recommends overall that the Executive Summary be considered the ARB's "risk characterization" document in the Toxic Air Contaminant listing process and that it answer the following question, "What do other risk-assessors, decision-makers, and the public need to know about the primary conclusions and assumptions and about the balance between confidence and uncertainty in the assessment?"

Response: As stated in the Executive Summary, this report was developed in response to certain provisions of state law (Health and Safety Code sections 39650-39666) which provides for a two phase process which clearly separates toxic air contaminant risk assessment (identification) from risk management (control). Acetaldehyde is in the risk assessment phase of the process and no control measures are being proposed for adoption. The Preface and Introduction of the

Executive Summary of the report has been modified to clarify this purpose.

This document will be the basis for the evaluation by the Scientific Review Panel of the cancer potency value and chronic reference exposure level. Once the cancer potency numbers and chronic reference exposure level are approved by the Scientific Review Panel, these values may be used in control measure development in accordance with Health and Safety Code sections 39665 and 39666. Finally, we added a brief discussion of the uncertainties in the risk assessment in the Executive Summary.

Comment 2: The Executive Summary should expand on the uncertainties in the available exposure data. It should be made clear to the reader that exposure to acetaldehyde comes from outdoor air, indoor air, through the diet, and through metabolism of endogenous substrates.

Response: In the Executive Summary, information is provided regarding the ARB staffs knowledge of the available data regarding exposure to acetaldehyde. However, in response to the comment we have added additional discussion to the paragraph "Are There Other Routes of Exposure to Acetaldehyde" in the Executive Summary.

Comment 3: Data from the ARB toxics monitoring network is sufficient to estimate ambient air concentration of acetaldehyde. However, there is no quantitative information on near source exposures available at this time. The assertion that air concentrations near oil refineries (for instance) may be elevated is not supported by any measurement data. Data of this type are essential to estimate individual risk and the population risk distribution.

Response: While air concentrations were not measured near oil refineries for the purposes of the report, we had stated that they may be elevated above ambient concentrations because, based on our emission inventory (see Table III-1 and Appendix B), oil refineries are a major stationary source of acetaldehyde. However, in response to the comment, we have removed direct reference to oil refineries in the discussions regarding near source exposure, in both the Executive Summary and the Part A report. In the control phase, sources of acetaldehyde, including refineries, will be evaluated for near source exposures. Also, with information from the AB 2588 program, we will be able to more fully assess "Hot Spot" sources.

Comment 4: While available data indicate that indoor air concentrations are typically higher than outdoor concentrations, lack

of quality data limits the staff's ability to apportion the resulting risk between indoor and outdoor exposure. Because people spend a majority of their time indoors, exposure to acetaldehyde may be dominated by indoor sources. Additional data on indoor concentrations are critical to estimate the "high end" of the risk distribution as well as other population exposure statistics.

Response: We have added some measurements of indoor acetaldehyde concentrations from inks, nail polish remover, polyurethane foam insulation, adhesives, coatings and lubricants and from one museum in Chapter IV under Indoor Sources and in Appendix E under Public Buildings. We agree that additional data would be useful to estimate risk from indoor and outdoor sources, however, the data are not available at this time.

o **Motor Vehicle Manufacturers Association, September 29, 1992**

Comment 1: The emission estimates used for the mobile source contribution to total ambient concentrations of acetaldehyde are based on 1987 inventories. Emission levels are significantly lower now based on fleet turnover, newer vehicle technology and changes in vehicle fuel composition. To best estimate likely future emissions and levels from mobile sources, MVMA recommends the ARB consider the most recent data obtained in the Auto/Oil air quality research study sponsored by major auto manufacturers and oil companies.

Response: We have modified the report in Chapter III under Trends on page A-16) to include conclusions from the Auto/Oil document, which support our analysis.

In summary, low emission vehicles that have improved emission technology and use reformulated gasoline are expected to gradually increase on California roadways. This will result in decreased reactive organic gases and acetaldehyde concentrations depending upon which oxygenate is used.

Comment 2: Use of the auto/oil air quality research data will address inaccuracies of the in-vehicle exposure estimates to acetaldehyde in Table IV-6 of the Part A report on exposure. In-vehicle exposures are directly a function of tailpipe emissions from vehicles in front of the exposed vehicle, and as such, should be based on the best emissions data.

Response: The Auto/Oil air quality report uses the same data (Shikiya et al. 1989) as ARB staff to characterize in-vehicle exposures to acetaldehyde. These data, to our knowledge, are the best and most recent data available. Further, in-vehicle exposures may be influenced by factors in addition to exhaust intrusion such as outgassing of acetaldehyde from car interiors, consumer products, or other sources. Therefore, no changes have been made to Table IV-6.

Comment 3: The acetaldehyde risk assessment does not separate the calculated risk of indoor versus outdoor exposures to acetaldehyde. Although insufficient data exists for calculating indoor exposures accurately, the ARB staff should pursue studies to determine indoor exposures. The MVMA recommends that the differences in calculated risk be explicity and clearly stated in the Executive Summary as well as the Technical Support Document. It is important to identify/account for the relative differences of risk from different sources, situations and activities, both voluntary and involuntary.

Response: There is insufficient data to calculate a separate risk of indoor versus outdoor risk. We agree that more research could help quantify the indoor risk. In accordance with the state program, we have provided the available information to characterize indoor risk. The document does provide data showing that outdoor ambient acetaldehyde concentrations pose a potential public health risk.

Comment 4: MVMA recommends ARB staff consider the results of the Health Effects Institute's (HEI) workshop held in January 1993.

Response: The HEI workshop recommended further research on motor vehicle related toxic air contaminants. We agree on the usefulness of more acetaldehyde research. As information becomes available from research efforts, it will be used in the program.

o **The Earth Technology Corporation (TETC), September 24, 1992**

Comment 1: The Commenter notes that the tone and presentation of the information in Part A suggests that the ARB staff and Office of Environmental Health Hazard Assessment (OEHHA) have concluded that acetaldehyde should be classified as a toxic air contaminant. TETC's understanding of the process is that ARB and OEHHA staff will review and respond to public comments and prepare a Response to Public Comments (Part C). Subsequently, it will be determined if acetaldehyde

should be identified as a TAC and, if so, whether there is evidence of a threshold exposure below which adverse effects are not expected to occur. TETC recommends that all public comments be considered prior to determining whether acetaldehyde should be identified as a TAC.

Response: This document was prepared under the AB 1807 process Health and Safety Code sections 39650-39675. The regulation requires the ARB and the OEHHA staff to evaluate the health effects and exposure of potential TACs, and prepare staff recommendations on whether it should be listed as a TAC. This report is then submitted to the public and reviewed by the SRP. While the report contains the staff recommendations, all comments submitted during the public process are considered by both the staff and the SRP. We note that AB 2728 which became effective January 1, 1993, requires the Board to identify all federal hazardous air pollutants (HAPs) as TACs. Acetaldehyde is a federal HAP and, therefore, is expected to be identified as a TAC at the April 8, 1993, Board Hearing. This information has been added to the Executive Summary.

Comment 2: A concern is the limited ambient air monitoring data collected at 19 monitoring stations over a one year period and the lack of description of the location of these stations. Since there are limited direct emitters of acetaldehyde in California, the concerns regarding the secondary formation of acetaldehyde are profound and the location of the monitoring stations is paramount.

Response: The ARB has the most extensive TAC ambient monitoring network in the country. It's purpose is to provide an assessment of background air concentrations in the most densely populated areas. Therefore, they are located in areas of high population density and are deliberately located distant from specific sources so as not to influence the measurement of "background" ambient concentrations. A map of the locations of the stations is on page A-31. We have addressed the secondary formation of acetaldehyde in the document and emphasized its importance to ambient concentrations.

Comment 3: TETC requests that the data assimilated from the monitoring stations be evaluated with identified emitters. Evaluation should include data from additional monitoring that was concurrently and/or subsequently collected but not utilized in the study. This evaluation should also include whether control device methodologies have proven effective in reducing airborne concentrations.

Response: As stated above, the ambient air monitoring stations, although located in urban areas, are purposefully sited away from identified emitters to evaluate background air concentrations for toxic air contaminants. To evaluate whether control devices have proven effective is beyond the purpose of the monitoring network and this report. During the risk management or control phase for acetaldehyde, the need for, and appropriate degree of, control measures to reduce acetaldehyde emissions will be developed in accordance with Health and Safety Code sections 39665 and 39666.

Comment 4: TETC strongly requests that the sampling and analysis protocol is critically reviewed to confirm the validity of the data.

Response: We understand the commenter to question the ARB's Quality Assurance/Quality Control (QA/QC) procedure for including or not including data. The Air Resources Board Monitoring and Laboratory Division has extensive quality assurance procedures which ensure the validity of the data.

QC procedures are followed for all data generated. A system blank, calibration, and control is performed before analyzing samples to assure proper instrument function. The control value must fall within specific control limits which are determined by instrument operation before samples may be analyzed. A check sample is analyzed after every tenth sample to assure the system is still within specified control limits. Duplicate analysis are performed every 10 samples to determine reproducibility. Collocated (separate samplers at the same site) samples are collected to determine reproducibility at several sites. Trip blanks and extraction solvent blanks are analyzed frequently to assure that there is no contamination from traveling or from the extraction solvent. Multipoint analyses studies are performed semi-annually to demonstrate that the method continues to produce accurate data with an acceptable limit of detection. All QC data from the aldehyde sampling and analyses are incorporated into a quarterly QC report that is reviewed by the Quality Management and Operations Support Branch of the Monitoring and Laboratory Division (MLD). In addition, semi-annual capture and recovery efficiency studies are performed on the aldehydes method.

Comment 5: Short-term measurements are generally lognormally distributed allowing the utilization of geometric as opposed to arithmetic calculations. The measure of central tendency (mean) in a lognormal description is the antilog of the mean logarithm of the sample values. The distribution is skewed, and the geometric mean is always smaller than the arithmetic mean by an amount which depends on

the geometric standard deviation. Therefore, a complete definition on the analyses of the data is requested, including the rationale utilized in selecting the application of the arithmetic mean.

Response: The Shapiro-Wilk test was used to test the distribution of acetaldehyde data (see page A-35). It showed that the acetaldehyde concentrations are not log-normally distributed. Since the geometric mean is a parameter for identifying a lognormal distribution, it was not used. Instead, the data was analyzed using an arithmetic mean.

Also, use of the geometric mean is not appropriate for calculating the population-weighted exposure and subsequent potential risk estimate. For this calculation, the arithmetic mean was used.

o **Takayuki Shibamoto Ph.D., Oral comment at the September 17, 1992 workshop**

Comment 1: Atmospheric acetaldehyde is difficult to quantitate. How much quality control and quality assurance is used in making these measurements?

Response: It is true that acetaldehyde is difficult to measure. However the ARB has modeled the analysis of aldehydes after EPA's method TO-11. TO-11 is a method that uses a sampling cartridge coated with 2,4-dinitrophenylhydrazine (DNPH) to trap aldehydes and ketones. These carbonyl substances readily form a stable derivative with the DNPH. The cartridge is then extracted with acetonitrile and analyzed by high performance liquid chromatography (HPLC) for the DNPH derivative. A backup cartridge is used with every sample to monitor for breakthrough of the substances of interest. Also see the response to TETC comment number 4.

III.

Office of Environmental Health Hazard Assessment Staff Responses to Summarized Comments on the Preliminary Draft Part B and the Executive Summary

PART C ADDENDUM

PUBLIC COMMENTS AND ARB/OEHHA STAFF RESPONSES ON THE SCIENTIFIC REVIEW PANEL VERSION OF THE ACETALDEHYDE IDENTIFICATION REPORT

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

August 1993

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PART C ADDENDUM

I.

Comment Letters Received on the April 1993 Scientific Review Panel Version of the Acetaldehyde Report

American Automobile Manufacturers Association
7430 Second Avenue, Suite 300 • Detroit, Michigan 48202
Tel. No. 313-872-4311 • Fax No. 313-872-5400

May 4, 1993

Ms. Genevieve Shiroma, Chief
ATTN: Acetaldehyde
Toxic Air Contaminant
Identification Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

The American Automobile Manufacturers Association (AAMA) is the trade association for domestic producers of cars and light-duty trucks. Members produce approximately 81 percent of the motor vehicles manufactured in the U.S. AAMA has reviewed the latest draft report on the Proposed Identification of Acetaldehyde as Toxic Air Contaminant (TAC) prepared by the staffs of the California Air Resources Board (ARB) and Office of Environmental Health Hazard Assessment.

AAMA is concerned that the exposure assessment of acetaldehyde is using data from 1987 rather than the latest emissions data which reflects a more realistic mix of vehicles with catalytic converters. For example, the lower limit of the contribution of on-road vehicles to the total direct emissions inventory of acetaldehyde is based on six year old data (1987 data, appendix B-2) and is derived from the percent of acetaldehyde in total hydrocarbon emissions. The percent of acetaldehyde in total hydrocarbons is, in turn, based on old data. The papers cited for deriving the percentages of acetaldehyde in total hydrocarbons were published as follows: one paper in 1979, three studies in 1980, two studies in 1981, and one study each in 1985 and 1987. Since these are the dates when the studies were published, the actual experiments were carried out much earlier.

AAMA is also concerned with the assumption about emission factors shown in Table A-2 and A-3, but not stated anywhere in the document, that the acetaldehyde fraction of catalyst equipped, non catalyst, or diesel fueled vehicles is the same regardless of the type of vehicle. It is likely that the fraction of acetaldehyde in total hydrocarbons is not the same for different classes of engines and fuels. The uncertainties in this assumption could be significantly reduced if measurements of acetaldehyde as a fraction of the total hydrocarbon emissions in other transportation related sources, listed as other mobile sources (Table A-3), were carried out. However, at a minimum, this assumption should be stated up front, possibly as a footnote to these tables.

AAMA also disagrees with the method used to estimate the amount of acetaldehyde produced photochemically. To estimate secondary formation of acetaldehyde an Urban Airshed Model calculation was carried out using data from a summer high ozone day (Aug. 28, 1987) in the most polluted region of California (Southern California). The use of such data for estimating an annual average photochemically generated concentration of acetaldehyde will result in a much higher concentration of acetaldehyde than would have been predicted if a more typical day had been used in the Urban Airshed Model simulation.

Finally, we are concerned with the clarity of the presentation of the data in Figures III-1 and III-2. These figures could be improved to reflect the contribution of on-road and other mobile sources to the total emissions of acetaldehyde (Figure III-1, A-12) and to direct emission sources of acetaldehyde (Figure III-2, A-13). This could easily be done by splitting the single slice of the pie chart labelled Mobile Sources into two slices labelled On-Road Mobile Sources and Other Transportation Sources. The mobile source slice could be apportioned further by vehicle type and fuel (i.e. car, light truck, heavy duty truck, gasoline and diesel). We believe this split is justified because on-road vehicles reflect the use of state-of-the-art catalyst technology to reduce emissions whereas none of the other mobile sources of acetaldehyde use any catalyst equipped emission control technology.

If you have questions or would like to discuss this further please call Richard T. Paul at 313/872-4311.

Sincerely,

Thomas J. Carr
Vice President
Technical Affairs Division

TJC/

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May 5, 1993

VIA HAND DELIVERY

Genevieve Shiroma, Chief
T.A.C. Identification Branch
California Air Resources Board
Attention: Acetaldehyde
c/o Linda Martz, 2020 L Street
Sacramento, CA 95814

Re: ARB's Scientific Review Panel
Consideration of Acetaldehyde

Dear Ms. Shiroma:

On behalf of the American Bakers Association, we are forwarding to you an original and ten copies of a written Comment on the draft report "Acetaldehyde as a Toxic Air Contaminant." The American Bakers Association is the national trade association of wholesale bakers and their suppliers. With approximately 300 members, the ABA's members produce approximately 85% of the baked goods sold in the United States. This comment, prepared by the Weinberg Consulting Group for the ABA, is for consideration by the ARB's Scientific Review Panel at or prior to its forthcoming meeting on May 12, 1993.

If you should have any questions or comments, please do not hesitate to contact me at 916-448-2266.

Very truly yours,

Nicole E. Montna

Nicole E. Montna
Legislative and Regulatory Analyst

RMS:cs

encl.

cc: Dr. Myron Weinberg (Weinberg Consulting Group)
Dr. Anne Giesecke (American Bakers Association)

THE AMERICAN BAKERS ASSOCIATION'S COMMENTS ON THE DRAFT VERSION OF "ACETALDEHYDE AS A TOXIC AIR CONTAMINANT" FOR THE SCIENTIFIC REVIEW PANEL OF THE AIR RESOURCES BOARD OF THE CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

Prepared for the American Bakers Association
by WEINBERG CONSULTING GROUP Inc.

May 5, 1993

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AMERICAN BAKERS ASSOCIATION'S COMMENTS ON THE DRAFT VERSION OF "ACETALDEHYDE AS A TOXIC AIR CONTAMINANT" FOR THE SCIENTIFIC REVIEW PANEL OF THE AIR RESOURCES BOARD CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

We have reviewed the draft report, "Acetaldehyde as a Toxic Air Contaminant," and provide the following comments for consideration by the State of California Air Resources Board (ARB) and its Scientific Review Panel (SRP). It is our understanding that the SRP will review the data, assessments, and conclusions presented in the draft report (the SRP Draft) and will judge the adequacy of the cancer unit risk numbers provided in the report. The cancer unit risk numbers, if approved by the SRP, may be used in the control phase of the AB 1807 process. They may also be used by the local districts for permitting decisions, and to assess the risk to public health in the AB 2588 "Hot Spots" program. Accordingly, our comments focus primarily on the data supporting the cancer risk analysis and cancer potency factor development portions of the draft document.

The draft recommends approval of a cancer potency factor and chronic reference exposure level. However, derivation of the chronic reference exposure level is not clearly described in the SRP Draft, and information presented in the Executive Summary and Health Assessment portions of the SRP Draft appears to be inconsistent. The ARB or its SRP should revise the discussions of the chronic reference exposure levels and provide an opportunity for review and comment on this issue.

The SRP Draft concludes that ambient acetaldehyde is an air pollutant which may cause or contribute to an increase in mortality or serious illness, or may pose a potential hazard to human health. This finding is based primarily on the SRP Draft's determination that this compound is a potential human carcinogen, based on sufficient evidence in experimental animals and inadequate data in humans, and on results of the quantitative risk assessment presented in the same document. However, it is our considered opinion that the SRP Draft's finding that ambient airborne acetaldehyde is a potential carcinogen is inconsistent

with the results of long experience with exposure to this compound in the workplace and through other sources (e.g., food). In fact, exposures to acetaldehyde at ambient levels appear to be unlikely to produce any adverse effects; and, at somewhat higher levels, it appears that any effects likely to be produced would be mild, transitory, and reversible. Furthermore, the SRP Draft's quantitation of the potential cancer risk associated with exposure to acetaldehyde at low doses relies on inappropriate modeling approaches and ignores important factors regarding likely mechanisms of toxic action.

ACETALDEHYDE INDUSTRIAL EXPOSURES

Acetaldehyde was first produced commercially in 1916, and is currently used worldwide in large quantities. Considerable industrial health experience regarding its use as a chemical intermediate, product, and byproduct has accumulated since its introduction into commerce. In 1983, the National Institute for Occupational Safety and Health (NIOSH) estimated that 14,000 individuals were exposed to acetaldehyde in workplaces in the United States. This estimate was based on workers potentially exposed during the handling of acetaldehyde and may very well underestimate the total number of workers exposed indirectly or in workplaces where acetaldehyde is present in trade-named or proprietary products (IARC 1985; NIOSH 1991).

The Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have established workplace exposure limits for acetaldehyde that the groups have concluded would be protective of human health. The OSHA standard is an 8-hour time weighted average level of 200 ppm (360 mg/m^3). The ACGIH standards comprise a time weighted average level of 100 ppm (180 mg/m^3) and a short term exposure level of 150 ppm (270 mg/m^3). In practice, it appears that actual exposures to acetaldehyde in the workplace generally are much lower than these exposure limits, probably in the low part per million range. Nevertheless,

they likely are considerably higher (i.e., more than 1,000 times higher) than typical ambient levels of this compound which are most often in the low parts per billion range. The long-term industrial experience with the safe handling of acetaldehyde in the workplace is not adequately considered in the SRP Draft.

Both OSHA and ACGIH have acknowledged the published reports of acetaldehyde carcinogenicity in experimental animals. To date, however, both organizations have elected to monitor the developing scientific evidence for this compound to determine the need for defining new safe limits for occupational exposure. Recently, NIOSH (1991) concluded that acetaldehyde is potentially carcinogenic to occupationally exposed workers. This determination was based primarily on consideration of the available animal studies and on short-term genotoxicity testing. NIOSH acknowledges, however, that the available human data are inadequate for evaluating the potential carcinogenicity of acetaldehyde, and has determined that the potential excess cancer risks for workers exposed to this compound have not been adequately established. Accordingly, citing a desire to implement prudent public health policy, NIOSH recommended that employers assess the conditions under which workers may be exposed to acetaldehyde and take reasonable precautions to reduce exposures to the lowest feasible concentrations. Thus, these three organizations have acknowledged the need to monitor the scientific progress on evaluating the potential risks to human health associated with airborne exposures to acetaldehyde and to minimize these exposures to the extent possible. However, they have chosen not to attempt to quantify any potential cancer risks in light of the limitations in the available data, and in the absence of any convincing demonstration of adverse effects in currently exposed individuals.

Recommendation: We believe that the cancer potency factor for acetaldehyde (4.8×10^{-6} per microgram per cubic meter) presented in the SRP Draft is not representative of potential risks associated with exposures of humans to ambient levels of this compound. This compound is virtually ubiquitous in the environment, but is present at

relatively low levels (thousands of times lower than the levels capable of producing tumors in experimental animals), even in so-called "hot spot" areas. It was not judged in the SRP Draft to be likely to pose risks of noncancer toxicities at typical ambient levels, and there have been no indications that acetaldehyde is carcinogenic in humans. The cancer potency value developed in the SRP Draft was extrapolated from data in experimental animals exposed to very high concentrations of this material, using techniques unlikely to appropriately reflect likely mechanisms of action in humans exposed to much lower ambient concentrations.

We recommend that the ARB take a more reasoned approach to evaluating acetaldehyde's potential risks to the general population. In the absence of an apparent imminent danger associated with this compound and in the presence of scientifically credible reasons to believe that it is not hazardous at ambient levels, the ARB would better serve the public by monitoring the developing scientific knowledge concerning acetaldehyde's potential toxicity and concerning the methods used for extrapolating quantitative estimates of these effects from animals to humans. In lieu of deferring action, the ARB should reevaluate the existing toxicity data and develop more scientifically defensible approaches to modeling the dose-response characteristics of acetaldehyde and to extrapolating its effects in experimental animals to potential effects in humans.

HUMAN EXPOSURES TO ACETALDEHYDE BY OTHER EXPOSURE ROUTES

There are numerous sources of acetaldehyde in natural components of the human diet. Acetaldehyde is naturally present in many fruits and vegetables, such as oranges, grapefruits, pears, and strawberies, in some cases at concentrations as high as several hundred parts per million. It also occurs naturally in a wide variety of other foods, including dairy products, bread, fish, meat, eggs, nuts, and various beverages. Acetaldehyde is an important component of many flavorings added to

food products. The Food and Drug Administration classifies acetaldehyde as a generally recognized as safe (GRAS) substance for use as a synthetic flavoring substance and adjuvant.

Acetaldehyde also naturally occurs in human tissues. It is both generated and consumed in various metabolic processes. The intake levels of exogenous acetaldehyde must be sufficiently great and the metabolic equilibrium pools of acetaldehyde metabolites must be saturated in order for exposures to exogenous acetaldehyde to have any appreciable effect on the actual tissue levels of this compound.

There is a scientific consensus that acetaldehyde does not pose health risks to humans exposed on a daily basis through natural exogenous sources or through endogenous products of normal metabolism. Most tissues in the human body are capable of metabolizing acetaldehyde of exogenous or endogenous origin rapidly and virtually completely. Furthermore, mammals (including humans) have a high reserve capacity for metabolizing acetaldehyde that does not exhibit saturation even with very large assimilated doses.

It is our conclusion that the ARB's approach for estimating the cancer potency of acetaldehyde in humans is unrealistically conservative when considered along with other chronic, low-level exposures to this compound. Given the current scientific understanding of the ability of humans to readily metabolize acetaldehyde and the apparent lack of adverse effects from daily exposures to this compound in the diet, it is intuitively inconsistent to conclude that similar mechanisms would not be protective for relatively low exposures by inhalation. In spite of these observations, the ARB bases its conclusion that acetaldehyde poses health risks to individuals exposed by inhalation at low ambient levels on experimental animal studies in which exposures far exceeded current ambient acetaldehyde concentrations and which clearly saturated the normal metabolic mechanisms for detoxifying acetaldehyde.

Recommendation: In light of the intuitive inconsistencies in the ARB's proposed regulatory approach for acetaldehyde, we recommend that the ARB reconsider the body of data concerning exposure to this compound by various routes and under realistic patterns of exposure prior to making a decision regarding its potential threat to the public health. Available data suggest that a careful monitoring of the developing information concerning the potential toxicity of acetaldehyde will allow the ARB to take appropriate actions based on a more complete understanding of this compound's mechanism of action without endangering the public health. This approach also will allow the ARB to avoid taking inappropriate, and possibly costly, actions based on inadequate data.

ACETALDEHYDE HEALTH EFFECTS

Historically, eye, skin, or respiratory tract irritations have been the adverse health effects of greatest concern in occupationally exposed individuals. Acetaldehyde's severe irritant properties at higher concentrations generally prevent prolonged exposures to levels capable of producing more serious toxic effects. The data generated to date on occupational cohorts have provided no indication of the existence of potential cancer risks associated with exposures to acetaldehyde. It is of special interest in this regard that the types of tumors observed in experimental animals exposed to acetaldehyde (i.e., nasal and laryngeal) are relatively uncommon in humans, and would be very likely to be easily identified epidemiologically in a worker cohort than would more common forms of cancer.

Human Studies of the Potential Toxicity or Carcinogenicity of Airborne Acetaldehyde.

The only study in the published literature purporting to address the potential carcinogenicity of acetaldehyde in humans is the study by

Bittersohl (1975). As described in the SRP Draft, "Major methodological limitations prevent the use of that study in determining acetaldehyde carcinogenicity," a conclusion also reached by the International Agency for Research on Cancer (1985). The Bittersohl (1975) study was an incidence study, where the numbers of cancers observed in an aliphatic aldehyde factory during a particular time period were compared to the numbers of cancers which would have been expected from general population incidence figures for the cancers of interest. Such a study is what epidemiologists call a "hypothesis-generating" study, and is not a "hypothesis-testing" study, the only type of epidemiological study that should be used for determining cancer causation.

There are at least three major methodologic flaws in the Bittersohl (1975) study. First, the observed rates of cancers were not age-specific nor adjusted for age, in spite of the fact that cancer rates vary tremendously by age. Another major problem with the study is that the data were not adjusted for cigarette smoking. Bittersohl (1975) acknowledged that the prevalence of smoking was high among the cohort members; at least five of the observed cancers (bronchial) would be consistent with a smoker bias. Therefore, it is impossible to distinguish in this study the potential carcinogenic effects of acetaldehyde from the potential carcinogenic effects of smoking. The third major difficulty in using the Bittersohl (1975) study to evaluate the potential human carcinogenicity of acetaldehyde is that the surveyed factory produced a large variety of chemicals, making it impossible to discern the potential carcinogenicity of any one entity. Consequently, there is general agreement within the scientific community that the Bittersohl (1975) study does not contain useful information about the potential human carcinogenicity of acetaldehyde.

It should be noted that the SRP Draft Executive Summary states that the U.S. Environmental Protection Agency (USEPA) characterizes the evidence for carcinogenicity of acetaldehyde in humans as limited. This is incorrect. As is correctly noted in the Health Assessment portion of the SRP Draft, the USEPA characterizes the evidence for carcinogenicity of

acetaldehyde in humans as inadequate (IRIS 1993). Likewise, the Summary section of the Health Assessment portion of the SRP Draft mischaracterizes the International Agency for Research on Cancer's (IARC's) conclusions regarding evidence for the carcinogeneicity of acetaldehyde in humans. Rather than concluding that the evidence is limited, as is stated in the SRP Draft, the IARC concludes that the evidence for carcinogenicity of acetaldehyde in humans is inadequate (IARC 1985).

Animal Studies of the Potential Carcinogenicity of Airborne Acetaldehyde.

The experimental evidence that inhalation of acetaldehyde can cause tumors in animals comes from a series of studies conducted by Feron, Woutersen, and several collaborators (Feron et al., 1982; Woutersen et al., 1984; Woutersen et al., 1986; Woutersen and Feron, 1987; Feron et al., 1991). There is little doubt that they were successful in inducing respiratory tumors in hamsters and rats; what remains extremely uncertain is the relevance of their findings to the potential carcinogenicity of ambient levels of acetaldehyde in humans. Nasal and laryngeal tumors were found in hamsters exposed to high levels of acetaldehyde (2500 ppm for the first 9 weeks, which was gradually decreased to 1650 ppm during weeks 45-52). Additionally, nasal tumors were found in rats exposed to 750 ppm, 1500 ppm, or 3000/1000 ppm acetaldehyde for up to 28 months.

These studies provide little support to justify the ARB's classification of acetaldehyde by inhalation as a potential human carcinogen. As has been increasingly accepted by the scientific community, the testing of chemicals at supertoxic doses in rodents can lead to tumors that are not found in humans at ambient exposures. The hamsters and rats exhibited evidence of distress from the exposures to excessively high levels of acetaldehyde, and showed decreased body weight gains, premature

mortalities, and severe, prolonged damage to their respiratory and olfactory tissues.

Some experimental data indicate that acetaldehyde may be genotoxic in various systems, and acetaldehyde has been characterized as being a weak initiator. At high exposure concentrations, it is cytotoxic and, as a result, could have promotional activity. Neither the initiator nor the promoter activities have been observed in humans, and neither would be expected to occur at the low levels likely to be encountered by humans in ambient air.

The SRP Draft does not give sufficient consideration, in a weight of evidence evaluation for carcinogenicity and in dose-response determinations, to the capability of upper respiratory tract tissues to metabolize and detoxify acetaldehyde. Experimental studies (e.g., Casanova-Schmitz 1984; Heck et al. 1986; Morris and Blanchard 1992) suggest that when acetaldehyde deposition exceeds the metabolic capacity of target upper respiratory tract tissues, tissue acetaldehyde concentrations may increase dramatically and lead to a nonlinear increase in the toxic response. Experimental studies in which increased incidences of tumors have been observed appear to have used exposure concentrations that far exceeded the metabolic capacities of the target tissues.

The very high levels of exposures to acetaldehyde employed in the animal studies and the unusual anatomical sites of the observed tumors make it very unlikely that humans are at risk of similar tumors at the much lower exposures of acetaldehyde encountered industrially or environmentally.

Difficulties in Using Rodents to Determine Potential Human Carcinogenicity of Chemicals Toxic to the Upper Respiratory Regions.

Laboratory rodents are commonly used in animal inhalation bioassays of the potential toxicities or carcinogenicities of chemicals. While tissues of the lower respiratory regions in humans and rats are similar in terms of cell types and functions, many anatomical and physiological differences exist in the upper respiratory regions of these two species. Consequently, rodents may be inappropriate models for potential human nasal carcinogenesis.

Humans and higher primates are oronasal breathers; that is, they breathe through both the mouth and nose (Reznik 1990). Their nasal passages are at right angles to the trachea, whereas the rat has a near linear nasal construction (Patra et al. 1986; Schreider 1986). The linearity of the rat's nasal passages to the trachea makes it an obligate nose breather (Proctor and Chang 1983).

A less obvious difference is related to the structure of the major turbinate bones. In humans there are three major turbinates. The rat has dorsal and ventral lamellae for each turbinate (Hebel and Stromberg 1986), creating a more complex nasal turbinate region. The arrangement of turbinate bones in the rat increases the relative surface areas of the nasal passages as compared to those of the human. The relative nasal surface area is determined by dividing the nasal surface area by the nasal cavity volume. The relative nasal surface area for humans is 6.4 and for rats almost eight-fold larger, 51.7. Inhaled chemicals may exert a relatively greater effect on the nasal passages of the rat due to the larger surface area available for deposition.

Rats and humans also differ in the proportions of their nasal surfaces lined by epithelia and in their mucociliary clearance patterns. Measurements have been performed on rats that calculate the surface

areas of the three major epithelia in the nasal passages (Gross et al. 1982), although only olfactory epithelia have been measured in humans (Bloom and Fawcett 1968). Rats are macrosmatic, indicating that the greater percentage of their total nasal epithelium is olfactory (50 percent). Humans are characterized as microsmatic with approximately 8 percent olfactory epithelium (Reznik 1990). In addition to the differences in cell types, the routes of mucus flow vary between the species. One function of the nasal passages is to remove particulate matter and this is accomplished by the nasal mucosae. A slight current is created by the beating of the cilia for transport of secretions. In humans the majority of secretions are transported posteriorly toward the nasopharynx (Snyder et al. 1975). Transport of secretions in the rat moves both anteriorly and posteriorly for mucociliary clearance (Morgan et al. 1986). This clearance system in the rat creates a greater chance for inhaled toxicants to come in contact with target cells.

Lastly, inspiratory air flow routes differ between rats and humans, causing toxicants to come in contact with different areas of the nasal cavities. These important differences indicate the potential problems associated with extrapolation to humans from toxicological studies on rats for inhalation exposures to the upper respiratory regions.

Implications for Risk Assessment of Possible Mechanisms of Action for Acetaldehyde Carcinogenicity.

Acetaldehyde may produce genotoxic and cytotoxic effects in specialized test systems. The chronic tissue damage, tissue repair, and cellular proliferation associated with exposures to high concentrations of acetaldehyde may be prerequisites for producing carcinogenic effects in experimental animals. As is generally true with aldehydes, acetaldehyde may react preferentially with single stranded DNA in producing genetic damage. However, the incidence of cell division in normal nasal epithelium and the concomitant generation of single stranded DNA is low and, accordingly, the ability of acetaldehyde to initiate carcinogenicity at

concentrations not leading to tissue damage may be low. If this is true, the dose response behavior of acetaldehyde in the observed experimental range may not be representative of its dose response behavior in the low dose range. Extrapolation from high to low doses could potentially overstate risk by several orders of magnitude. Under these conditions, measurements of DNA-protein or DNA-DNA cross-links may provide more accurate estimates of intracellular exposure and of risk than the ARB's current approach of using a long-term weighted average administered dose.

Under the scenario described above for acetaldehyde's mechanism of action, the dose rate (airborne acetaldehyde concentration) may be more important than the total or average lifetime dose. Use of lifetime average concentrations for risk quantitation may overestimate the potential cancer risk by arbitrarily lowering the dose at which relevant adverse effects (e.g., tissue damage) are observed. Rather, the absolute concentration at which acetaldehyde produces tissue damage should be used to characterize the dose for use in quantitative risk characterization. For example, the SRP Draft adjusts very high doses of acetaldehyde administered for 6 hours/day and 5 days/week to give lower average values for continuous exposure. Currently available data suggest that greater weight should be given to the highest doses administered.

Acetaldehyde can produce eye and respiratory tract discomfort at airborne concentrations of 50-200 ppm (90-360 mg/m^3) in unacclimated individuals, and at somewhat lower concentrations in sensitive persons. Concentrations greater than 200 ppm (360 mg/m^3) may cause shortness of breath and central nervous system depression. These effects are reversible upon cessation of excessive exposures to the compound. The severe cytotoxicity associated with chronic exposures to high concentrations of acetaldehyde appears to be a key factor in its ability to cause cancer in experimental animals. Acetaldehyde's irritant properties make it extremely unlikely that continued exposures to airborne concentrations capable of producing sustained tissue damage and regeneration would be tolerated voluntarily by exposed humans. These

issues are not adequately considered in a weight of evidence evaluation for potential carcinogenicity in the SRP Draft.

Recommendation: The ARB should consider all the available data in its weight of evidence evaluation of the potential carcinogenicity of ambient airborne acetaldehyde in humans, and in its quantitative assessment of acetaldehyde's cancer potency in humans. We believe that several issues were given insufficient consideration in the SRP Draft: (1) the effects of exposures in animals at the maximum tolerated dose; (2) alternative, and possibly more appropriate, approaches for interspecies scaling and dose characterization; (3) use of alternative, and possibly more appropriate, models for dose-response assessment; (4) use of maximum likelihood estimates instead of or in addition to upper 95 percent confidence limit estimates; and (5) a more detailed consideration of the uncertainties associated with risk assessments for acetaldehyde.

IMPLICATIONS OF IDENTIFICATION OF ACETALDEHYDE AS A TOXIC AIR CONTAMINANT AND USE OF THE RECOMMENDED CANCER RISK VALUES

The cancer slope factor calculated by the ARB provides a basis for deriving a target ambient air level for acetaldehyde that is not appreciably different from background levels of this compound. Use of this value as a target would make it virtually impossible to differentiate among sources of acetaldehyde emissions. Furthermore, it is conceivable that considerable expenditures to reduce acetaldehyde emissions from any identifiable sources would not result in appreciable reductions in ambient levels. Any reductions that could be achieved would be likely to produce negligible effects with regard to the protection of public health.

The SRP Draft identified four major categories of ambient acetaldehyde sources in California: stationary point sources, mobile sources, stationary area sources, and atmospheric hydrocarbon photooxidation reactions. Photooxidation reactions contribute more to

overall acetaldehyde emissions (an estimated 41-67 percent of all emissions) than all other known sources combined. Other major emissions sources include (approximately in order of total emissions): wildfires, mobile sources, agricultural and management burning, wood fuel/residential combustion, processing refineries, and other relatively minor sources.

Based on the results of air monitoring data collected throughout the state, the ARB estimated a mean ambient acetaldehyde concentration of approximately 2 ppb (4$\mu g/m^3$). The highest acetaldehyde concentrations tended to occur in the South Coast Air Basin. Since 1980, acetaldehyde concentrations in this region ranged from <1 ppb (<1.8 $\mu g/m^3$) to 39 ppb (70.2 $\mu g/m^3$). The most recent data cited by the ARB for this region (1987) reported acetaldehyde concentrations ranging from 0.9 ppb (1.6 $\mu g/m^3$) to 24.5 ppb (44.1 $\mu g/m^3$). Although the available monitoring data are limited, these values are not substantially different from airborne acetaldehyde values reported for numerous rural, urban, and suburban locations throughout the United States. For example, at two rural sites 40 km outside of Tucson, AZ, investigators (Snider and Dawson 1985) reported an average acetaldehyde concentration of 6.9 ppb (12.4 $\mu g/m^3$). Both higher and lower concentrations have been reported for other suburban and urban locations.

The cancer slope factor derived by the ARB, combined with a target excess cancer risk of 10^{-5} (1 excess cancer in 100,000 exposed individuals), results in a calculated allowable ambient airborne acetaldehyde concentration of approximately 2 ppb (4 $\mu g/m^3$), a value 375,000 times less than the lowest concentration at which acetaldehyde-associated tumors were produced in experimental animals. Coincidentally, this calculated target ambient concentration is actually similar to airborne acetaldehyde concentrations in many rural, suburban, and urban locations in the United States.

More than half of the acetaldehyde in ambient air is associated with photooxidation reactions unrelated to actual acetaldehyde emissions

sources. In addition, more than half of the remaining direct emissions of acetaldehyde to the ambient air, such as agricultural/management burnings and wildfires, are essentially unpredictable, unavoidable, or uncontrollable. Accordingly, the ability to reduce the already relatively low ambient acetaldehyde emissions by controlling existing known sources without considerable expenditures of resources appears to be limited. First, relatively little is known about the relative contributions of various acetaldehyde emissions and production sources to ambient acetaldehyde levels; second, it may be difficult to distinguish the contributions from individual acetaldehyde sources from ambient background levels; third, a large proportion of the known sources of acetaldehyde in the environment are essentially uncontrollable; fourth, it is not clear that existing ambient acetaldehyde levels are adversely affecting human health; and lastly, given the uncertainties noted above and the practical limitations of any control technology, little incremental benefit in terms of reducing ambient levels or protecting human heath may be obtained by regulating identifiable and controllable sources.

Even if the cancer slope factor of 4.8×10^{-6} per ppb derived by the ARB was based on the use of appropriate scientific approaches (which we do not believe is the case), it simply implies that it is unlikely that more than approximately five excess cancers would occur per one million individuals exposed to acetaldehyde at 1 ppb, and that this number could be much less, or even zero. In fact, the recently observed annual mortalities due to nasal cavity tumors in California are approximately 50, substantially lower than the ARB's best estimate of 288 cancers associated with exposure to acetaldehyde at current ambient levels estimated at 2 ppb (CDOH 1993). The observed mortalities for other upper respiratory tract tumors (e.g., larynx, trachea) also are low, especially when the contribution of other more firmly established potential causes for at least a portion of these tumors is considered. Given the uncertainties and difficulties noted above, use of the cancer slope factor derived by the ARB has the potential to lead to an ill-founded mobilization of public health resources.

Recommendation: We believe that the ARB is proposing to set in motion a series of regulatory initiatives that may be impossible to enforce fairly, that may not be capable of achieving significant reductions in ambient acetaldehyde concentrations, that may impose technically or economically infeasible requirements on identified emitters, and that may not achieve appreciable public health benefits. This approach is likely to create administrative and economic difficulties for public, private, and commercial entities in California, with little or no benefit to the public health. Based on consideration of existing exposure and hazard data for acetaldehyde, it does not appear that the ARB can effectively demonstrate a potential to improve the public welfare by controlling acetaldehyde emissions sources in the state using its calculated cancer slope factor as a basis for developing criteria for allowable exposures. We recommend that the ARB monitor the development of scientific knowledge regarding the sources, fate, and transport of acetaldehyde in ambient air, and, at least temporarily, defer action that could prove to be unnecessary, but extremely costly to the citizens of California. In lieu of deferring action, the ARB could reevaluate the existing toxicity data and develop a more scientifically defensible approach to modeling the dose-response characteristics of acetaldehyde and extrapolating its effects in experimental animals to humans.

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Health, Environment and Safety Group

May 5, 1993

**SCIENTIFIC REVIEW PANEL (SRP)
CONSIDERATION OF CANCER RISK
STATISTICS - MAXIMUM LIKELIHOOD
ESTIMATE (MLE) AND UPPER 95
PERCENT CONFIDENCE LIMIT (UCL)**

Genevieve Shiroma
Toxic Air Contaminant Identification Branch
Air Resources Board
P.O. Box 2815
2020 L Street
Sacramento, CA 95812

Dear Ms. Shiroma,

The Air Resources Board report, "Acetaldehyde as a Toxic Air Contaminant" will be considered at the May 12, 1993 meeting of the SRP. In response to my September 28, 1992 suggestion that the MLE as well as the UCL be included in the Executive Summary text and in Table 1, ARB staff wrote in Part C, page 29, "The Scientific Review Panel would need to be consulted on the appropriateness of such a change in presentation of risks." I understand that this will occur at their May 12 meeting.

There are good reasons to make this simple change;

- One of the critical objectives of risk characterization is to convey the uncertainty associated with any estimate of risk. Inclusion of the MLE along side of the UCL would provide part of this perspective to the reader of the Executive Summary or Table 1.

- The objective of risk assessment is not to be "health protective" but to be accurate. The risk management phase will decide the level of acceptable risk. Providing a prospective on the uncertainty of the cancer potency estimate will let the risk manager make an informed decision.

- The data are readily available.

Please contact me at (510) 242-7038 if there are any questions about these comments.

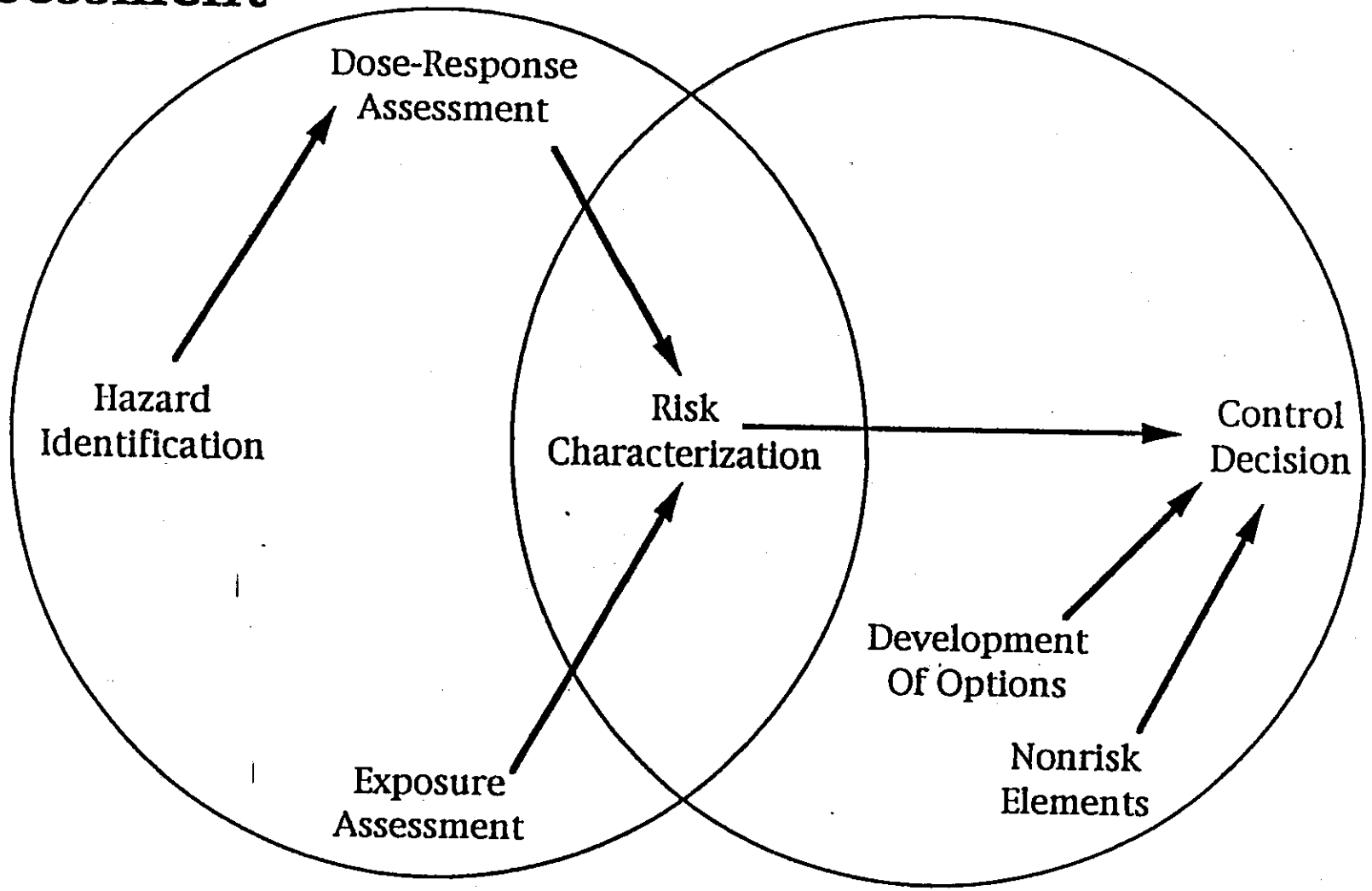
Sincerely,

Russell White

Russell White
Chevron Research and Technology Company

RDW:jeh-CO-0593/48
Attachment

cc. Bruce Oulrey
Scientific Liaison
Air Resources Board
P.O. Box 2815
2020 L Street
Sacramento, CA 95812


Risk
Assessment
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Of Options
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Risk
Management

II.

Air Resources Board Staff Responses to Summarized Comments on the Scientific Review Panel Version Part A and the Executive Summary

Air Resources Board Staff Responses to Summarized Comments on the Scientific Review Panel Version Part A and the Executive Summary

o **American Automobile Manufacturers Association, May 4, 1993**

Comment 1: The American Automobile Manufacturers Association (AAMA) is concerned that the emissions inventory data used from 1987 is dated and does not reflect a more realistic mix of vehicles with catalytic converters.

Response: In our report we used only emission inventory data which has been thoroughly evaluated. More recent data have not been thoroughly reviewed under ARB's rigorous quality assurance program. In addition, we reviewed the more recent auto-oil data and included a discussion of that data in our report under the "Trends" section.

Comment 2: AAMA is concerned with the emission factors shown in Tables 2 and 3 of Appendix A which list identical acetaldehyde fractions for catalyst equipped, non catalyst, or diesel fueled vehicles regardless of the type of vehicle. AAMA believe that the fraction of acetaldehyde in total hydrocarbons is not the same for different classes of engines and fuels.

Response: We agree with the comment and would use speciated emission factors if they were available. We have added the following footnote to both tables "Because of the lack of specific data for these engines and fuels, we assumed acetaldehyde emissions from different classes of engines and fuel to be similar."

Comment 3: AAMA disagrees with using the Urban Airshed Model (UAM) to estimate the amount of acetaldehyde produced photochemically because the model used data from a summer high ozone day in the most polluted region of California. AAMA believes that using such data will result in much higher concentrations than if a more typical day had been used.

Response: We acknowledge that a worst case scenario was used for the UAM analysis of secondary acetaldehyde. The UAM is the only model available to assess the impact of secondary acetaldehyde and, "by convention", is the accepted model routinely used for urban photochemical modeling. We do not, at this time, have an alternative

database to use with the UAM. We note that the use of the UAM does not affect the overall estimation of risk, since the risk is calculated using an annual average ambient concentration derived from the air toxics monitoring network. The information was provided to give a comprehensive picture.

Comment 4: AAMA suggests that Figures III-1 and III-2 be changed to reflect the contribution of on-road and other mobile sources to the total emissions of acetaldehyde and to direct emission sources of acetaldehyde by splitting the single slice labelled "Mobile Sources," into two slices labeled "On-Road Mobile Sources" and "Other Transportation Sources." The Mobile Source could be separated further into vehicle type and fuels.

Response: We have changed the "Mobile Sources" portion of the pie chart in Figures III-1 and III-2 to reflect "On-Road Mobile" and "Other Transportation" sources. In the text on page A-17 we have added language to describe the contribution of vehicle types and fuels to acetaldehyde emissions.

- **American Bakers Association, May 5, 1993**

Comment 1: The Bakers Association believes that the ARB proposes to set in motion a series of regulatory initiatives that may be impossible to enforce fairly, that may impose infeasible requirements on identified emitters, and may not achieve public health benefits.

Response: This report was developed in response to the provisions of Health and Safety Code, sections 39650-39662. However, with the adoption of the AB 2728 legislation, the procedure for identifying substances already classified as federal hazardous air pollutants (HAPs) as toxic air contaminants (TACs) was changed. On April 8, 1993, the Board identified as TACs all substances listed as federal HAPs including acetaldehyde.

No control measures were proposed in this report. During the risk management or control phase for acetaldehyde, the need for, and appropriate degree of, control measures to reduce acetaldehyde emissions will be developed with full public participation in accordance with Health and Safety Code sections 39665 and 39666.

III.

Office of Environmental Health Hazard Assessment Staff Responses to Summarized Comments on the Scientific Review Panel Report Part B and the Executive Summary

OEHHA Responses to Comments by American Bakers Association

Comments on part B by the American Bakers Association were received on May 5, 1993. In their own words their "... comments focus primarily on the data supporting the cancer risk analysis and cancer potency factor development portions of the draft document." Some of the comments reiterated those of other commenters. We will address their comments by focusing on the four recommendations made in their comments.

Comment: The American Bakers Association believes that the cancer potency factor for acetaldehyde (4.8×10^{-6} per microgram per cubic meter) presented in the SRP Draft is not representative of potential risks associated with exposures of humans to ambient levels of this compound. This compound is virtually ubiquitous in the environment, but is present at relatively low levels (thousands of times lower than the levels capable of producing tumors in experimental animals), even in so-called "hot spot" areas. It was not judged in the SRP Draft to be likely to pose risks of noncancer toxicities at typical ambient levels, and there have been no indications that acetaldehyde is carcinogenic in humans. The cancer potency value developed in the SRP Draft was extrapolated from data in experimental animals exposed to very high concentrations of this material, using techniques unlikely to appropriately reflect likely mechanisms of action in humans exposed to much lower ambient concentrations. The commenter recommends that the ARB take a more reasoned approach to evaluating acetaldehyde's potential risks to the general population. In the absence of an apparent imminent danger associated with this compound and in the presence of scientifically credible reasons to believe that it is not hazardous at ambient levels, the ARB would better serve the public by monitoring the developing scientific knowledge concerning acetaldehyde's potential toxicity and concerning the methods used for extrapolating quantitative estimates of these effects from animals to humans. In lieu of deferring action, the ARB should reevaluate the existing toxicity data and develop more scientifically defensible approaches to modeling the dose-response characteristics of acetaldehyde and to extrapolating its effects in experimental animals to potential effects in humans.

Response: Acetaldehyde was judged to not have noncancer toxicity at ambient levels because its level is below the Reference Concentration (RfC). Noncancer effects generally have a threshold. Cancer effects are considered to not have a threshold, especially if the chemical is mutagenic as is acetaldehyde. The cancer potency value was developed following the 1985 document California Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale. The methods in the guidelines are very similar to those in the United States Environmental Protection Agency guidelines for carcinogenic risk assessment. The unit risk of 2.7×10^{-6} per microgram per cubic meter (4.8×10^{-6} per ppb, not 4.8×10^{-6} per microgram per cubic meter as stated in the comment letter) is very similar to that currently presented on USEPA's Integrated Risk Information System (IRIS) of 2.2×10^{-6} per microgram per cubic meter, since essentially the same data were used in both risk assessments. If the American Bakers Association has epidemiologic data on cancer in their workers with reliable exposure data for acetaldehyde, we would be glad to consider it after it is properly peer-reviewed. The enabling legislation of the Toxic Air Contaminant (TAC) program states: " That, while

absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health." (Health and Safety Code Section 39650(e)). If the commenter is aware of "more scientifically defensible approaches to modeling the dose-response characteristics of acetaldehyde and to extrapolating its effects in experimental animals to potential effects in humans," he should have detailed their use for acetaldehyde as we are not aware of any such information. OEHHA is using currently established procedures similar to those used by the USEPA.

Comment: In light of the intuitive inconsistencies in the ARB's proposed regulatory approach for acetaldehyde, the American Bakers Association recommends that the ARB reconsider the body of data concerning exposure to this compound by various routes and under realistic patterns of exposure prior to making a decision regarding its potential threat to the public health. Available data suggest that a careful monitoring of the developing information concerning the potential toxicity of acetaldehyde will allow the ARB to take appropriate actions based on a more complete understanding of this compound's mechanism of action without endangering the public health. This approach also will allow the ARB to avoid taking inappropriate, and possibly costly, actions based on inadequate data.

Response: OEHHA staff acknowledges that acetaldehyde exposure occurs by several routes. However, there are many precedents where the toxicity by inhalation is greater than that by ingestion. For example, hexavalent chromium, cadmium, nickel, and beryllium are all orders of magnitude more carcinogenic by the inhalation route than by the oral route. Also the level of hydrochloric acid that exists in the stomach would be very irritating to the lungs. In animals toxicity appears to occur in specific cells that lack the ability to metabolize acetaldehyde to acetate. Staff will add to the document a new section 8.4 on the carcinogenicity of ethanol which contains information about the appreciable exposure of the respiratory tract to acetaldehyde which occurs after ingestion and metabolism of ethanol, information that is also in the USEPA draft document on Health Effects of Acetaldehyde.

Staff do not believe that there is "developing information" on acetaldehyde which clearly reduces its potential for adverse health effects. If the commenter was aware of important peer-reviewed data, especially epidemiologic data on cancer and acetaldehyde exposure, or better animal cancer data, it should have been submitted so that it could have been evaluated for possible incorporation into the risk assessment.

Comment: The ARB should consider all the available data in its weight of evidence evaluation of the potential carcinogenicity of ambient airborne acetaldehyde in humans, and in its quantitative assessment of acetaldehyde's cancer potency in humans. The American Bakers Association believes that several issues were given insufficient consideration in the SRP Draft: (1) the effects of exposures in animals at the maximum tolerated dose; (2) alternative, and possibly more appropriate, approaches for interspecies scaling and dose characterization; (3) use of alternative, and possibly more appropriate, models for dose-response assessment; (4) use of maximum

likelihood estimates instead of or in addition to upper 95 percent confidence limit estimates; and (5) a more detailed consideration of the uncertainties associated with risk assessments for acetaldehyde.

Response: OEHHA staff followed the California Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale. These methods are very similar to the 1986 USEPA guidelines for chemical carcinogen risk assessment and the unit risk of 2.7×10^{-6} per microgram per cubic meter is very close to that currently presented on IRIS of 2.2×10^{-6} per microgram per cubic meter. If the commenter has more appropriate approaches for interspecies scaling or dose-response, the approaches should be presented in detail and defended. The use of upper confidence limits is a standard procedure in the Toxic Air Contaminant Program primarily because the upper bound is protective of sensitive populations, while the MLE is not. The MLE rewards poor data by weighting it equally with good data and it is statistically unstable. The MLE can be zero, even when the data show a strong carcinogenic response. For example, in the male rat data used in the risk assessment for acetaldehyde the response at the 750 ppm level was 17 nasal tumors in 52 animals while there was 1 in 49 controls and 41 in 53 animals in the 1500 ppm group (Table 9-1). If the same data are run in the GLOBAL 86 model except that the response is changed to 16 in 52 in the 750 ppm group, the MLE becomes 0 in spite of a strong carcinogenic response. The uncertainties in the risk assessment are detailed in Chapter 9 of part B. If the commenter believes that additional statements are necessary, they should have been provided. The use of data obtained at the Maximum Tolerated Dose (MTD) is currently a matter of intense controversy. In the Wouterson et al. (1986) study there was an exposure group which was initially treated at 3000 ppm but whose exposure was gradually decreased to 1000 ppm because of excessive toxicity. Data from this group were not used in the risk assessment.

Comment: The American Bakers Association believes that the ARB is proposing to set in motion a series of regulatory initiatives that may be impossible to enforce fairly, that may not be capable of achieving significant reductions in ambient acetaldehyde concentrations, that may impose technically or economically infeasible requirements on identified emitters, and that may not achieve appreciable public health benefits. This approach is likely to create administrative and economic difficulties for public, private, and commercial entities in California, with little or no benefit to the public health. Based on consideration of existing exposure and hazard data for acetaldehyde, it does not appear that the ARB can effectively demonstrate a potential to improve the public welfare by controlling acetaldehyde emissions sources in the state using its calculated cancer slope factor as a basis for developing criteria for allowable exposures. They recommend that the ARB monitor the development of scientific knowledge regarding the sources, fate, and transport of acetaldehyde in ambient air, and, at least temporarily, defer action that could prove to be unnecessary, but extremely costly to the citizens of California. In lieu of deferring action, the ARB could reevaluate the existing toxicity data and develop a more scientifically defensible approach to modeling the dose response characteristics of acetaldehyde and extrapolating its effects in experimental animals to humans.

Response: This comment addresses risk management. The ARB is not proposing any risk management initiatives at this stage of the process. If and when the ARB considers controls for acetaldehyde emissions, this concern can be addressed. Any proposed control strategies can be discussed in a public comment forum.

A second comment letter by Chevron on part B was received on May 5, 1993.

Comment: The MLE should be included in the range of risk because it conveys uncertainty. The goal of risk assessment is not to be health protective but to be accurate.

Response: To reiterate our response to a similar comment by the American Bakers Association and our earlier response to Chevron which is given on page 29 of Part C, OEHHA staff followed the California Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale. The use of upper confidence limits is a standard procedure in the Toxic Air Contaminant Program primarily because the upper bound is protective of sensitive populations, while the MLE is not. The MLE rewards poor data by weighting it equally with good data and it is statistically unstable. According to the National Research Council (1993), "Only an upper confidence limit on the low-dose slope is used for extrapolation on the grounds that point estimates of the slope (q_1) are highly unstable. Indeed, point estimates of risk based on downward extrapolation of various mathematical models that fit the same experimental data adequately can differ by several orders of magnitude at low risk levels, whereas upper-confidence-limit estimates differ less dramatically (Kodell and Park, 1991). Low-dose linear extrapolation from an upper confidence limit on excess risk obtained in the experimental range is generally regarded as conservative in the sense of tending to overestimate rather than underestimate risk. The procedure will be conservative as long as the dose-response relationship in the low-dose region is convex, regardless of its actual mathematical formulation (Gaylor and Kodell, 1980)."

The MLE can be zero when the data show a strong carcinogenic response. For example, in the male rat data used in the risk assessment for acetaldehyde the response at the 750 ppm level was 17 nasal tumors in 52 animals while there was 1 in 49 controls and 41 in 53 animals in the 1500 ppm group (Table 9-1). If the same data are run in the GLOBAL 86 model except that the response in the 750 ppm group is changed to 16 tumors in 52 animals, the MLE becomes 0 in spite of a strong carcinogenic response. The effect of varying the tumor incidence in the low dose group on the MLE and UCL is shown in the table on the next page.

Variation in the MLE and the UCL with changes in the low dose group tumor incidence

Incidence	MLE	UCL
20	1.4×10^{-6}	4.9×10^{-6}
19	9.3×10^{-7}	4.4×10^{-6}
18	4.7×10^{-7}	3.8×10^{-6}
17 (observed incidence)	1.6×10^{-8}	3.2×10^{-6}
16	0	2.7×10^{-6}
15	0	2.3×10^{-6}
14	0	2.0×10^{-6}

The data in Table 9-1 of part B were used in the GLOBAL86 program. The observed incidence was 17 tumors in 52 male animals exposed to a nominal exposure of 750 ppm. The incidence in this group only was varied up and down from the observed incidence, while the incidences observed in the control (1/49) and 1500 ppm (41/53) groups were held constant, to determine the effect on the MLE (q_1) and the 95% UCL (q_1^*).