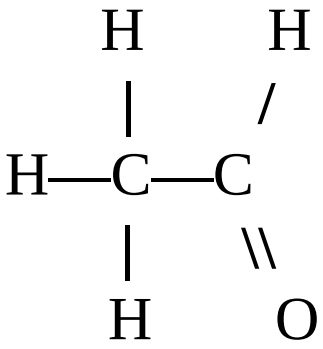
California Environmental Protection Agency

~ Air Resources Board

Acetaldehyde

as a Toxic Air Contaminant



Executive Summary

Stationary Source Division

November 1993

EXECUTIVE SUMMARY

ACETALDEHYDE AS A TOXIC AIR CONTAMINANT

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

APPROVED BY THE SCIENTIFIC REVIEW PANEL MAY 1993

November 1993

Preface

This report was developed in response to the provisions of Health and Safety Code, sections 39650-39662, which became effective January 1984. This legislation requires a two-phase process which separates risk assessment from risk management. During the identification phase, a report is developed which-considers whether-there are adverse health effects of a substance which may be, or is, emitted in California. However, in January 1993, AB 2728 was enacted and the procedure for toxic air contaminant (TAC) identification of federal hazardous air pollutants (HAPs) was changed. Pursuant to the new legislation, the state board was required to identify, by regulation, any substance listed as a federal HAP as a TAC. Although this report was developed under AB 1807, acetaldehyde is a HAP, and was identified as a TAC on April 8, 1993, when the Board identified all 189 HAPs as TACs.

The title of this report has also changed. The original report, "Proposed Identification of Acetaldehyde as a Toxic Air Contaminant," was released for public comment in August 1992. The report was revised, and this final version, "Acetaldehyde as a Toxic Air Contaminant," was approved by the Scientific Review Panel on May 12, 1993, and includes a review of exposure, the cancer potency number, and the chronic reference exposure level.

No control measures are proposed in this report. The cancer potency number and chronic reference exposure level were approved by the Scientific Review Panel, and may be used in the development of control measures.

In preparing this report, staff reviewed pertinent literature through March 1992.

EXECUTIVE SUMMARY

Introduction

This report was developed in response to provisions of state law (Health and Safety Code sections 39650-39662), which became effective in January 1984. This legislation requires a two-phase process which separates risk assessment (identification) of toxic air contaminants (TACs) from risk management (control). During the identification phase, a report is developed which considers whether there are adverse health effects of a substance which may be, or is, emitted in California. After conducting a public hearing, the Board decides whether or not the substance should be identified as a TAC. If identified, the substance is listed by regulation as a TAC in the California Administrative Code and enters the control phase.

With the adoption of the AB 2728 legislation, which was signed by the Governor in September 1992 and became effective in January 1993, the procedure for identification of federal hazardous air pollutants (HAPs) as TACs was changed. Pursuant to the new legislation, the state board was required to identify, by regulation, all HAPs as TACs. Acetaldehyde is a HAP and, therefore, was identified as a TAC by regulation at a Board hearing on April 8, 1993.

What is contained in this report?

This report summarizes the emissions, exposure, and atmospheric persistence and fate of acetaldehyde in California. It also describes the health effects of acetaldehyde which includes an estimate of the cancer potency number and a chronic reference exposure level. The Scientific Review Panel (SRP) evaluated the entire report including a review of the data, and approved the cancer potency number and the chronic reference exposure level on May 12, 1993. The cancer potency number and the chronic reference exposure level may be used in the development of control measures for acetaldehyde.

This report contains several parts. Part A, developed by the ARB staff contains information on exposure to Acetaldehyde in California. Part B, developed by the Office of Environmental Health Hazard Assessment (OEHHA), contains information on the health effects of acetaldehyde. Part C contains public comments received during the first and second comment period (August 7 - October 1, 1992 and April 5 - May 5, 1993) and the ARB/OEHHA responses to these-comments.

What is acetaldehyde?

Acetaldehyde is a colorless, flammable liquid, volatile at ambient temperature and pressure, with an irritating odor. Acetaldehyde can be used in a wide variety of chemical reactions, many of which are useful in commercial processes. The commercial uses of acetaldehyde include the manufacture of acetic acid, acetic anhydride, pyridines, peracetic acid, penteerthritol, ethyl acetate, alkylamines, lactic acid and crotonaldehyde. Acetaldehyde is also known by a variety of synonyms which include acetic aldehyde, ethanol, ethyl aldehyde and methyl formaldehyde. The molecular formula of Acetaldehyde is CH3CHO.

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Acetaldehyde (CH3CHO)

Why was acetaldehyde evaluated as a toxic air contaminant?

The staffs of the ARB and OEHHA have reviewed the available scientific evidence on the presence of acetaldehyde in the atmosphere of California and its potential adverse effect on public health. The ARB staff has determined that acetaldehyde is the product of incomplete combustion, is emitted from a variety of sources, and can be detected in the ambient air throughout California. It can be formed in polluted ambient atmospheres from a variety of precursors. It is highly mobile in the environment, and is not naturally removed or detoxified at a rate that would significantly reduce public exposure. The International Agency for Research on Cancer (IARC) classified acetaldehyde as a possible human carcinogen (2B), based on sufficient evidence in animals and inadequate evidence in humans. The United States Environmental Protection Agency (U.S. EPA) has decided that acetaldehyde is a "probable human carcinogen" (B2). The OEHHA staff has concluded that at ambient concentrations acetaldehyde may cause or contribute to an increase in mortality or serious illness and may therefore pose a potential hazard to human health.

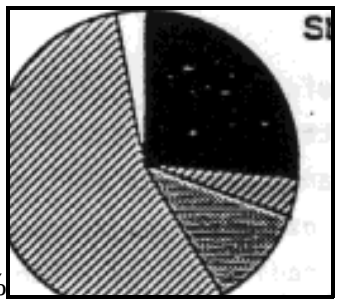
What are the sources of acetaldehyde emissions?

Acetaldehyde is not manufactured in California. It is both directly emitted into the atmosphere through incomplete combustion from such sources as stacks, tailpipe exhaust and fires, as well as formed in the atmosphere as a result of photochemical oxidation of hydrocarbons and free radical reactions involving hydroxyl radicals. In urban areas, emissions are primarily from mobile sources with some contribution from stationary sources. The largest sources statewide of directly emitted acetaldehyde are from combustion of fuels from mobile sources, agricultural burning, and wildfires. Direct sources are estimated to contribute approximately 44 percent of the acetaldehyde in the atmosphere.

Photochemical oxidation is estimated to contribute 56 percent of the ambient acetaldehyde as predicted by the Urban Airshed model. Concentrations via photochemical oxidation can vary significantly depending on the season, location, meteorological conditions, and time of day. Mobile and stationary sources emit reactive organic gases such as ethyl peroxide, and ethoxy radicals which are precursors of photochemically generated acetaldehyde. Reductions of these hydrocarbon precursors can be expected to reduce the contribution of acetaldehyde from photochemical oxidation.

Figure 1 shows the percentages of acetaldehyde emissions in California from all sources in 1987. The ARB staff estimates that approximately 14,000 - 30,000 tons, were produced from photochemical oxidation of organic precursors. Stationary point sources, stationary area sources, on-road mobile sources, and other transportation sources contribute approximately 11,000 - 24,000 tons/year. The estimate of photochemical production is based on information from the Emissions Data System (EDS) and could vary by 50 percent.

Figure 1
Sources of Acetaldehyde for 1987
in California



Indoor acetaldehyde sources are numerous and include such diverse combustion sources as cigarette smoke, fireplaces, woodstoves and cooking.

How much acetaldehyde is released directly into California air?

Total direct outdoor acetaldehyde emissions from mobile, stationary and area sources as based on ARB's 1987 emission inventory in California are estimated to be approximately 11,000 - 24,000 tons per year. Figure 2 is a breakdown of direct emissions only. Mobile sources, which include on-road motor vehicles and other transportation sources such as trains, ships, farm and utility equipment, emitted approximately 3,7OO to 7,800 tons of acetaldehyde or 15 to 32 percent of direct emissions. Stationary point sources such as fuel combustion sources, refineries and coffee bean roasters emitted approximately 820 to 1,000 tons (3 to 4 percent) of acetaldehyde. Stationary area sources include wildfires, agricultural burning and management burning, and diesel combustion in internal combustion engines at oil and gas fields, etc. The staff estimates that these stationary area sources emitted approximately 7,000 to 15,000 tons (29 to 62 percent) of acetaldehyde.

Figure 2
Direct Sources of Acetaldehyde
for 1987 In California

What are the effects of the ARB motor vehicle control program on acetaldehyde and its precursors?

The emissions standards applied by the ARB to new vehicles over the past years have caused steady declines in vehicular reactive organic gases (ROG) including acetaldehyde and nitrogen oxides (NOx) emissions. Further, reductions in ROG and NOx are expected to result in a decline in secondary acetaldehyde due to vehicular emissions. Declines in this source of emissions is expected to continue because of the recently adopted low emission vehicle (LEV) emission standards. Additionally, the primary, directly emitted acetaldehyde, also, a ROG, is expected to decline.

The ARB adopted new gasoline specifications ("Phase 2 gasoline standards") which become effective in 1996. These standards also will reduce ROG and NOx emissions from all gasoline vehicles (vehicles currently on the road plus LEVs) made before 1996, thereby reducing the formation of both primary and secondary acetaldehyde.

The Wintertime Oxygenate Program requires that refiners add oxygen to gasoline in the wintertime to reduce carbon monoxide. Depending upon the oxygenated additive used, acetaldehyde emissions from combustion of motor vehicle fuels may, or may not, increase. The addition of methanol and methy tert-butyl ether (MTBE) to fuel does not increase acetaldehyde emissions. Gasoline containing the oxygenate additives ethanol or ethy tert-butyl ether (ETBE), upon combustion, may result in increased acetaldehyde emissions. However, it is not know to what extent ethanol or ETBE will be used as a winter oxygenate in California fuels and, therefore, the resulting effect on acetaldehyde emissions.

The overall effect of the vehicular emission standards and the gasoline specifications on acetaldehyde concentrations is a complex issue. Future acetaldehyde emissions will depend on the turnover rate of older vehicles to LEVs, the primary acetaldehyde contributions from oxygenated additives, such as ethanol and ethyl tert-butyl ether, the decrease of ROG from the combustion of Phase 2 reformulated gasoline, and possible use of ethanol.

What are the ambient outdoor air concentrations of acetaldehyde?

Acetaldehyde is routinely monitored by the statewide ARB tonics monitoring network. Basin-specific mean annual concentrations vary from a minimum of 1.63 parts per billion volume (2.93 micrograms per cubic meter) in the South Central Coast Air Basin to a maximum of 2.81 parts per billion volume (5.06 micrograms per cubic meter) in the South Coast Air Basin (based on 24 hour sample averages). The overall estimated mean statewide exposure, weighted by population, is estimated to be 2.33 parts per billion volume (4.19 micrograms per cubic meter). The population-weighted exposure is based on 20 million people represented by the tonics monitoring network (out of the 30 million total California populations).

Studies conducted in the South Coast Air Basin since 1980 have reported data for short-term (30 minute to 2 hour sample averages) ambient outdoor concentrations to vary from one part per billion volume (1.8 microgram per cubic meter) to 39 parts per billion volume (70.2 micrograms per cubic meter), with the most recent concentrations measured during the South Coast Air Quality Study (SCADS) (1987) with a range of 0.9 to 24.5 parts per billion volume (1.6 to 44.1 micrograms per cubic meter) in one hour samples. The SCADS was an integrated air quality study whose overall goal was to develop a comprehensive and properly archived air quality and meteorological data base for the South Coast Air Basin which can be used to test, evaluate, and improve elements of air quality simulation models for oxidants, NO2, PMl0, fine particles, visibility, toxic air contaminants, and acid species.

Reports of ambient air sampling of two rural regions, Point Barrow, Alaska and Whiteface Mountain, New York provide examples of 'background' concentrations of O to 0.8 parts per billion volume (1.4 micrograms per cubic meter) of acetaldehyde.

Is there evidence of indoor air exposure to acetaldehyde?

Yes. In general, concentrations are higher indoors than outdoors due in part to the abundance of combustion sources such as cigarettes, fireplaces, and woodstoves. Acetaldehyde emissions have been reported from frying hamburger, suggesting that cooking may be an indoor source of acetaldehyde. Acetaldehyde can also be emitted from some building materials such as rigid polyurethane foams, and some consumer products such as adhesives, coatings, lubricants, inks, and nail polish remover. Other potential sources of indoor acetaldehyde concentrations are the infiltration of vehicle exhaust and, perhaps, the volatilization of acetaldehyde from certain foods.

Surveys have shown that indoor air concentrations of acetaldehyde in residences without smokers can be about two to eight times higher than the outdoor mean population-weighted statewide concentration of 2.3 parts per billion. The results of limited surveys allow a crude estimate of an average acetaldehyde concentration inside residences of about 3.0 parts per billion volume (5.4 micrograms per cubic meter) to 15 parts per billion volume (27.0 micrograms per cubic meter). Limited data suggest that the acetaldehyde concentrations in offices and public buildings are similar in magnitude to those inside residences. Higher levels may occur in some indoor environments; in the case of a tavern occupied by a number of smokers, levels of up to 113 parts per billion volume (203.4 micrograms per cubic meter) were reported. Average and maximum in-vehicle acetaldehyde concentrations measured in southern California [7.7 and 37.0 parts per billion volume (13.7 and 66.6 micrograms per cubic meter), respectively] appear to be similar in magnitude to those inside residences.

Are there near source exposures to acetaldehyde in California?

Some Californians may be exposed to near-source, or "Hot Spot" concentrations of acetaldehyde which are above the average ambient concentrations. "Hot spot" exposure may increase the potential cancer risk to individuals living near large combustion sources. Acetaldehyde emissions and risk information is currently under development by facilities under the AB 2588 Air Toxics "Hot Spots" emissions reporting program. This information will be used during the risk management phase to help determine priority and need for control of sources emitting acetaldehyde.

Are there other routes of exposure to acetaldehyde?

Yes. It is commonly ingested, but ingestion of acetaldehyde is not known to be a significant cause of respiratory tract cancers, the focus of the health assessment for this compound. Acetaldehyde is found as a natural constituent of a number of foods such as ripe fruits and alcoholic beverages. It is also used as a food preservative and a flavoring agent for a variety of foods including margarine, baked goods, and milk products. Ingestion of alcohol is a major source of acetaldehyde in the body; acetaldehyde is a metabolic intermediate in the oxidation of ethanol by liver enzymes. Acetaldehyde levels in water are relatively low. Dermal absorption of acetaldehyde is surmised to be negligible.

What is the persistence of acetaldehyde in the atmosphere?

Depending on atmospheric conditions, the overall half-life of acetaldehyde is calculated to be approximately 12 hours which under normal meteorological conditions is sufficient time to allow dispersion throughout an air basin. Stagnant air conditions which may occur in California

can impede this dispersion. The dominant atmospheric removal mechanism for acetaldehyde during daylight hours is by photolysis and oxidation by hydroxyl radicals. Peroxyacetyl nitrate (PAN), a component of photochemical smog and a strong eye and mucous membrane irritant, and formaldehyde are the major breakdown products. The episodic nature of precipitation events, the small degree of acetaldehyde hydration and a calculated low washout ratio indicate that wet deposition (rain/fog) is not a significant removal mechanism.

W**hat are the health effects of acetaldehyde exposure?**

The health effects of acetaldehyde exposure have been reviewed and evaluated to determine whether acetaldehyde meets the definition of a TAC. The following text summarizes OEHHA staff findings regarding the health effects of acetaldehyde exposure.

What evidence exists that exposure to acetaldehyde poses a public health hazard?

The OEHHA staff agrees with the U.S. EPA classification of acetaldehyde (EPA Group B2) as a probable human carcinogen. The U.S. EPA bases this on "adequate evidence for carcinogenicity in animals and inadequate evidence in humans." In California, acetaldehyde was classified on April 1, 1988, as a chemical known to the state to cause cancer (Safe Drinking Water and Toxic Enforcement Act of 1986, Proposition 65). Acetaldehyde causes cancer in rodents, producing squamous cell carcinomas and adenocarcinomas originating in the respiratory and olfactory epithelium, respectively, in the nasal passages of male and female rats. In hamsters, acetaldehyde-induced tumors were found predominantly in the larynx. Epidemiological evidence for human cancer from exposure to acetaldehyde is limited because it is based on one imperfect study. The study lacked age and sex distribution, all of the small number of subjects had previously smoked, and there was concurrent exposure to other chemicals.

Because acetaldehyde is a reactive molecule it is mostly bound to proteins and other blood components while in the bloodstream. Acetaldehyde has been shown to cause a number of genotoxic effects in a variety of cell culture and in vitro assays, including DNA-protein crosslinks, sister chromatic exchanges, gene mutations, single strand breaks and chromosomal aberrations.

Exposure of experimental animals to acetaldehyde in high doses may be related to reproductive and developmental effects. It crosses the placenta and can present an exposure to the fetus. In studies with rodents, acetaldehyde has been shown to cause growth retardation, to damage developing fetuses, and to kill embryos. Reproductive in vitro toxicity studies have shown that acetaldehyde is an inhibitor of testicular testosterone production. There are no data available to relate the adverse animal effects to possible human exposure. The mechanisms by which acetaldehyde causes these effects in vitro and in vivo are not known. It is not possible at present to determine if acetaldehyde poses a reproductive or developmental hazard to humans.

What is the cancer risk assessment for exposure to acetaldehyde?

The inhalation risk is the calculated, theoretical possibility of contracting cancer when exposed to acetaldehyde at a concentration of one part per billion volume or one microgram per cubic meter of air for a lifetime. Since several unit risks can be obtained depending on the different animal test groups considered and calculation procedures used, a range of values can be obtained. From the range a best value was selected which in the judgement of OEHHA has the strongest scientific support. The staff of the OEHHA recommends that the unit risk of 4.8×10^{-6} per part per billion (2.7×10^{-6} per microgram per cubic meter) be considered the "best value of

the upper bound of risk." This is similar to the value calculated by the U.S. EPA to 2.2×10^{-6} per microgram per cubic meter. This value is based on data from a recent bioassay in male rats. This unit risk, coupled with a lifetime exposure to one part per billion, would yield 4.8 excess potential cancer cases per million people. The use of this "best value" with California's average ambient acetaldehyde exposure concentration of two parts per billion volume (3.6 microgram per cubic meter) yields 9.6 excess potential cancer cases per million people exposed throughout their lives. It can be estimated that up to 288 acetaldehyde-induced potential cancer cases would occur statewide among a population of 30 million people exposed to current ambient concentrations throughout their lives. The "best value" unit risk is a plausible upper bound estimate based on health-protective assumptions; the actual risk may be significantly lower. Table I shows a comparison of acetaldehyde potency with other compounds the Board has identified as TACs.

The upper limit estimate of the number of potential excess cancers due to outdoor airborne acetaldehyde exposure ranges from 2 to 54 per million people exposed throughout their lives, based on California's present average ambient acetaldehyde exposure concentration of 2 parts per billion volume (4 microgram per cubic meter), and an excess cancer risk range of 0.97×10^{-6} to 27.0×10^{-6} per part per billion (0.54×10^{-6} to 15×10^{-6} per microgram per cubic meter). This range of risk is based on data from studies in male and female rats. The upper limit estimate of the number of potential excess cancer cases for the South Coast Air Basin (with an average exposure concentration of 2.8 parts per billion volume or 5.0 micrograms per cubic meter) is 3 to 76 per million people exposed throughout their lives.

The range of risk values represents several sources of uncertainty, including statistical uncertainty due to the relatively small number of animals used in the bioassay (less than the usual 50 per group). Other general sources of uncertainty, include the choice of the animal-to-human

Table I

COMPOUNDS APPROVED BY THE SCIENTIFIC REVIEW PANEL FROM 1984 TO 1993

(in order of cancer potency)

Compound	Unit Risk microgram per cubic meter	Unit Risk part per billion volume
Dioxins	3.8×10^{1}	Particulate Matter
Chromium VI	1.4×10^{-1}	Particulate Matter
Cadmium	4.2×10^{-3}	Particulate Matter
Inorganic Arsenic	3.3×10^{-3}	Particulate Matter
Nickel	2.6×10^{-4}	Particulate Matter
1,3-Butadiene	1.7×10^{-4}	3.7×10^{-4}
Ethylene Oxide	8.8×10^{-5}	1.6×10^{-4}
Vinyl Chloride	7.8×10^{-5}	2.0×10^{-4}
Ethylene Dibromide	7.1×10^{-5}	5.5×10^{-4}
Carbon Tetrachloride	4.2×10^{-5}	2.6×10^{-4}
Benzene	2.9×10^{-5}	9.3×10^{-5}
Ethylene Dichloride	2.2×10^{-5}	8.9×10^{-5}
Perchloroethylene	5.9×10^{-6}	4.0×10^{-5}
Formaldehyde	6.0×10^{-6}	7.0×10^{-6}
Chloroform	5.3×10^{-6}	2.6×10^{-5}
Acetaldehyde	2.7×10^{-6}	4.8×10^{-6}
Trichloroethylene	2.0×10^{-6}	1.1×10^{-5}
Methylene Chloride	1.0×10^{-6}	3.5×10^{-6}
Asbestos	1.9×10^{-4} per 100 fibers per cubic meter	

scaling factors, the choice of the extrapolation model, and the large range of extrapolation (five orders of magnitude) from the acetaldehyde concentrations used in the animal experiments to current ambient levels.

Based on the information available on acetaldehyde-induced carcinogenicity and the results of the risk assessment, the OEHHA staff conclude that acetaldehyde is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

What is the potential for acute or chronic non-carcinogenic health effects from exposure to ambient concentrations of acetaldehyde?

Acute exposure to acetaldehyde vapor leads to eye, skin and respiratory tract irritation. Prolonged exposure of the skin to liquid acetaldehyde causes erythema and burns; repeated contact may lead to dermatitis due to primary irritation or sensitization. Long-term or chronic exposure has been shown to damage the respiratory tract in rats. Applying an uncertainty factor of 1,000 using standard methodology produces a daily Reference Exposure Level of five parts per billion (9 micrograms per cubic meter).

The OEHHA staff concluded that it is unlikely that noncarcinogenic adverse health effects would be caused at the average levels of acetaldehyde currently found in the ambient air. However, acetaldehyde concentrations could be significantly higher near emission sources.

Is there a threshold level for acetaldehyde?

There is compelling evidence of acetaldehyde genotoxicity because of binding to DNA and mutagenicity and there is experimental evidence for acetaldehyde acting as an initiator of tumorigenesis. Therefore, the OEHHA staff considers acetaldehyde-induced carcinogenesis as a genotoxic event and were unable to determine a threshold for the phenomenon.

What are the findings of the Scientific Review Panel?

Findings of the Scientific Review Panel on
THE REPORT ON ACETALDEHYDE
As Adopted from the Panel's May 12, 1993 Meeting

Pursuant to Health-and Safety Code-section 39661, the Scientific Review Panel (SRP) has reviewed the report "Acetaldehyde as a Toxic Air Contaminant" prepared by the staffs of the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA) on the public exposure to, and health effects of acetaldehyde. The Panel also reviewed the public comments received on this report. Based on this review, the SRP makes the following findings also pursuant to Health and Safety Code section 39661:

1. Acetaldehyde was declared a toxic air contaminant by the Air Resources Board on April 8, 1993.

2. There is evidence that exposure to acetaldehyde results in animal carcinogenicity and therefore has the potential for human carcinogenicity. The International Agency for Research on Cancer (IARC) classified “acetaldehyde as a possible human carcinogen (2B) based on sufficient evidence in animals and inadequate evidence in humans." The United States Environmental Protection Agency (U.S. EPA) classified acetaldehyde "as a probable human carcinogen (B2) on the basis of sufficient evidence for carcinogenicity in animals and inadequate evidence in humans."

3. Based on available scientific information, a level of acetaldehyde exposure below which no carcinogenic effects are anticipated cannot be identified.

4. Based on a health protective interpretation of available scientific evidence, the upper 95 percent confidence limits on the potential lifetime risk of cancer from acetaldehyde at ambient concentrations range from O.97 to 27.0 x 10^{-6} per part per billion (0.54 to 15.0 x 10^{-6} per microgram per cubic meter). Furthermore, based on available Scientific evidence, 4.8 x 10^{-6} per part per billion (2.7 x 10 per microgram per cubic meter) is the best value of the upper confidence limit of risk. Table I compares the best value of the upper bound acetaldehyde potential unit cancer risk with those of other compounds reviewed by the SRP. These 95 percent upper confidence limits for excess lifetime risks are health-protective estimates; the actual risk may be significantly lower.

5. The range of risk values represents several sources of uncertainty. They include uncertainty due to the small number of animals used in the bioassay, the choice of the animal to human scaling factors, and the choice of the extrapolation model.

6. The major identified sources of ambient outdoor acetaldehyde are direct emissions from mobile sources, fuel combustion, burning, wildfires, oil refineries, and secondary formation by photochemical reactions

7. The addition of methanol and methyl tert-butyl ether (MTBE) to fuel does not increase acetaldehyde emissions. Alternate fuels containing the oxygenate additives ethanol or ethyl tert-butyl ether (ETBE), upon combustion, result in acetaldehyde emissions. However, it is not known to what extent ethanol or ETBE will be used as a winter oxygenate in California fuels, and therefore the resulting affect on acetaldehyde emissions.

8. One of the main products of the photooxidation of acetaldehyde is peroxyacetyl nitrate (PAN). Airborne acetaldehyde in the presence of nitrogen oxides can be converted to PAN which is a strong eye irritant and plant toxicant.

9. Based on data collected by the ARB's ambient toxic air contaminant monitoring network, the estimated mean annual population-weighted outdoor ambient exposure for approximately 20 million Californians is 2.3 parts per billion in volume (4.1 micrograms per cubic meter).

10. "Hot spot" exposure may increase the potential cancer risk to individuals living near large combustion sources. Acetaldehyde emissions and risk information are being submitted by facilities subject to the AB 2588 Air Toxics "Hot Spots" reporting program (Chapter 1252, Statutes of 1987, Health and Safety Code section 44300 et seq.). This information will be used during the risk management phase to help determine priority and need for control of sources emitting acetaldehyde.

11. Based on its gas-phase reactivity from photolysis and oxidation by the hydroxyl radical, acetaldehyde's estimated tropospheric lifetime is calculated to be approximately 12 hours under average meteorological conditions.

12. Results from indoor monitoring of acetaldehyde in California's homes, offices, and public buildings indicate that people are exposed frequently to higher indoor concentrations than outdoor acetaldehyde concentrations due to the abundance of combustion sources and consumer products in buildings that emit acetaldehyde. The results of surveys indicate that acetaldehyde concentrations inside California residences generally range from less than

1 part per billion (1.8 micrograms per cubic meter) to 35 parts per billion (63 micrograms per cubic meter). Mean concentrations can range from 1 part per billion in office and public buildings to 113 parts per billion (203 micrograms per cubic meter) for a smoke filled tavern, with approximately 10 parts per billion (18 micrograms per cubic meter) found in conventional homes.

13. A number of acute adverse health effects are associated with acetaldehyde exposure. Such effects include irritation of the skin, eyes and mucous membranes, as well as nausea and headaches. Skin contact with acetaldehyde can induce long-term allergic dermal sensitization, and limited evidence suggests that inhalation of high concentrations of acetaldehyde can cause respiratory tract sensitization. Adverse health effects other than cancer are not expected to occur at mean statewide outdoor ambient concentrations. However, there is evidence that adverse acute health effects may result from exposure to levels found in indoor environments for those sensitive to acetaldehyde.

14. Long-term or chronic exposure has been shown to damage the respiratory tracts of rats. Using standard methodology to calculate a Reference Exposure Level (REL) produces a daily chronic REL of 5 parts per billion (9 micrograms per cubic meter).

15. The staffs of the ARB and OEHHA have developed a risk assessment based on relative exposure to outdoor concentrations. Using the OEHHA staff's best value for unit cancer risk of 4.8×10^{-6} parts per billion volume, and the corresponding concentrations found in outdoor environments, the number of excess cancer cases due to outdoor exposure to acetaldehyde is estimated to be approximately 10 per million, for a 70 year lifetime. This corresponds to an excess cancer burden of 288 for outdoor exposures for a California population of 30 million.

I certify that the above is a
true and correct copy of the
findings adopted by the
Scientific Review Panel on
May 12, 1993

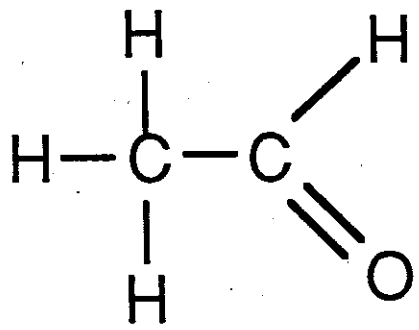
//s//
Dr. James N. Pitts, Jr.
Chairman, SRP

California Environmental Protection Agency

Air Resources Board

Acetaldehyde

as a Toxic Air Contaminant



Part A

Exposure Assessment

Stationary Source Division

November 1993

ACETALDEHYDE AS A TOXIC AIR CONTAMINANT

PART A

TECHNICAL SUPPORT DOCUMENT
PUBLIC EXPOSURE TO SOURCES AND EMISSIONS OF
ACETALDEHYDE IN CALIFORNIA

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November 1993

ACKNOWLEDGMENTS

The Stationary Source Division acknowledges the valuable assistance of the following people who contributed to the preparation and review of this document: Michele Burkett, Faye Palmer, Doug Lawson, Eric Fujita, Peggy Jenkins, and Michael Poore. We also thank and acknowledge the staff who dedicated their time in the research and written portions of the report, and to the staff who conducted the field work including the monitoring, analysis, and methods development. In preparing this report, staff reviewed pertinent literature through March 1992.

November 1993

REPORT SUBMITTED TO THE SCIENTIFIC REVIEW PANEL

Part A- Public Exposure To Sources and Emissions of Acetaldehyde in California

TABLE OF CONTENTS

	Page
List of Appendices	ii
List of Tables	iii
List of Figures	iv
I. INTRODUCTION	A-1
A. Acetaldehyde as a Chemical Compound	A-2
B. References	A-4
II. PROPERTIES OF ACETALDEHYDE	A-5
A. Physical Properties	A-5
B. References	A-8
III. PRODUCTION, USES, AND EMISSIONS OF ACETALDEHYDE	A-9
A. Production	A-9
B. Uses	A-12
C. Emissions	A-13
D. References	A-29
IV. EXPOSURE TO ACETALDEHYDE	A-33
A. Ambient Monitoring in California	A-33
B. Ambient Concentrations	A-35
C. Population Weighted Exposure Estimates	A-43
D. Exposure to Acetaldehyde Near Emission Sources	A-46
E. Indoor Exposure	A-46
F. References	A-55
V. ATMOSPHERIC FORMATION, PERSISTENCE, AND FATE OF ACETALDEHYDE	A-58
A. Atmospheric Formation	A-59
B. Persistence	A-61
C. Fate	A-66
D. References	A-68

APPENDICES

A. PHOTOCHEMICALLY FORMED ACETALDEHYDE AS A PERCENT OF AMBIENT CONCENTRATION

B. EMISSION ESTIMATES

C. ANALYSIS OF ACETALDEHYDE

D. BOOTSTRAP STATISTICAL METHODS

E. EXPOSURE TO ACETALDEHYDE FROM INDOOR AIR

F. INFORMATION REQUEST LETTER WITH ATTACHMENT AND RESPONSES

G. HEALTH EFFECTS REQUEST LETTER TO DEPARTMENT OF HEALTH SERVICES AND LETTER OF RESPONSE

H. GLOSSARY

LIST OF TABLES

Table		Page
II-1	PHYSICAL PROPERTIES OF ACETALDEHYDE	A-6
III-1	SUMMARY OF CALIFORNIA ACETALDEHYDE EMISSIONS IN 1987	A-11
IV-1	SUMMARY OF ACETALDEHYDE DATA	A-36
IV-2	SUMMARY OF AMBIENT ACETALDEHYDE CONCENTRATIONS	A-37
IV-3	MEASUREMENTS OF ACETALDEHYDE CONCENTRATIONS IN AMBIENT AIR IN CALIFORNIA	A-42
IV-4	SUMMARY OF MEAN ANNUAL ACETALDEHYDE EXPOSURE ESTIMATES	A-44
IV-5	SUMMARY OF MEAN ANNUAL ACETALDEHYDE CONCENTRATIONS AND BOOTSTRAP ESTIMATES OF UNCERTAINTY	A-45
IV-6	INDOOR AIR CONCENTRATIONS OF ACETALDEHYDE	A-49
IV-7	ESTIMATES OF THE INHALED DOSE OF ACETALDEHYDE FROM RESIDENTIAL INDOOR AIR AND ENVIRONMENTAL TOBACCO SMOKE	A-52
IV-8	CONCURRENT INDOOR AND OUTDOOR ACETALDEHYDE CONCENTRATIONS	A-54
V-1	ATMOSPHERIC LIFETIME OF ACETALDEHYDE AND REMOVAL PROCESSES	A-63

LIST OF FIGURES

Figures | Page

111-1 SOURCES OF ACETALDEHYDE FOR 1987 IN CALIFORNIA.....A-14

III-2 DIRECT SOURCES OF ACETALDEHYDE FOR 1987 IN CALIFORNIA.....A-15

IV-1 ARB TOXICS NETWORK MONITORING SITES.....A-34

IV-2 DISTRIBUTION OF AMBIENT ACETALDEHYDE CONCENTRATIONS PLOTTED USING EXTENDED BOX PLOTS.....A-39

IV-3 DISTRIBUTION OF MONTHLY AMBIENT ACETALDEHYDE CONCENTRATIONS PLOTTED USING EXTENDED BOX PLOTS (ALL SITES COMBINED).....A-40

IV-4 POPULATION ESTIMATES FOR VARIOUS MEAN ANNUAL AMBIENT CONCENTRATIONS.....A-47

I.

INTRODUCTION

This report summarizes the emissions, concentrations, exposure, and atmospheric persistence and fate of acetaldehyde in California. It also summarizes the health effects of acetaldehyde which includes an estimate of cancer potency.

This report was developed in response to provisions of AB 1807 (Health and Safety Code sections 39650-39662), which became effective in January 1984. This legislation requires a two-phase process which separates risk assessment (identification) of toxic air contaminants (TACs) from risk management (control). During the identification phase, a report is developed which considers whether there are adverse health effects of a substance which may be, or, is emitted in California. After conducting a public hearing, the Board decides whether or not the substance should be identified as a TAC. If identified, the substance is listed by regulation as a TAC in California Code of Regulations and enters the control phase.

With the adoption of the AB 2728 legislation (signed by the Governor in September 1992 and effective in January 1993), the procedure for identifying substances already classified as federal hazardous air pollutants (HAPs) as TACs was changed. Pursuant to the new legislation, the state board identified as TACs on April 8, 1993, substances listed as federal HAPs through a simplified process. Acetaldehyde is a HAP and, therefore, was identified as a TAC under the new process.

After the Board hearing, where all HAPs were identified as TACs, the cancer unit risk numbers for acetaldehyde developed by the Office of Environmental Health Hazard Assessment (OEHHA), were approved by the Scientific Review Panel (SRP) on May 12, 1993. The role of the SRP is to review the data, assessments and conclusions presented in the report as the basis for approving the potency number. The potency number will be used in the control phase of the AB 1807 process. It 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.

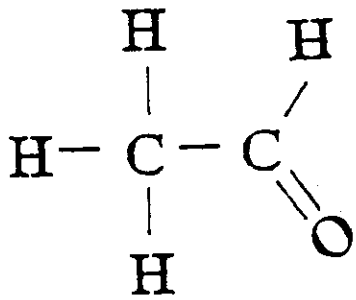
A. ACETALDEHYDE AS A CHEMICAL COMPOUND

Acetaldehyde is an aliphatic aldehyde: a saturated hydrocarbon with a terminal carbonyl group (C=O). Acetaldehyde is known by a variety of synonyms which include: acetic aldehyde, ethanal, ethyl aldehyde and methyl formaldehyde [Chemical Abstracts Service (CAS) Registry Number 75-07-0]. Acetaldehyde is not known to contribute to either global warming or depletion of the ozone layer.

Gasoline containing the oxygenate additives ethanol or ethyl tert-butyl ether (ETBE) upon combustion results in increased acetaldehyde emissions. These oxygenates may be used as additives to meet the requirements of the CARB Phase 2 Reformulated Gasoline Regulations and Wintertime Oxygenates Program which may increase acetaldehyde emissions.

The major acetaldehyde decomposition products are formaldehyde and peroxyacetyl nitrate (PAN) both of which are of concern as toxic species. In neither case is acetaldehyde the dominant source of these species (EPA, 1993).

Acetaldehyde has the molecular formula C_2H_4O and the chemical structure shown here.



B. References for Chapter I

EPA (1993) "Motor Vehicle-Related Air Toxics Study", Technical Support Branch, Emission Planning and Strategies Division, Ann Arbor, MI.

II.

PROPERTIES OF ACETALDEHYDE

A. PHYSICAL PROPERTIES

Synonyms for acetaldehyde are acetic aldehyde, ethanal, ethyl aldehyde and methyl formaldehyde. Acetaldehyde is a saturated aldehyde with the chemical formula CH_3CHO. It is a colorless liquid, volatile at ambient temperature and pressure. Although it has a pungent irritating odor, at dilute concentrations it has a fruity and pleasant odor. The threshold odor concentration in air is 7.8 to 33.3 ppbv (0.014 mg/m^3 to 0.06 mg/m^3). Both the liquid and the vapors are highly flammable (Cooke, 1971) and acetaldehyde is a dangerous fire hazard when exposed to heat or flame (Sax, 1975). As a liquid it is lighter than water and the vapors are heavier than air. Acetaldehyde is soluble in water, acetone, gasoline, alcohols, toluene, xylene, benzene, ether, paraldehyde and organic solvents. It decomposes at temperatures above 400°C (Kirk-Othmer, 1980). The decomposition products are principally methane and carbon monoxide. Acetaldehyde undergoes photochemical decomposition when irradiated by ultraviolet light and some of the products are PAN and formaldehyde. The physical and chemical properties of acetaldehyde are listed in Table II-1.

Acetaldehyde is an intermediate product in the respiration of higher plants and can be found in ripening fruit such as apples. Also, acetaldehyde is an intermediate product of fermentation of alcohol and the metabolism of sugars in the body.

Table II-1

PHYSICAL PROPERTIES OF ACETALDEHYDE

Properties	Value	Reference
Conversion factor: 1 ppm = 1.8 mg/m^3 at 760 mm Hg and 25° C		
Chemical formula	CH_3CHO	
Cas Registry number	75-07-0	a
Molecular weight	44.05	b
Boiling Point, 1 Atm	21 ^oC	b
Vapor Density (air = 1)	1.52	a
Melting Point	-123.5 ^oC	b
Flash pt. closed cup	-38	b
Density (specific gravity at 18^oC/4^oC)	0.79	a
Dissociation constant (at 0^oC, Ka)	0.7×10^{-14}	a
Refraction index (n_D^{20})	1.33113	a
Partition coefficient (Log P octanol/water)	0.43	a
Vapor pressure at 20^oC	755 mm Hg	a
Autoignition temperature	193^oC	c
Coefficient of expansion per ^oC	0.00169	a
Surface tension at 20^oC,mN/m	21.2	a
Explosive limits of mixtures with air, vol % acetaldehyde	4.5-60.5	a
Ionization potential,eV	10.50	a
Critical temperature, ^oC	181.5	a
Critical pressure, MPa (atm)	6.40 (63.2)	a
Latent heat of vaporization, kJ/mol	25.71	a

a Kirk and Othmer, 1980

b Merck Index, 1983

c WHO, 1985

Acetaldehyde is highly reactive, exhibiting the general reactions of aldehydes; under proper conditions, the oxygen or any hydrogen can be replaced (Kirk and Othmer, 1980). Further, reaction with oxygen may lead to explosion (Sax and Lewis, 1989). It is a strong reducing agent and undergoes numerous condensation, addition and polymerization reactions. In the presence of catalysts such as trace metals or acids, acetaldehyde rapidly polymerizes to form paraldehyde (Fairhall, 1957). Acetaldehyde can react violently with acid anhydrides, alcohols, ketones, phenols, ammonia, hydrogen cyanide, hydrogen sulfide, halogens, phosphorus, isocyanates, strong alkalis and amines (Sax and Lewis, 1989).

Because of its high chemical reactivity acetaldehyde is used as an intermediate in the production of acetic acid, acetic anhydride, ethyl acetate, peracetic acid, pentaerythritol, chloral, glyoxal, alkylamines and pyridines (Kirk and Othmer, 1980).

B. References for Chapter II

Cooke, W.G. (1971) "Acetaldehyde", Encyclopedia of Occupational Health and Safety, Volume 1, New York, McGraw-Hill Book Company, pp. 23-24.

Fairhall, L.I. (1957) "Carbon Compounds: Acetaldehyde", Industrial Toxicology, 2nd ed. Baltimore, MD, Williams and Wilkins, pp. 138-140.

Kirk, R. and D. Othmer (1980) Encyclopedia of Chemical Technology, 3rd Edition, Volume 1, John Wiley and Sons Inc., New York, NY, pp. 97-99.

Merck Index (1983) An Encyclopedia of Chemicals, Drugs and Biologicals, Tenth Edition, Merck & Co., Inc., p. 6.

Sax , N.I. (1975) Dangerous Properties of Industrial Materials, 4th ed., New York, NY, Van Nostrand Reinhold company, p. 348.

Sax, N.I. and R.J. Lewis, Sr. (1989) Dangerous Properties of Industrial Materials, 7th ed., New York, NY, Van Nostrand Reinhold company, p. 6.

World Health Organization (WHO) (1985) "Allyl Compounds, Aldehydes, Epoxides and Peroxides", IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 36, pp. 101-102.

III.

PRODUCTION, USES AND EMISSIONS OF ACETALDEHYDE

Acetaldehyde is both directly emitted into the atmosphere as well as formed in the atmosphere as a result of photochemical oxidation of organic pollutants in urban atmospheres. Photochemical oxidation is the largest source (could be as high as 67 percent) of annual concentrations in the outdoor ambient air in California. Mobile and stationary sources emit reactive organic gases such as ethyl, ethyl peroxide, and ethoxy radicals which are precursors of photochemically generated acetaldehyde. Reductions of these hydrocarbon precursors can be expected to reduce the contribution of acetaldehyde from photochemical oxidation.

The direct release of acetaldehyde from combustion processes include vehicular exhaust from mobile sources and fuel combustion from stationary internal combustion (IC) engines, boilers and process heaters. Combustion of gasoline containing the oxygenate additives ethanol or ETBE may result in increased acetaldehyde emissions. Other sources of acetaldehyde include refineries, coffee bean roasters, residential wood combustion, wildfires, agricultural burning and management burning.

A. PRODUCTION

Acetaldehyde is produced two different ways: formation by photochemical oxidation in the atmosphere and commercial manufacture. In California, photochemical oxidation is the major source of acetaldehyde formation.

1. Photochemical Contribution

Although several kinetic mechanisms for the formation of acetaldehyde in the atmosphere have been proposed (Finlayson-Pitts, B.J. and J.N. Pitts, Jr., 1986; and Atkinson et al., 1990), as of this writing, there are no published estimates of the annual concentrations of acetaldehyde from photo-oxidation formation in the atmosphere. As an approximation, the ARB staff performed an Urban Airshed Model (UAM) simulation using ambient data for August 28, 1987, in the South Coast Air Basin (SoCAB) to estimate the portion of the ambient concentration of acetaldehyde due to secondary formation. The UAM simulates the ambient acetaldehyde concentrations from both direct and secondary formation (Ligocki and Whitten, 1991). Because August 28, 1987, was a summer high-ozone day, the staff believes that this simulation overpredicted the annual average secondary acetaldehyde. Based on this simulation, the staff estimates that the worst-case SoCAB average ambient surface concentration of acetaldehyde in the atmosphere resulting from secondary formation ranges from approximately 41 percent during the night to 67 percent during the day of the total acetaldehyde concentration in the atmosphere (Wagner, 1991). If the same location and time of emissions in the UAM model are assumed, then from the emission inventory in Table III-1 a ratio can be used to approximate the statewide secondary acetaldehyde component (Appendix A 2). We estimate that the secondary acetaldehyde is equivalent to a range of 14,000 to 31,000 tons of primary acetaldehyde emissions annually.

2. Commercial Production

As of 1990, there are two acetaldehyde producers in the United States; neither is located in California (SRI International, 1989). Acetaldehyde is also produced as a by-product in the production of polyesters, dimethyl terephthalate, acetone, mixed esters, ethanol, ethyl ether, vinyl acetate, ethylene glycol and acrolein. None of these facilities is located in California [Midwest Research Institute (MRI), 1987]. However, there are seven producers of polyester resins in California (SRI International, 1989). Information is not available to assess whether these facilities emit acetaldehyde.

Table III-1

SUMMARY OF CALIFORNIA ACETALDEHYDE EMISSIONS IN 1987

Source	Emissions* (Tons Per Year)	Notes (see following page)
PRODUCTION		
As a Photo-oxidation Product	14,000-30,000	a
EMISSIONS		
Mobile Sources		
On-Road Vehicles	1,600-5,700**	b,c,d,e
Other Mobile Sources	2,100	c,d,e
Stationary Area Sources		f
Residential Wood Combustion	110-660	
Natural Gas Combustion	7-14**	
Diesel Combustion	43	
Oil Combustion	1-2	
Agricultural Burning	1,000-2,100	g
Management Burning	1,200-2,500	g
Open Burning	87-180	g
Wildfires	4,500-9,200	g
Stationary Point Sources		h
Fuel Combustion		
Coal	1-2	
Diesel	1	
Gasoline	10	
Natural Gas	15-31	
Process Gas	***	
Oil	10-20	
Wood	560	
Refineries - Processing	190-770	i,j
Coffee Bean Roasting	2	k
Food Preparation	7	l

* Emissions have been rounded to, at most, two significant figures.

** A small portion (less than 1%) of this estimate is for activities occurring in the outer continental shelf area.

*** Acetaldehyde emissions from process gas combustion may equal approximately 50 percent of the estimated emissions from natural gas combustion.

Notes:

a. Atmospheric formation of acetaldehyde varies widely during the period of day, meteorological conditions and geographical location. Estimates can vary by 50 percent. Using data from the the Urban Airshed Model it is estimated that 41 to 67 percent of acetaldehyde is photochemically formed in the atmosphere (see Appendix A). In the UAM simulations, the model species ALD2 is assumed to approximate acetaldehyde.

b. ARB (1990a)

c. ARB (1990b)

d. ARB (1990c)

e. ARB (1989)

f. See Appendix B, Stationary Area Sources, Table 6

g. These combustion sources may contribute a relatively low exposure concentration due to lack of proximity to significant populations and high plume rise.

h. See Appendix B, Stationary Point Sources

i. Oil and Gas Journal (1989)

j. See Appendix B, Stationary Point Sources, Refineries

k. ARB (1990i)

l. SARA 313 data

B. USES

Acetaldehyde is used in the synthesis of many chemicals such as acetic acid, paraldehyde, pyridines, terephthalic acid, pentaerythritol, perfumes, plastics, 1,3-butalene glycol and synthetic rubber. It is also used as an industrial solvent and as a food flavoring agent preservative (Serth et al., 1978). None of the above mentioned chemical manufacturers is located in California. No information is available on the use of acetaldehyde as an industrial solvent or as a food flavoring agent preservative.

C. EMISSIONS

Table III-1 summarizes acetaldehyde emissions from all accountable sources in California. Figures III-1 and III-2 show the percentages of acetaldehyde emissions from the listed sources. Mobile sources which include on-road motor vehicles and other mobile sources such as trains, ships, farm and utility equipment emitted approximately 3,700 tons to 7,800 tons of acetaldehyde in 1987. Stationary point sources such as fuel combustion sources, refineries and coffee bean roasters emitted approximately 820 to 1,000 tons of acetaldehyde in 1987.

Stationary area sources are those stationary sources not otherwise included in the point source category. These sources include diesel combustion in internal combustion engines at oil and gas fields, wildfires, agricultural burning and management burning, etc. The staff estimates that these stationary area sources emitted approximately 7,000 to 15,000 tons of acetaldehyde in 1987. The following sections discuss each category in detail.

1. Mobile Sources

a. On-Road Motor Vehicles

The staff estimates that on-road motor vehicles including light-duty passenger cars, medium-duty trucks, heavy-duty trucks, buses and motorcycles emitted approximately 1,600 to 5,700 tons of acetaldehyde in 1987 (see Appendix B). Other transportation sources emitted approximately 2,100 tons. The lower limit was estimated based on the emission factors from several studies and the total organic gas (TOG) emissions from vehicular exhaust (ARB, 1990a) while the upper limit was estimated based on the volatile organic compound (VOC) speciation profiles and the TOG emissions in the ARB's Emission Data System (EDS) (ARB, 1990b and ARB, 1990c).

Figure III-1
Sources of Acetaldehyde for 1987 in California

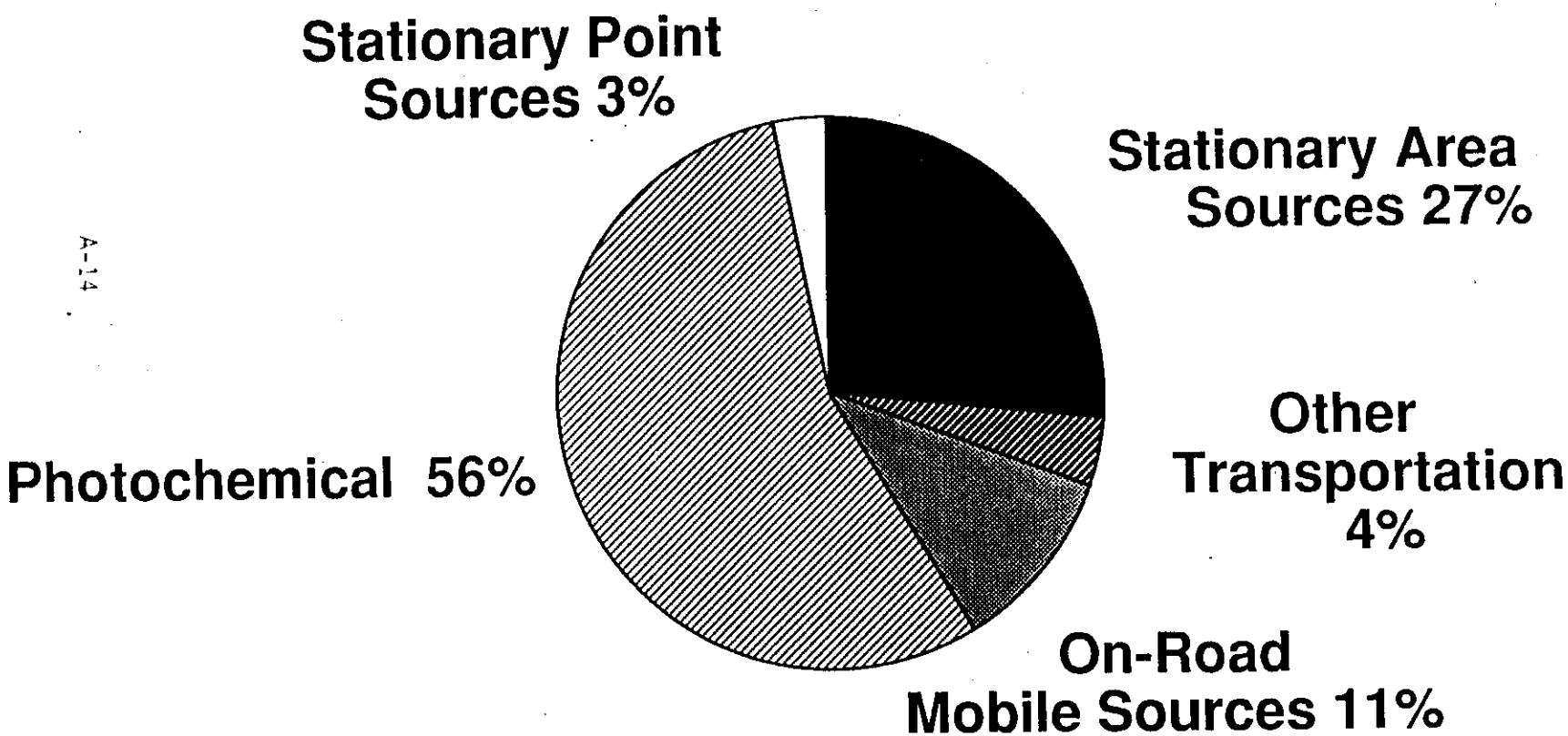
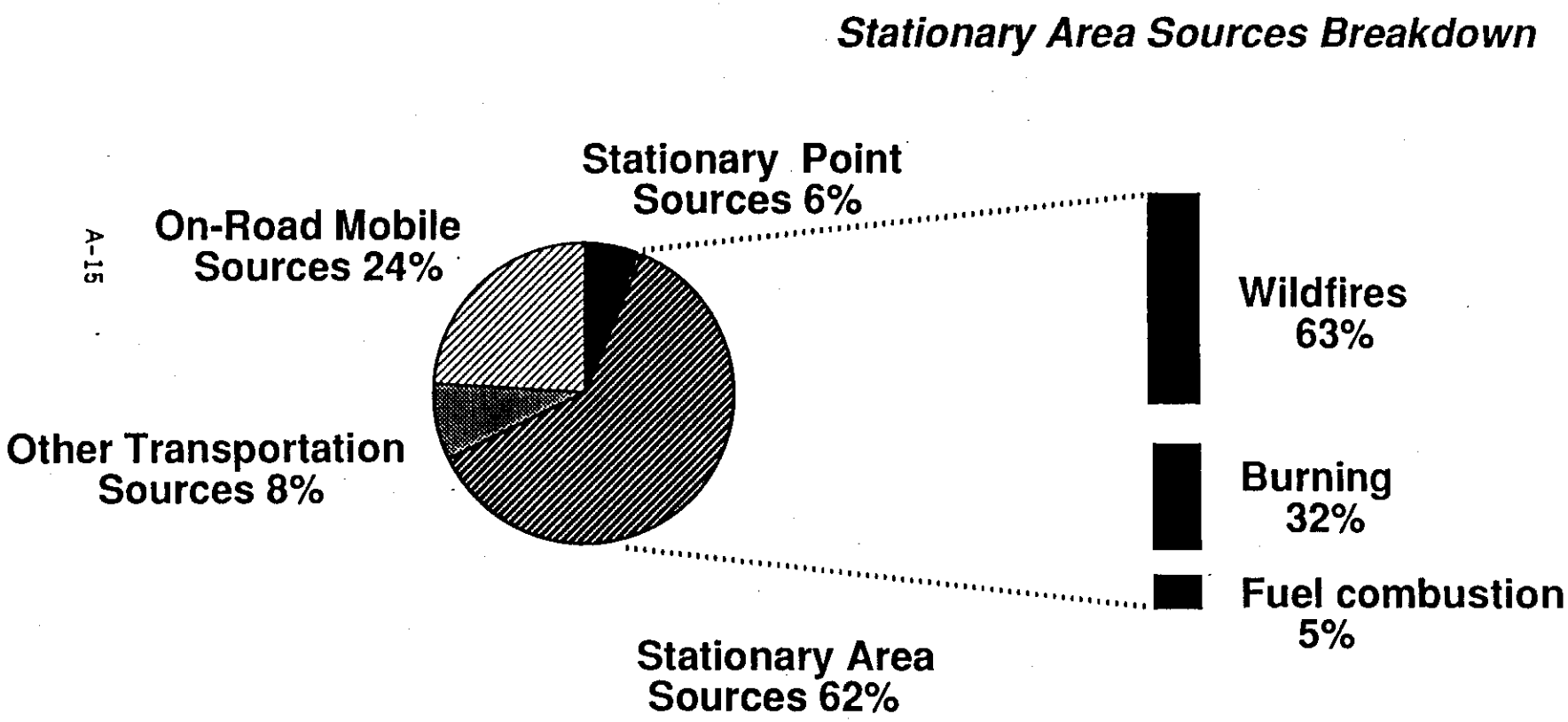


Figure III-2
Direct Sources of Acetaldehyde for 1987 in California



During the past few years, a number of independent investigators have conducted studies that show that the total hydrocarbon emission inventory (representing all types of sources) may be underestimated by substantial amounts. Investigations conducted during the last year by the ARB staff have shown that these underestimates are in the neighborhood of 50 to 100 percent. ARB staff believes that a significant portion of this error is in the on-road motor vehicle portion of the inventory; however, studies to date have not been able to establish error bands for specific categories of the inventory. Efforts towards improving both the mobile and stationary source portions of the inventory continue and a major effort is underway to obtain improved emission rates and vehicular activity data for the on-road motor vehicle emission estimates.

Acetaldehyde and other aldehydes were studied as non-regulated chemicals from automotive exhaust (Carey, 1981; Urban, 1981; Urban, 1980a; Urban, 1980b; Urban, 1980c; Sigsby, Jr. et al., 1987; Springer, 1979; Ullman, and Hare, 1985). The absolute acetaldehyde emission factors in milligrams per kilometer and the total hydrocarbon (THC) emission factors in these studies were used to normalized acetaldehyde as fractions of THC. The staff used these fractions along with the ratios of THC to TOG emissions from motor vehicles in California (ARB, 1988) to estimate the lower limit of acetaldehyde emissions.

The ARB has also compiled VOC speciation profiles for on-road motor vehicles. These profiles express specific substances as a weight fraction of TOG. The staff used acetaldehyde fractions in these profiles and the TOG emissions from on-road vehicular exhaust to estimate the upper limit of acetaldehyde emissions.

Lower and upper limits of estimated acetaldehyde emissions for each of the vehicular classes are reported in the following paragraphs.

Non-catalyst, light-duty passenger cars emitted approximately 500 to 2,300 tons of acetaldehyde while those equipped with catalytic converters emitted approximately 390 to 820 tons in 1987. For those light-duty

passenger cars that burn diesel fuel, the acetaldehyde emissions were approximately 8 to 54 tons.

Light and medium-duty gasoline trucks equipped with catalytic converters emitted less acetaldehyde (approximately 170 to 350 tons) when compared to those not equipped with catalytic converters (about 180 to 810 tons) in 1987. In the same inventory year, the staff estimates that light and medium-duty diesel trucks emitted approximately 4 to 14 tons of acetaldehyde.

Acetaldehyde emissions from all heavy-duty gasoline trucks (non-catalytic) were significantly higher (approximately 94 to 390 tons) than acetaldehyde emissions (about 1 ton) from heavy-duty diesel trucks equipped with catalytic converters. The staff estimates that heavy-duty diesel trucks emitted approximately 280 to 870 tons of acetaldehyde in 1987.

Urban buses burning diesel emitted approximately 12 to 37 tons of acetaldehyde in 1987. In the same inventory year, motorcycles were responsible for approximately 22 to 100 tons of acetaldehyde emissions.

b. Other Mobile Sources

Acetaldehyde emissions associated with all off-road motor vehicles and other mobile sources total about 2,100 tons for 1987 (see Appendix B). Of this total, trains accounted for 320 tons, while ships and aircraft accounted for 110 tons. Off-road motor vehicles such as recreational vehicles and commercial boats were responsible for approximately 780 tons. Mobile and utility equipment such as tractors, refrigeration units, fork lifts and lawnmowers accounted for approximately 870 tons of acetaldehyde (see Appendix B).

2. Trends

Most of the contribution by motor vehicles to the ambient burden of primary acetaldehyde is from the exhaust of gasoline vehicles. They also contribute to the ambient burdens of oxides of nitrogen (NOx) and reactive organic gases (ROG), which react via photosynthesis in the atmosphere to create secondarily formed acetaldehyde.

a. Motor vehicle technology

The emissions standards applied by the ARB to new vehicles over the past years have led to significant reductions in vehicular ROG and NOx directly emitted by motor vehicles. Further, these reductions in ROG and NOx have resulted in a decline of secondary acetaldehyde. Declines in motor vehicle emissions will continue because of the recently adopted "low-emission vehicle" (LEV) standards for non-methane organic gases and NOx. Additionally, the primary, directly emitted acetaldehyde, also a ROG, is expected to decline. This conclusion is supported by the Auto/Oil data (Auto/Oil, 1991) and ARB studies (ARB 1991c, ARB 1990d, ARB 1990e, ARB 1990f).

b. Gasoline specifications

The ARB adopted two new gasoline regulations, Phase 2 Reformulated Gasoline standards which become effective in 1996 and the Wintertime Oxygenates Program which became effective in 1992. The Phase 2 gasoline standards were designed to achieve reductions in criteria and toxic pollutants and will reduce ROG and NOx emissions from all gasoline vehicles (vehicles currently on the road plus LEVs made before 1996). Reduction of reactive hydrocarbons and NOx will decrease the formation of both primary and secondary acetaldehyde.

The Wintertime Oxygenate Program sets standards for the oxygen content in gasoline sold in California during the winter months in an effort to reduce carbon monoxide emissions. Gasoline oxygenate additives used to provide the minimum oxygen content required by the standards could increase

acetaldehyde emissions (Auto/Oil, 1990-1991). The addition of methanol and methyl tert-butyl ether (MTBE) to fuel does not increase acetaldehyde emissions. Alternate fuels containing the oxygenate additives ethanol or ethyl tert-butyl ether (ETBE), upon combustion, result in acetaldehyde emissions. However, it is not known to what extent ethanol or ETBE will be used as a winter oxygenate in California fuels and, therefore, the resulting affect on actaldehyde emissions.

Acetaldehyde increases could elevate peroxyacetyl nitrate (PAN) and formaldehyde concentrations. PAN is one of the main products of the photooxidation of acetaldehyde in the presence of NOx and is a strong eye irritant and plant toxicant. However, acetaldehyde is not the dominant source of PAN as many other hydrocarbon species are important PAN precursors in urban atmospheres (EPA, 1993) (Atkinson, 1993).

The overall effect of the vehicular emission standards and the gasoline standards is a complex issue. The acetaldehyde concentration trend will depend on the turnover rate of older vehicles from the fleet mix to LEVs, the primary acetaldehyde contributions from oxygenate additives, and the decrease of ROG from the Phase 2 reformulated gasoline.

3. Stationary Area Sources

The stationary sources such as internal combustion engines in the oil and gas fields are sources that are not included in the point source category. These sources are scattered throughout the State. Individually, they may not contribute significantly to air pollution; however, in the aggregate, their toxic air emissions are of potential concern. The staff estimates that these sources emitted approximately 7,000 to 15,000 tons of acetaldehyde in 1987 as a result of fuel and waste combustion (see Appendix B).

a. Residential Wood Combustion

Based on data from source tests conducted on several woodstoves and fireplaces, acetaldehyde emission factors range from 0.06 to 0.19 lb/ton of

wood burned (MRI, 1987). Using a weighted average of these data and the amount of wood burned for residential purposes (ARB, 1990g), the staff estimates that residential woodstoves and fireplaces emitted approximately 110 tons of acetaldehyde in 1987 (see Appendix B). Alternatively, using the TOG emissions from residential wood combustion and an applicable speciation profile (ARB, 1989), the staff estimates that residential woodstoves and fireplaces emitted approximately 660 tons of acetaldehyde in 1987 (ARB, 1990b).

b. Diesel and Oil Combustion

Stationary area sources of diesel, distillate and residual oil combustion include boilers and IC engines in oil and gas fields and other sources such as orchard heaters in agricultural production. The staff estimates that these combustion sources emitted approximately 44 to 45 tons of acetaldehyde in 1987, primarily as a result of incomplete combustion (see Appendix B).

c. Natural Gas Combustion

In 1987, California used approximately 844 billion cubic feet of natural gas for heating, cooking, etc. (ARB, 1990a). Emissions from these combustion sources may be considered to be a source of indoor air pollution. However, the staff assumed that emissions from these sources escape to the outside. Based on the amount of natural gas burned and the acetaldehyde emission factors developed by MRI from a formaldehyde emission factor, the staff estimates that natural gas combustion sources emitted approximately 7 to 14 tons in 1987 (see Appendix B).

d. Agricultural, Management, Open Fires and Wildfires

The nature of wildfires and management and agricultural fires make it almost impossible to control or predict them even through these fires may emit large amounts of acetaldehyde. The ARB compiles activity and criteria pollutant emission data for these fires. The staff is not aware of any specific acetaldehyde emission factor for wildfires and management and

agricultural fires. Based on the aldehyde emission factor from backyard burning, MRI estimated that wildfires, management and agricultural fires emitted approximately 0.73 to 1.5 lbs of acetaldehyde per ton of material burned (MRI, 1987). These emission factors were developed using national data and may not necessarily be representative of California conditions. However, for lack of any better data, the staff used the emission factors developed by MRI and the activity data compiled by the ARB to estimate that agricultural, management, open fires and wildfires emitted approximately 6,800 to 14,000 tons of acetaldehyde in 1987 (see Appendix B).

4. Stationary Point Sources

a. Fuel Combustion

Acetaldehyde is formed from combustion processes as a result of incomplete combustion. The degree of acetaldehyde emissions depends on factors such as the type of fuel burned, the fuel-to-air ratio, the operating conditions and the design of the combustion devices. However, the staff is not aware of any studies relating the combustion parameters to the concentration of acetaldehyde in the exhaust. Based on the amounts of fuel burned in California or the TOG emissions and the emission factors for specific types of fuel, the staff estimates that stationary point sources of fuel combustion (including the combustion of coal, distillate and residual oil, diesel, gasoline, natural gas and wood) emitted approximately 600 to 630 tons of acetaldehyde in 1987.

There is a great deal of uncertainty in the acetaldehyde emission estimates from the combustion of coal, natural gas and residual and distillate oil. In these cases, MRI used formaldehyde emission factors to estimate total aldehyde emissions by assuming that formaldehyde represents 70 percent of total aldehydes. Once total aldehyde emissions were estimated, MRI further assumed that total aldehydes consist of 7 to 14 percent acetaldehyde to estimate acetaldehyde emissions (MRI, 1987). The percentages of acetaldehyde in total aldehydes were derived from source tests of residential wood combustion (MRI, 1987). The following sections discuss acetaldehyde emissions for each fuel type for which quantitative

estimates of emissions have been made. Other fuel types for which emissions could not be quantified are discussed in Section 4.

Coal

In 1987, California used approximately 1.6 million tons of coal resulting in 1 to 2 tons of acetaldehyde emissions (see Appendix B). There is no specific acetaldehyde emission factor for coal combustion. MRI used an emission factor for formaldehyde and assumed that formaldehyde represents 70 percent of total aldehydes in the combustion exhaust and that the percentage of acetaldehyde to total aldehydes in coal combustion is the same as that in wood combustion (MRI, 1987). Based on these assumptions, acetaldehyde emission factors for coal combustion range from 0.0014 to 0.0029 lb/ton.

Diesel

The staff estimates that stationary point sources in California emitted approximately 1 ton of acetaldehyde in 1987 as a result of diesel combustion. This estimate was based on the TOG emissions from all California stationary point sources burning diesel and the fraction of acetaldehyde in TOG (ARB, 1990g and ARB, 1989).

Gasoline

Besides motor vehicles, which are a major user of gasoline, stationary point sources also use gasoline. In 1987, these sources used approximately 4.53 million gallons of gasoline and emitted approximately 10 tons of acetaldehyde in California. The staff estimates these emissions using the fraction of acetaldehyde in TOG (ARB, 1989) and the TOG emissions from stationary point sources (ARB, 1990h).

Natural Gas

The staff estimates that natural gas combustion sources in California emitted approximately 15 to 31 tons of acetaldehyde in 1987 (see Appendix B). This estimate was based on the amount of natural gas burned at stationary point sources in California and the estimated emission factor for natural gas combustion developed by MRI (MRI, 1987). This emission estimate is very rough because the emissions were derived from the emissions of formaldehyde to total aldehydes and then backcalculated to acetaldehyde.

Oil

The staff is not aware of any specific acetaldehyde emission factors from distillate or residual oil combustion. For lack of better data, the staff has applied the methodology developed by MRI to estimate acetaldehyde emissions from oil combustion.

In 1987, California burned approximately 3.25 billion gallons (approximately 12.6 million tons) of distillate and residual oil in stationary point sources. Using the methodology developed by MRI, the staff estimates stationary point sources of oil combustion in California emitted approximately 10 to 20 tons of acetaldehyde (see Appendix B).

Wood

The staff has applied an acetaldehyde emission factor from residential wood combustion to estimate emissions from industrial wood combustion. The staff developed this emission factor as a weighted average of several source tests for woodstoves and fireplaces burning different types of woods. Using the data on the amount of wood burned for industrial purpose (ARB, 1990i) and the assumed emission factor, the staff estimates industrial wood combustion sources emitted approximately 560 tons of acetaldehyde in 1987 (Appendix B).

b. Refineries - Processing

Acetaldehyde is a product of incomplete combustion in petroleum refineries. Catalytic cracking, coking operations and fuel combustion are major sources of acetaldehyde from refineries. Other operations such as catalytic reforming, catalytic hydrorefining and catalytic hydrotreating may also be sources of acetaldehyde. However, there is no information regarding aldehyde emissions from these sources.

Catalytic cracking refers to operations where catalysts are used to break down heavy oils (high molecular weight compounds) to lighter products. The spent catalysts are then regenerated by combusting the deposited coke. This combustion process emits acetaldehyde. Coking operations involve the thermal coking of heavy residual oil to other products and petroleum coke (EPA, 1984). Incomplete combustion of coke generates acetaldehyde. Acetaldehyde emissions from fuel combustion in refineries have been estimated in the fuel combustion section. This section only discusses acetaldehyde emissions from petroleum processing.

There is no specific acetaldehyde emission factor for refinery processes. The Science Applications International Corporation (SAIC) assumed in general that 20 percent of total aldehydes is acetaldehyde was based on the percentages of acetaldehyde to total aldehydes in vehicular exhaust from several studies (SAIC, 1987). In 1980 EPA published total aldehyde emission factors for catalytic cracking and coking operations (EPA, 1980). By assuming that acetaldehyde represents 20 percent of total aldehydes from petroleum refinery processing, acetaldehyde emission factors are calculated to be 1.4 lbs per 1,000 barrels (bbls) of fresh feed from fluidized catalytic cracking (FCC); 0.63 lb per 1,000 bbls of fresh feed from moving-bed cracking or thermal catalyst cracking (TCC); and 0.34 lb per 1,000 bbls of fresh feed from coking operations.

In 1988, California refineries had a combined rated charge capacity of approximately 2.28 million bbls per calendar day (Oil & Gas Journal (OGJ, 1989). According to OGJ, catalytic cracking units had a rated charge capacity of 645,500 bbls per stream day and thermal operations (assuming

coking operations) had a rated charge capacity of 503,200 bbls per stream day in 1988 (OGJ, 1989). There are no data to estimate the exact amount of fresh feed going into either FCC or TCC units. However, EPA estimated that 94 percent of the fresh feed in 1979 is used in FCC units and that the TCC units have become obsolete since 1979 (EPA, 1987). To be conservative (because the acetaldehyde emission factor for FCC units is greater than that of for TCC units), the staff assumes that all of the fresh feed going to catalytic cracking is going into the FCC units.

Using data on feed rates to catalytic cracking units and to thermal operations and applying the appropriate emission factors, the staff estimates that refineries emitted approximately 190 to 770 tons of acetaldehyde in 1988 (see Appendix B).

c. Food Processing

In response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, Section 313, a food processing facility in the San Francisco Bay Area Air Basin reported emissions of approximately 7 tons of acetaldehyde in 1990 (Rydbrink, 1991). This information has not been validated by the Bay Area Air Quality Management District (BAAQMD).

d. Coffee Roasting

In the coffee roasting process, green coffee beans are roasted to obtain the characteristic aroma and flavor associated with coffee. Aldehydes have been detected in green coffee beans; therefore aldehydes are emitted during the coffee roasting process. During roasting, green beans are exposed to temperatures as high as 410°F; chemical reactions such as pyrolysis or thermal decomposition occur within the beans releasing aldehydes such as acetaldehyde and other volatile organic compounds (MRI, 1987).

Based on the amount of green coffee beans roasted in California (ARB, 1990j) and a controlled emission factor for acetaldehyde developed from actual source tests by an Environmental Protection Agency (EPA) contractor

(MRI, 1987), the staff estimates that coffee bean roasters in California emitted approximately 2 tons of acetaldehyde in 1987 (see Appendix B).

5. Other Potential Sources

There are several potential sources of acetaldehyde in California which probably have very low emissions. Although the emission factors for these sources are unknown, they deserve some mention.

a. Coke Combustion

There are no acetaldehyde emission factors from coke combustion. However, based on the process rate and the acetaldehyde emission factor from coal combustion, the staff estimates that acetaldehyde emissions from coke combustion are insignificant.

b. Jet Fuel Combustion

Even though criteria pollutant emissions have been estimated for the combustion of jet fuel used at stationary IC engines and for aircraft, acetaldehyde emissions have not been measured. For aircraft, the districts estimated criteria pollutant emissions using the emission factors per landing and take off (LTO). The process rates in terms of the fuel used for several airfields are not available. However, using process rates for other sources in this category and an acetaldehyde emission factor from oil combustion, the staff estimates that acetaldehyde emissions from jet fuel combustion are insignificant.

c. Liquid Material Combustion

The ARB's EDS lists several stationary point sources burning unspecified liquid material. The staff believes that this category includes the combustion of diesel, distillate, jet fuel and residual oil. Based on the relative activities for these liquid material combustion sources, the staff estimates that of the 42.6 million gallons of liquid material burned, approximately 5.1 million gallons may be jet fuel combustion; the other 37.5 million gallons can be diesel, distillate, or residual oil (ARB, 1990i).

If acetaldehyde emission factors for oil are applicable to the liquid material combustion category, the staff estimates that acetaldehyde emissions from this category are not significant.

d. Liquified Petroleum Gas (LPG)

From the EDS, the staff has identified several point sources in California that burn LPG. The districts estimated criteria pollutant emissions for these combustion sources. The staff believes these combustion sources emit aldehydes and acetaldehyde in particular. However, based on the amount of LPG burned in California, the staff estimates that acetaldehyde emissions from these combustion sources are not significant.

e. Process Gas Combustion

Several stationary point sources in California reported emissions from the combustion of process gas. Because the constituents of each process gas are unique, the acetaldehyde emissions are unique for individual process gas combustion sources. Streams of process gas may even be different from one another within a facility. Thus emissions of process gas can not be generalized and acetaldehyde emissions for these combustion sources are not available at this time.

However, based on the amount of process gas burned at stationary sources in California, and assuming that the emission factors from natural gas combustion are applicable for these process gas combustion sources, the staff estimates that process gas combustion sources could emit approximately 50 percent of the estimated emissions from natural gas combustion.

f. Landfill Gas Combustion

Based on the amount of landfill gases burned in California, the staff estimates that acetaldehyde emissions from landfill gas combustion sources are not significant.

g. Incineration

Incineration has been considered an alternative method to dispose of waste and may be used as a method to recover energy to produce electricity. There are municipal waste, sewage sludge, hazardous waste and biomedical waste incinerators throughout the State. Some of these incinerators have been tested for dioxins and dibenzofurans emissions. However, there are no data on acetaldehyde emissions. Because the process rates of incinerators are relatively small as compared to fuel combustion processes such as coal combustion and because control measures are being proposed for incinerators, the staff estimates that acetaldehyde emissions from incinerators are relatively insignificant.

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IV.

EXPOSURE TO ACETALDEHYDE

A. AMBIENT MONITORING IN CALIFORNIA

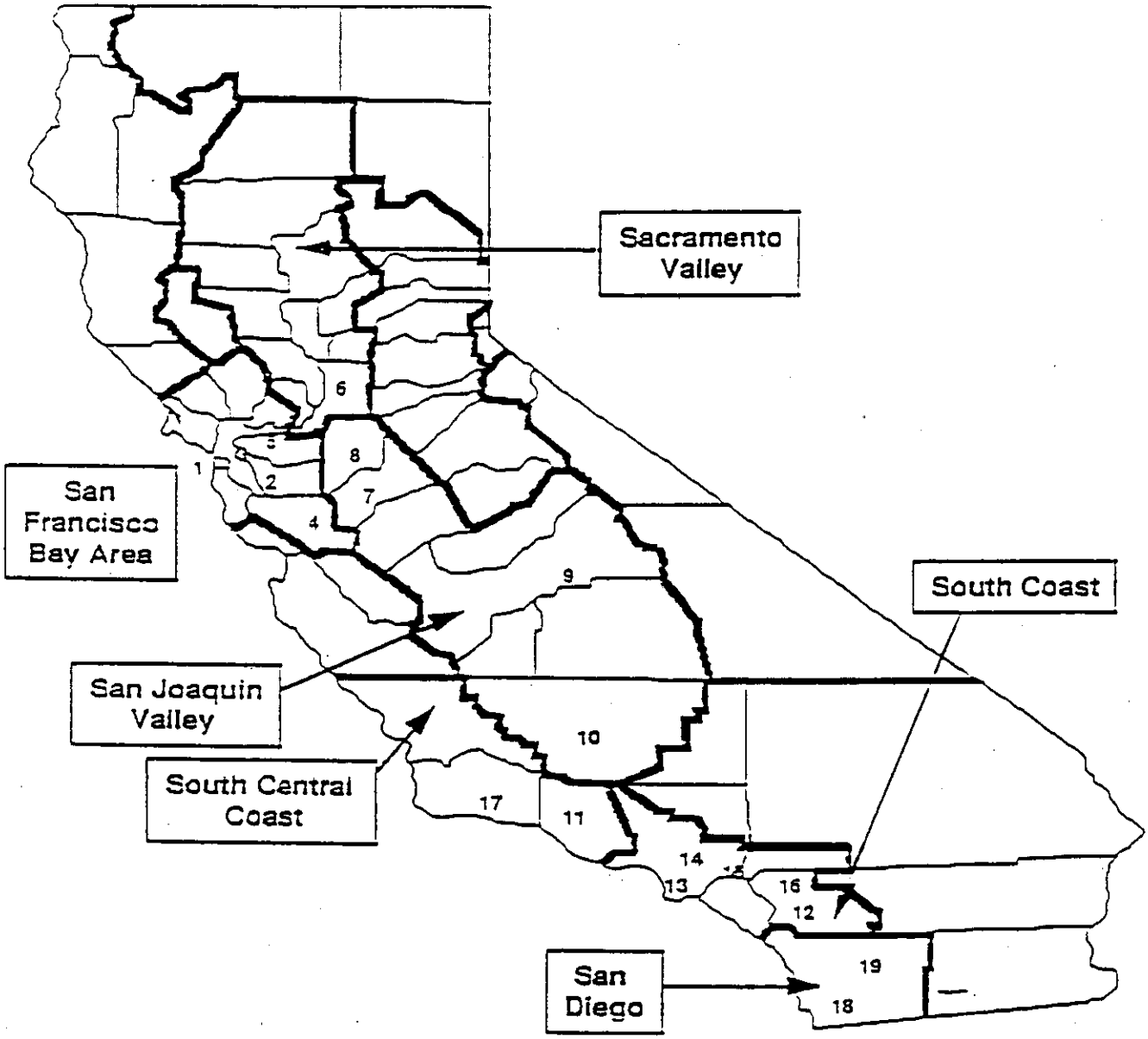
The toxics sampling network in California for acetaldehyde consisted of 19 monitoring stations statewide (Figure IV-1). Nine of these monitors were located in Southern California (south of Bakersfield), while the other 10 were situated in the northern portion of the state.

Data used in this exposure analysis were collected during the period of September 1988 through August 1989. The data for this period (hereafter referred to as "the study period") represent the most recent period for which the data are of consistent and verifiable quality. The data analysis and ambient exposure estimate are based on ambient data collected by the Air Resources Board (ARB) and maintained in the toxics air quality database.

Individual samples were collected over a 24 hour period using two cartridges containing 2,4-dinitrophenyl hydrazine coated support in tandem. The aldehydes present in the air react with the 2,4-dinitrophenylhydrazine coating to form the respective hydrazones. The hydrazone derivatives are extracted from the cartridges with acetonitrile, and the extract is analyzed using Reverse-Phase High Performance Liquid Chromatography with a ultraviolet detector. The limit of detection (LOD) of this procedure is 0.1 ppbv (0.18 $\mu g/m^3$). For the analytical procedure see Appendix C. Quality control is performed with all generated data sets and an extensive quality assurance program assures the accuracy of the measurements.

Figure IV-1

ARB Toxics Network Monitoring Sites



1. San Francisco
2. Fremont
3. Richmond
4. San Jose
5. Concord
6. Citrus Heights
7. Modesto
8. Stockton
9. Fresno
10. Bakersfield
11. Simi Valley
12. Riverside
13. Long Beach
14. Los Angeles
15. El Monte
16. Upland
17. Santa Barbara
18. Chula Vista
19. El Cajon

A summary of data for each of the monitoring sites used in the analysis is presented in Table IV-1. The statewide acetaldehyde data for the study period represent 19 sites and a small percentage of all possible days during the sampling period. The number of samples available per site during the study period range from 21 to 26 in northern California, averaging 24 observations per site for the study period; the number of samples available per site in southern California range from 21 to 57, averaging 40 observations per site.

Acetaldehyde was sampled on an every sixth day schedule in the South Coast Air Basin. This increase in sampling frequency accounts for the increased number of observations recorded for the South Coast in comparison to the other five air basins. There were no concentrations reported below the LOD.

B. AMBIENT CONCENTRATIONS

Summary statistics for each site during the study period are summarized in Table IV-2. The minimum, maximum, median, and estimated mean annual concentration, along with the coefficient of variation and standard deviation are reported for each site. Basin results are included for each statistic except the coefficient of variation.

Mean annual acetaldehyde concentrations were calculated as the mean of available monthly means. This approach provides equal weighting for each month even when the number of samples per month varies. The mean of monthly means is a more reliable estimator of annual exposure than the arithmetic average of all study period concentrations. Mean annual concentrations ranged from a minimum of 1.13 ppbv (2.03 $\mu g/m^3$) at Richmond to a maximum of 3.31 ppbv (5.96 $\mu g/m^3$) at El Monte. Basin mean concentrations ranged from 1.63 ppbv (2.93 $\mu g/m3$) in the South Central Coast to 2.81 ppbv (5.06 $\mu g/m3$) in the South Coast.

Table IV-1

SUMMARY OF ACETALDEHYDE DATA [1]
September 1988 - August 1989

Site Location	S	O	N	D	J	F	M	A	M	J	J	A	Samples
SOUTHERN CALIFORNIA SITES													
South Coast Air Basin													
El Monte	o	o	o	o	o	o	o	o	o	o			45
Long Beach	o	o	o	o	o	o	o	o	o	o	o	o	57
Los Angeles	o	o	o	o	o	o	o	o	o	o	o	o	56
Rubidoux	o	o	o	o	o	o	o	o	o	o	o	o	57
Upland	o	o	o	o	o	o	o	o	o	o	o	o	51
South Central Coast Air Basin													
Santa Barbara	o	o	o	o	o	o	o	o	o	o	o	o	21
Simi Valley	o	o	o	o	o	o	o	o	o	o	o	o	26
San Diego Air Basin													
Chula Vista	o	o	o	o	o	o	o	o	o	o	o	o	25
El Cajon	o	o	o	o	o	o	o	o	o	o	o	o	25
NORTHERN CALIFORNIA SITES													
San Francisco Bay Area Air Basin													
Concord	o	o	o	o	o	o	o	o	o	o	o	o	25
Fremont	o	o	o	o	o	o	o	o	o	o	o	o	25
Richmond	o	o	o	o	o	o	o	o	o	o	o	o	24
San Francisco		o	o	o	o	o	o	o	o	o	o	o	21
San Jose	o	o	o	o	o	o	o	o	o	o	o	o	23
San Joaquin Valley Air Basin													
Bakersfield	o	o	o	o	o	o	o	o	o	o	o	o	25
Fresno	o	o	o	o	o	o	o	o	o	o	o	o	26
Modesto	o	o	o	o	o	o	o	o	o	o	o	o	25
Stockton	o	o	o	o	o	o	o	o	o	o	o	o	24
Sacramento Valley Air Basin													
Citrus Heights	o	o	o	o	o	o	o	o	o	o	o	o	24

1 A "o" indicates at least one sample was collected during the month.

Table IV-2

SUMMARY OF AMBIENT ACETALDEHYDE CONCENTRATIONS
September 1988 - August 1989
(parts per billion)

AIR BASIN Site Location	Minimum Conc.	Maximum Conc.	Median Conc.	Mean[1] Conc.	Std.[2] Dev.	CV[3]
SOUTHERN CALIFORNIA SITES						
South Coast Air Basin						
El Monte	0.9	8.8	2.8	3.31	1.03	52.2
Long Beach	0.5	7.7	2.1	2.49	1.28	69.7
Los Angeles	0.1	8.8	2.5	2.97	0.98	61.8
Rubidoux	0.3	6.6	2.3	2.40	0.94	54.8
Upland	0.2	7.7	2.7	2.88	0.63	46.6
Basin Summary	0.1	8.8	2.5	2.81	0.99	
South Central Coast Air Basin						
Santa Barbara	0.7	3.4	1.3	1.47	0.70	50.6
Simi Valley	0.3	4.0	1.9	1.79	0.72	58.1
Basin Summary	0.3	4.0	1.5	1.63	0.71	
San Diego Air Basin						
Chula Vista	0.6	4.5	1.0	1.39	0.78	64.7
El Cajon	0.8	6.1	2.3	2.49	0.91	53.5
Basin Summary	0.6	6.1	1.7	1.94	0.85	
NORTHERN CALIFORNIA SITES						
San Francisco Bay Area Air Basin						
Concord	0.3	3.9	1.4	1.77	0.87	55.0
Fremont	0.6	6.1	1.2	1.74	1.04	73.0
Richmond	0.4	2.3	1.0	1.13	0.41	46.4
San Francisco	0.3	7.7	1.2	1.95	1.30	93.8
San Jose	0.2	6.1	1.5	1.62	1.01	75.2
Basin Summary	0.2	7.7	1.3	1.64	0.97	
San Joaquin Valley Air Basin						
Bakersfield	0.2	3.4	1.3	1.45	0.58	62.6
Fresno	0.3	6.3	2.0	2.26	1.03	63.6
Modesto	0.3	7.2	1.6	2.00	1.11	73.7
Stockton	0.2	4.7	1.9	1.97	0.73	55.1
Basin Summary	0.2	7.2	1.6	1.98	0.89	
Sacramento Valley Air Basin						
Citrus Heights	0.5	4.1	2.1	2.01	0.88	50.2

1 Basin Means are the mean of the site means.
2 Basin Standard Deviations are pooled values of the standard deviations across sites within a basin.
3 Coefficient of Variation is calculated as the standard deviation of all values divided by the mean of all values expressed as a percentage. Basin results are not given.

The median is defined as the 50th percentile and can be used as an alternative measure of central tendency to the mean. The median was less than the mean at 18 of the 19 monitoring sites. Citrus Heights and Simi Valley were the only sites reporting a median higher than the mean. During the study period, median concentrations ranged from a minimum of 1.0 ppbv (1.8 $\mu g/m^3$) at Chula Vista and Richmond to a maximum of 2.8 ppbv (5.0 $\mu g/m^3$) at El Monte. Basin medians were calculated as the median of all values reported for each individual basin. The basin-wide median concentrations range from a minimum of 1.3 ppbv (2.34 $\mu g/m^3$) for the San Francisco Bay Area to a maximum of 2.5 ppbv (4.5 $\mu g/m^3$) for the South Coast. When the median concentration is significantly different from the mean this indicates the data most likely come from a non-normal distribution. The Shapiro-Wilk (Shapiro and Wilk, 1965) test was used on a site-by-site basis to test the distribution of the acetaldehyde data. Even though the data from most sites are skewed, the Shapiro-Wilk test showed that the acetaldehyde concentrations are not log-normally distributed.

A coefficient of variation (CV) statistic provides information about the distribution of data and is reported for each monitoring site. The CV expresses as a percentage the magnitude of the variation relative to the magnitude of the concentrations being measured. The CV is equal to the standard deviation of all observations divided by the mean of all observations multiplied by 100. The CV for the study period ranges from a low of 46.4 percent at Richmond to a high of 93.8 percent at San Francisco. There appears to be no significant difference in the range of values for the CV between northern and southern California indicating that the distribution of values is the same.

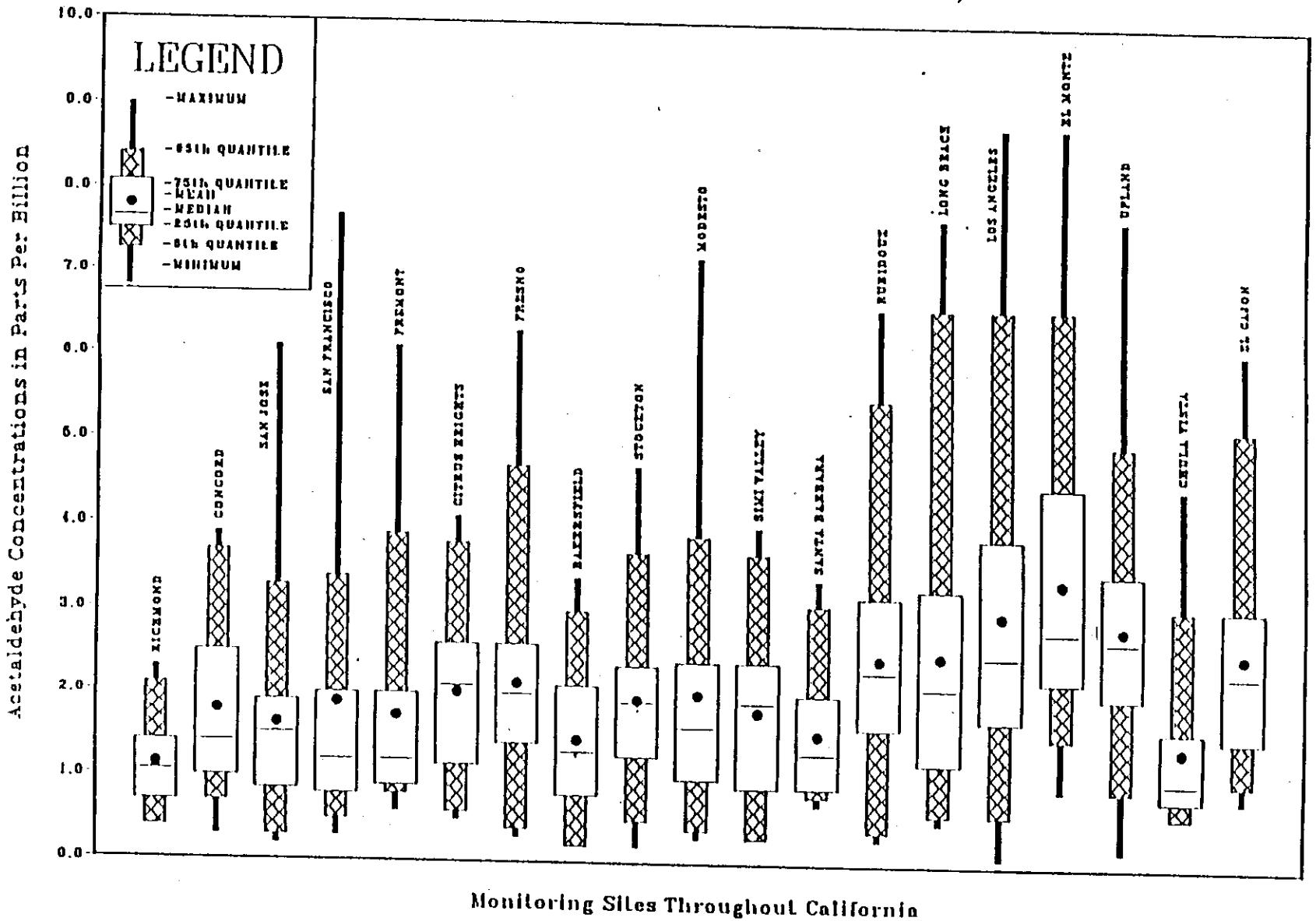
The observed distribution of values from each site is presented graphically in Figure IV-2. In general, the southern California sites appear to have slightly higher concentrations than the northern California sites. Figure IV-3 presents the same data on a month-by-month basis without regard to sites. Figure IV-3 suggests there is a seasonal pattern

FIGURE IV-2

DISTRIBUTION OF AMBIENT ACETALDEHYDE CONCENTRATIONS

PLOTTED USING EXTENDED BOX PLOTS

(BASED ON SEPTEMBER 1988 – AUGUST 1989 DATA)



Monitoring Sites Throughout California

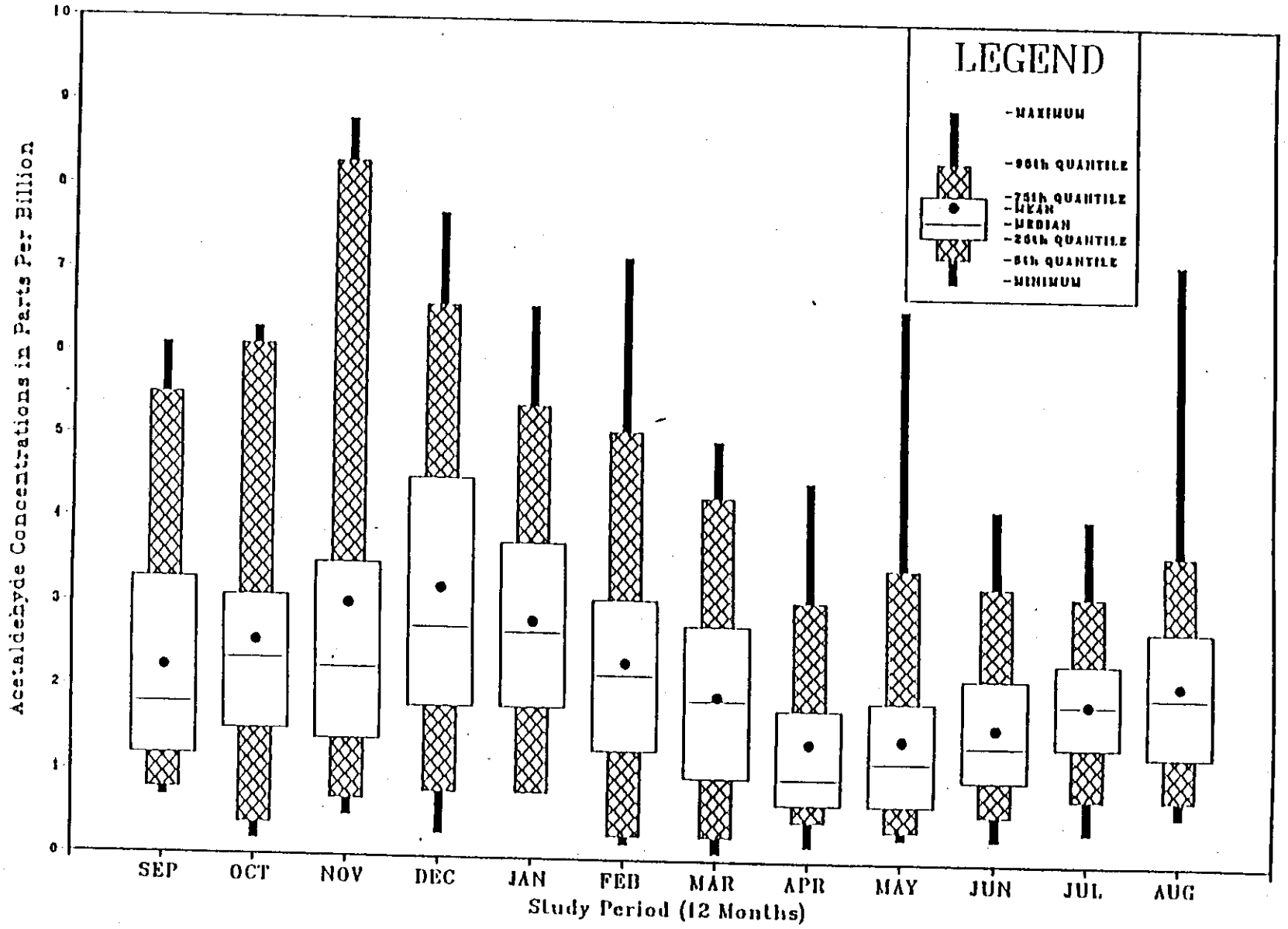
ARB/TSD:April 90

FIGURE IV-3

DISTRIBUTION OF MONTHLY AMBIENT ACETALDEHYDE CONCENTRATIONS

PLOTTED USING EXTENDED BOX PLOTS (ALL SITES COMBINED)

BASED ON OCTOBER 1988 – SEPTEMBER 1989 DATA



ARB/TSD:April 90

to the distribution of ambient acetaldehyde concentrations. However, at this time we are unable to determine whether this pattern is the result of meteorological influences, changes in emission patterns, or fluctuations in secondary formation potential.

It may be expected that the ambient atmosphere acetaldehyde levels encountered in the Los Angeles air basin are among the highest to be expected in California because of the number of combustion sources associated with periods of high photochemical reactivity and the meteorological conditions present in the atmosphere. Reported data for the ambient concentrations of acetaldehyde in California since 1980 are given in Table IV-3. These figures demonstrate high smog events, varied hours of sampling times and variability between cities. Four studies performed by Grosjean revealed similiar results. These studies showed how acetaldehyde tends to have high levels in the daytime hours and low levels during the nighttime hours. During the Nitrogen Methods Comparison Study (NSMCS) At Claremont, CA, high levels of acetaldehyde existed during daytime hours and high motor vehicle travel. There were low levels at night (Grosjean, 1988). Peak concentrations ocurred at midday with concentrations of 6.1 ppbv (11 $\mu g/m^3$). The low occurred from midnight until dawn with concentrations of 2.1 ppbv (3.8 $\mu g/m^3$).

In 1987, acetaldehyde was measured during the South Coast Air Quality Study (SCAQS) in the South Coast Air Basin. The SCAQS was an integrated air quality study whose overall goal was to develop a comprehensive and properly archived air quality and meteorological data base for the South Coast Air Basin which can be used to test, evaluate, and improve elements of air quality simulation models for oxidants, NO_2, PM_{10}, fine particles, visibility, toxic air contaminants, and acidic species. Acetaldehyde concentrations ranged from 0.9 to 24.5 ppbv (1.6 to 44.1 $\mu g/m^3$) in 1 hour samples. In the South Coast Air Basin, on average, the levels peaked around midday at locations like Anaheim, Burbank, downtown Los Angeles, Hawthorne and Long Beach while they peaked later in the afternoon downwind at smog receptor sites like Azuza, Claremont, Rubidoux, Palm Springs, and Perris (Fung, 1989; Grosjean, 1991, 1992).

Table IV-3

MEASUREMENTS OF ACETALDEHYDE CONCENTRATIONS IN AMBIENT AIR IN CALIFORNIA

Acetaldehyde (ppbv)	Sampling Time (hours)	Measurement Date and Place	Reference
up to 26	0.5	5-6/1980, East Los Angeles	a
3-5	1	9-10/1980, Claremount	a
up to 10	1-2	10/1980, Azusa	b
up to 3	1-2	10/1980, Lennox	b
13-37	0.5	7-10/1980, Los Angeles	b
8-16	0.5	7-10/1980, Burbank	b
13	0.5	7/1980, Pasadena	b
25-33	0.5	10/1980, El Monte	b
16	0.5	10/1980, Rosemead	b
19	0.5	10/1980, Upland	b
2-39	0.45	9-11/1981, Los Angeles	c
2-15	2.0	2/1986, Downey	d
5.0	24.0	6/89-6/90, Palm Springs	e
10.3	24.0	6/89-6/90, Perris	e

a Grosjean, 1982.

b Grosjean, 1983.

c Grosjean and Fung, 1984.

d Salas and Singh, 1986

e Grosjean and Williams, 1992.

Reports of ambient air samples from two rural regions, Point Barrow, Alaska (Cavanagh et. al, 1969) and Whiteface Mountain, New York (Schulam et. al, 1984) provide examples of 'background' concentrations of 0.0 to 0.8 ppbv (1.4 $\mu g/m^3$) of acetaldehyde.

C. POPULATION WEIGHTED EXPOSURE ESTIMATES

Mean population exposure estimates were calculated using the study period acetaldehyde data. Exposure for the South Coast Air Basin and San Francisco Bay Area Air Basin were estimated by interpolating station values to census tract centroids. For the other air basins, a basin-wide mean concentration was estimated from the means for all sites in the basin.

It was then assumed that all people in those basins (except the Sacramento Valley Air Basin since it had only one monitoring station) with a sampling site were exposed to this estimated basin-wide mean concentration. Population data used in the exposure analysis represent 1980 census data updated to 1985. The results of the exposure analysis are summarized in Table IV-4. The table shows outdoor ambient annual exposures for different air basins and an overall population weighted exposure for the state of California.

Bootstrap confidence bounds are provided as a measure of uncertainty in the exposure estimates. The larger the difference between the mean annual exposure estimate and the upper and lower bounds, the greater the uncertainty in the estimate. The bootstrap method allows data contained in a single sample to be applied when estimating the accuracy of a statistical measure provides freedom from the assumption that the data conform to a predetermined distribution (Peterson, 1991) (Appendix D). Table IV-5 provides the bootstrap confidence bounds. These bounds represent the uncertainty in exposure estimates, not actual exposure. The upper and lower bounds used in this study were obtained through a random resampling of the monthly means at each site. The use of monthly means maintains compatability with the mean annual exposure estimates.

Table IV-4

SUMMARY OF MEAN ANNUAL ACETALDEHYDE EXPOSURE ESTIMATES
(parts per billion)

AIR BASIN	ESTIMATED EXPOSURE	POPULATION
SOUTHERN CALIFORNIA BASINS		
South Coast	2.85	10,092,133
South Central Coast	1.63	934,800
San Diego	1.94	2,131,600
NORTHERN CALIFORNIA BASINS		
San Francisco Bay Area	1.69	4,394,374
San Joaquin Valley	1.92	1,778,400
Sacramento Valley[1]	2.01	893,800
OVERALL POPULATION-WEIGHTED EXPOSURE		
	2.33	20,225,107

1 Exposure estimates are for Sacramento County residents only.

Table IV-5

SUMMARY OF MEAN ANNUAL ACETALDEHYDE CONCENTRATIONS
AND BOOTSTRAP ESTIMATES OF UNCERTAINTY
(parts per billion)

Air Basin Site Location	LOWER BOUND	ANNUAL MEAN	UPPER BOUND
SOUTHERN CALIFORNIA SITES			
South Coast Air Basin			
El Monte	2.73	3.31	3.84
Long Beach	1.78	2.49	3.14
Los Angeles	2.44	2.97	3.40
Rubidoux	1.86	2.40	2.84
Upland	2.55	2.88	3.19
South Central Coast Air Basin			
Santa Barbara	1.10	1.47	1.83
Simi Valley	1.42	1.79	2.17
San Diego Air Basin			
Chula Vista	0.93	1.39	1.78
El Cajon	1.99	2.49	2.93
NORTHERN CALIFORNIA SITES			
San Francisco Bay Area Air Basin			
Concord	1.30	1.77	2.21
Fremont	1.18	1.74	2.30
Richmond	0.90	1.13	1.33
San Francisco	1.11	1.95	2.55
San Jose	1.03	1.62	2.08
San Joaquin Valley Air Basin			
Bakersfield	1.11	1.45	1.72
Fresno	1.69	2.26	2.79
Modesto	1.35	2.00	2.57
Stockton	1.56	1.97	2.34
Sacramento Valley Air Basin [1]			
Citrus Heights	1.50	2.01	2.42

1 Exposure estimates are for Sacramento County residents only.

The overall ambient outside statewide acetaldehyde exposure, weighted by population, is best estimated to be 2.33 ppbv (4.19 $\mu g/m^3$). A total of approximately 20 million people are estimated to reside in the study areas, representing approximately 80 percent of the State's population. Basin-specific, population-weighted mean concentrations vary from a minimum of 1.63 ppbv (2.93 $\mu g/m^3$) in the South Central Coast Air Basin to a maximum of 2.85 ppbv (5.13 $\mu g/m^3$) in the South Coast Air Basin (See Table IV-4). The South Coast also accounted for five of the six sites with the highest mean annual exposure estimates in California. Figure IV-4 shows the total number of people exposed to various mean annual acetaldehyde concentrations.

The geographic mean-annual acetaldehyde concentration calculated as the average of the six basin averages was 2.00 ppbv (3.6 $\mu g/m^3$). This value is approximately 15 percent lower than the population-weighted exposure best estimate of 2.33 ppbv (4.19 $\mu g/m^3$) indicating that the highest amounts of acetaldehyde tended to be in areas of higher population density.

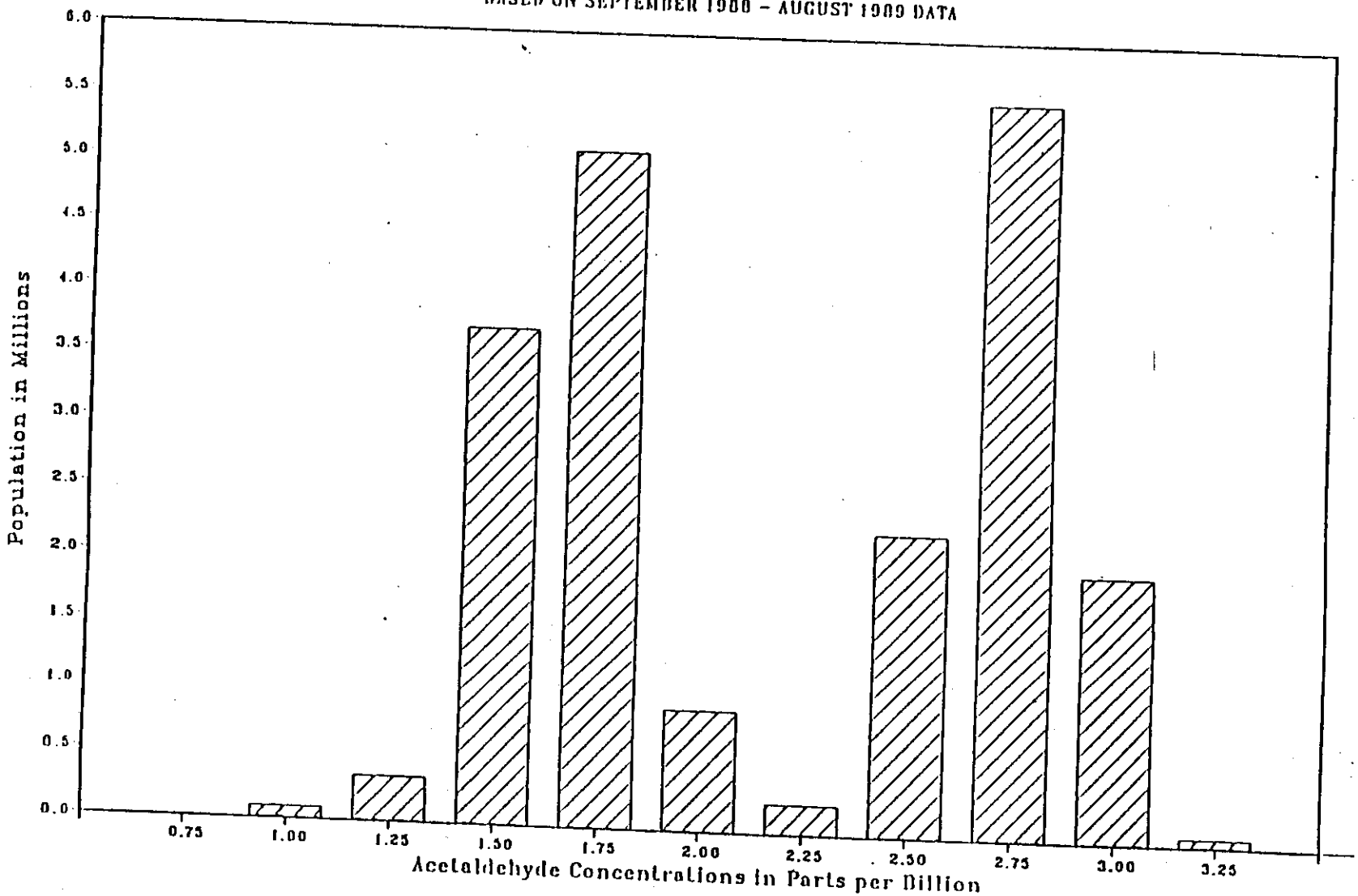
D. EXPOSURE TO ACETALDEHYDE NEAR EMISSION SOURCES

Some Californians may be exposed to near-source, or "Hot Spot" concentrations of acetaldehyde which are above the average ambient concentrations. "Hot Spot" exposure may increase the potential cancer risk to individuals living near large combustion sources. Acetaldehyde emissions and risk information is currently under development by facilities under AB 2588 Air Toxics "Hot Spots" emissions reporting program. This information will be used during the risk management phase to help determine priority and need for control of sources emitting acetaldehyde.

E. INDOOR EXPOSURE

Indoor exposure assessment has become increasingly important as an integral part of assessing exposure to toxic air contaminants because:

FIGURE IV-4
POPULATION ESTIMATES
FOR VARIOUS MEAN ANNUAL AMBIENT CONCENTRATIONS
BASED ON SEPTEMBER 1988 - AUGUST 1989 DATA



ARB/TSD:March 90

1. Californians spend most of their time (about 87 percent on average) indoors (Wiley et al., 1989); and

2. personal and indoor air monitoring data indicate that some pollutant concentrations are regularly higher indoors than outdoors.

Thus, consideration of indoor air exposure data is critical in developing a realistic estimate of personal exposures through the air environment.

1. Indoor Concentrations

Only a small number of limited surveys that measured acetaldehyde concentrations in indoor air have been published (summarized in Table IV-6). Those surveys monitored a small number of homes, and the homes that were monitored were not selected randomly. With such limitations, it is not possible to extrapolate the monitoring results to apply to the general population of homes in the respective areas surveyed. However, when viewed together, the results of individual surveys can at least provide a general idea of the magnitude of indoor acetaldehyde concentrations. A very crude estimate of an average acetaldehyde concentration that would be expected to occur inside residences is about 3 to 15 ppbv (~ 5 to 27 $\mu g/m^3$). The highest acetaldehyde concentration reported inside a residence was 37 ppbv (67 $\mu g/m^3$). The results of one study suggest that higher levels may occur in some indoor environments, in this case a tavern occupied by a number of people who were smoking, where levels of up to 113 ppbv (203 $\mu g/m^3$) were reported. Average and maximum in-vehicle acetaldehyde concentrations [~ 8 and 37 ppbv, (~ 14 and 67 $\mu g/m^3$) respectively] appear to be similar in magnitude to those inside residences (Shikiya et al., 1989). Extremely limited data suggest that acetaldehyde concentrations in offices and public buildings are also similar in magnitude to those inside residences (Bufalini, 1990; Druzik et al., 1990).

Table IV-6

INDOOR AIR CONCENTRATIONS OF ACETALDEHYDE*
(parts per billion)

LOCATION	AVERAGE CONCENTRATION	RANGE	N	COMMENTS	REFERENCES
RESIDENCES					
Boise, ID	9.3-11.8		20	non-smokers	Zweidinger et al., 1988
California		2.6 & 7.1	2		Rogozen et al., 1984
Raleigh, NC	4.0-8.5		3	non-smokers	Zweidinger, et al., 1987 Highsmith, et al., 1988
Roanoke, VA	8.3	3-26**	20	non-smokers	Zweidinger, personal communication
Baltimore, MD	14.8	6.2-37$	8	smokers may be included	Nelson, personal communication
Raleigh/ Durham, NC	20.4 15.2		15 12	+3 mobile -3 mobile	Tejada, personal communication
Raleigh/ Durham, NC		3.6-15	2		Bufalini, personal communication
PUBLIC BLDGS.					
Los Angeles, CA 5 museums, 1 library		4.2-35	6		Druzik et al., 1990
North Carolina office bldg.		1.2 12.8	1 1	non-smoking smoking	Bufalini, personal communication
North Carolina tavern		102 & 113	1	heavy smoking	Lofroth et al., 1989

(continued on next page)

INDOOR AIR CONCENTRATIONS OF ACETALDEHYDE continued

LOCATION	AVERAGE CONCENTRATION	RANGE	N	COMMENTS	REFERENCES
INSIDE VEHICLES					
Southern California	7.6	max. 37.0	194	commute driving	Shikiya et al., 1989
SMOKING CHAMBER					
		48 & 52		1 cig./30 min.	Lofroth et al., 1989
		114 & 129		1 cig./15 min.	

* Data on indoor air concentrations are limited; data cannot be extrapolated to apply to general population of homes in the respective areas surveyed. The data presented here are intended to provide a general idea of the magnitude of indoor acetaldehyde concentrations.

** Contamination of some field blanks casts doubt on the validity of some of the high values.

2. Indoor Sources

Acetaldehyde is formed as a combustion by-product and can be emitted from a number of indoor sources including cigarettes, fireplaces, woodstoves, and cooking. Limited information indicates that acetaldehyde also is emitted from some building materials such as rigid polyurethane foam insulation (Hodgson and Wooley, 1991). It may be present in a variety of consumer products such as adhesives, coatings, lubricants, inks, and nail polish remover (ibid.). A concentration of 1060 ppm has been detected in vinegar (Feron et al., 1991). Acetaldehyde occurs in traces in all ripe fruit and may form in alcoholic beverages after exposure to air (Fishbein, 1979), although it is not known if volatilization from those sources could affect indoor acetaldehyde concentrations to any significant degree.

3. Ingestion

Acetaldehyde is found commonly in a number of foods as a natural constituent and as an intentional food additive. The daily amount ingested through food cannot be estimated using readily available information. Levels in water are relatively low; a high estimate of the amount a Californian may ingest through water is 8 μg/day. See Appendix E. Dermal absorption is surmised to be negligible. It should be noted that, with respect to the potential carcinogenicity of acetaldehyde, the ingestion route may not be of major significance. There are well-developed means of detoxifying absorbed acetaldehyde; it is surmised that only in specialized organs such as the nasal cavity that inhalation of appreciable amounts may overcome local defense mechanisms (Casarett et al., 1986).

4. Inhalation

The inhalation route is of major importance to the toxic (e.g. carcinogenic) effects of acetaldehyde. Estimates of the daily amounts of acetaldehyde inhaled through residential indoor air and from environmental tobacco smoke are shown in Table IV-7. These estimates are based on very limited data and are thus very crude. No attempt has been made to use any estimates of the fraction absorbed so that the already high level of uncertainty in the values reported is not increased further. See Appendix E.

Table IV-7

ESTIMATES OF THE INHALED DOSE OF ACETALDEHYDE
FROM RESIDENTIAL INDOOR AIR AND ENVIRONMENTAL TOBACCO SMOKE

	Acetaldehyde (micrograms per day)
Residential indoor air*	
a. average amount inhaled	108 - 540
b. high range of estimate	1,440
Environmental tobacco smoke**	1,740 - 4,660

* Based on very limited data; office building and in-vehicle exposures are estimated to be very similar to residential exposures.

** Based on chamber and tavern concentrations measured by Lofroth et al. (1989) under specific conditions; does not necessarily represent range of all possible levels.

Assumptions:

1. The average person inhales about 20 cubic meters of air per day.
2. Ingestion and skin absorption are not significant routes of exposure.
3. A person inhales about the same acetaldehyde concentration all day.
4. The inhaled dose may not represent the true dose, since it does not take into account the fraction of the inhaled amount that is absorbed.

5. Contribution to Total Exposures

Acetaldehyde concentrations are generally higher indoors than outdoors. This is likely due to a variety of indoor sources of acetaldehyde. Table IV-8 shows that indoor acetaldehyde concentrations measured in recent surveys range from 2.6 to 37.4 ppbv (4.7 to 67.3 $\mu g/m^3$) inside residences. In contrast with available indoor data, ARB ambient monitoring data (Table IV-2) show that the highest 24 hour average ambient outdoor acetaldehyde concentration measured was 8.8 ppbv (15.8 $\mu g/m^3$) recorded at the Los Angeles and El Monte stations. Although some of the difference between these indoor and outdoor data may be due to the differences in measurement techniques and other factors, indoor concentrations have been consistently higher in surveys that obtained concurrent indoor and outdoor acetaldehyde measurements. Table IV-8 compares indoor and outdoor acetaldehyde concentrations measured concurrently in some of those surveys. Although the data presented are derived from limited surveys, they show that indoor concentrations can be about two to eight times higher than outdoor concentrations. The sites surveyed may not exhibit acetaldehyde levels representative of California residences and offices because of different building construction, heating practices, energy consumption and inhabitants' lifestyles.

6. Summary

Individuals are estimated to inhale 108-540 μg of acetaldehyde daily in indoor environments where inhaled doses may range up to 1,440 μg. If a person were to spend the entire day in a smoke-filled environment such as a tavern, the daily inhaled dose could total from 1,740 to 4,660 μg. These estimates are all based on very limited data and may not be representative of the California population. A more detailed review of indoor acetaldehyde is included in Appendix E.

Table IV-8

CONCURRENT INDOOR AND OUTDOOR ACETALDEHYDE CONCENTRATIONS

Range of indoor concentrations (ppbv) 12 hour sample	Outdoor concentrations (ppbv) 12 hour sample	Reference
9.3 - 11.8	2.1 - 2.6 $	Zweidinger et al., 1988 Boise, ID
4.0 - 8.5	1.3 - 4.4	Zweidinger et al., 1987 Raleigh, NC
6.2 - 37.4	0.3 - 4.1	Nelson, personal communication, 1990 Baltimore, MD

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V.

ATMOSPHERIC FORMATION, PERSISTENCE, and FATE OF ACETALDEHYDE

The concentration of acetaldehyde in the atmosphere depends upon direct emissions, secondary formation, and chemical and physical removal activities. Direct emissions from mobile and stationary sources are discussed in Chapter IV while secondary formation, persistence, and fate of acetaldehyde are discussed here. The following summarizes the key points which are described in more detail in Sections A, B, and C:

- In polluted atmospheres, secondary acetaldehyde formation from the degradation of organic pollutants frequently dominates direct emissions by contributing 41 to 67 per cent of the total atmospheric acetaldehyde.

- Regardless of whether acetaldehyde is directly emitted or derived from secondary formation, its atmospheric persistence is generally one day which is sufficient time to allow dispersal throughout an air basin under normal meteorological conditions. However, it may take longer under multi-day stagnation episodes such as can occur in the South Coast Air Basin.

- The dominant atmospheric removal mechanism for acetaldehyde is oxidation by hydroxyl radicals during daylight hours.

- The end product of the acetaldehyde-hydroxyl radical reaction is another serious pollutant, peroxyacetyl nitrate (PAN).

A. ATMOSPHERIC FORMATION

Acetaldehyde formation from the degradation of organic pollutants in urban atmospheres contributes 41 to 67 per cent of the total atmospheric acetaldehyde. Therefore, secondary acetaldehyde formation frequently exceeds direct emissions from combustion sources in urban areas (Grosjean et al. 1983). In addition, the degradation of naturally-occurring ethane contributes a small amount of acetaldehyde to polluted and non-polluted atmospheres.

1. Acetaldehyde Formation in Polluted Atmospheres

In polluted atmospheres, major sources of ethyl radicals include the reaction of propionaldehyde with hydroxyl radicals

$$OH + CH_3CH_2CHO \rightarrow H_2O + CH_3CH_2CO$$

$$\downarrow O_2$$

$$CH_3CH_2C(O)OO$$

$$\downarrow NO$$

$$C_2H_5 + CO_2 ,$$

and the decomposition reactions of the more complex alkoxy radicals, e.g., 2-butoxy radical decomposition yields acetaldehyde as well as ethyl radicals

$$CH_3\overset{\overset{\displaystyle O}{|}}{C}HCH_2CH_3 \rightarrow CH_3CHO + C_2H_5 .$$

In each case the ethyl radical is oxidized to form acetaldehyde

$$C_2H_5 \rightarrow\rightarrow CH_3CH_2O$$

$$CH_3CH_2O + O_2 \rightarrow CH_3CHO + HO_2 \ .$$

Hydroxyl radical addition to propene and certain 2-alkenes forms β-hydroxyalkoxy radicals which decompose to form acetaldehyde or the α-hydroxy radical CH_3CHOH

$$CH_3\overset{\overset{\displaystyle O}{|}}{C}HCH_2OH \rightarrow CH_3CHO + CH_2OH$$

$$CH_3CHOHCH_2O \rightarrow CH_3CHOH + HCHO$$

The α-hydroxy radical is then oxidized to form acetaldehyde (Atkinson and Lloyd 1984, Atkinson 1989)

$$CH_3CHOH + O_2 \rightarrow CH_3CHO + HO_2 \ .$$

In addition, the gas-phase reactions of ozone with propene ($CH_3CH{=}CH_2$) and certain 2-alkenes leads to the formation of acetaldehyde

$$O_3 + CH_3CH{=}CH_2 \rightarrow CH_3CHO + HCHO + X$$

where X represents H_2O, OH, HO_2, H_2 and various hydrocarbons formed in much smaller amounts than acetaldehyde and formaldehyde (Atkinson 1990).

2. Acetaldehyde Formation in Non-polluted Atmospheres

In a non-polluted or "clean" troposphere, acetaldehyde is formed as a product of atmospheric ethane reactions which rapidly yield the ethyl peroxy radical ($CH_3CH_2O_2$). The ethyl peroxy radical reacts with nitric oxide, nitrogen dioxide, hydroperoxyl, and organic peroxy radicals leading to the formation of the ethoxy radical (CH_3OH_2O) which reacts with oxygen to form acetaldehyde

$$OH + C_2H_6 \rightarrow H_2O + C_2H_5$$

$$C_2H_5 \rightarrow\rightarrow CH_3CH_2O$$

$$CH_3CH_2O + O_2 \rightarrow CH_3CHO + HO_2$$

(Atkinson and Lloyd 1984, Atkinson 1990).

B. PERSISTENCE

The persistence of atmospheric acetaldehyde (the length of time acetaldehyde remains unaltered in the atmosphere) is determined by its tropospheric lifetime (τ). Tropospheric lifetime is the time required to decrease the concentration of acetaldehyde to 1/e or 0.368 of its initial concentration. The chemical reaction of acetaldehyde and hydroxyl radicals in the atmosphere is primarily responsible for the estimated one day tropospheric lifetime of acetaldehyde. Acetaldehyde removal by photolysis and physical means such as precipitation is expected to be less significant (Atkinson 1989b). All of these processes occur in the troposphere, the region of the atmosphere extending from the earth's surface to an altitude of approximately 15 km (Finlayson-Pitts and Pitts 1986).

1. Chemical Removal from the Atmosphere

The chemical removal of atmospheric acetaldehyde is the result of the sum of several distinct oxidative reactions and photolysis.

Acetaldehyde is oxidized in reactions with hydroxyl radicals, ozone, nitrate radicals, and hydroperoxyl radicals. Each of these chemical degradations of acetaldehyde is associated with a particular reaction speed determined by the reaction rate constant (k) and the atmospheric concentrations of reactants:

$$CH_3CHO + B \xrightarrow{k} \text{products}$$

where B is the atmospheric oxidant, and

$$\tau = 1/k[B].$$

Table V-1 lists the estimated average atmospheric lifetime of acetaldehyde relative to each oxidative removal reaction. Since the shortest lifetime is associated with the acetaldehyde-hydroxyl radical reaction, it is the single most important chemical removal mechanism. The acetaldehyde-hydroxyl radical reaction, photolysis, and the remaining oxidative reactions are discussed in order of importance in Subsections 1.a., 1.b., and 1.c., respectively.

a. Reaction with the Hydroxyl (OH) Radical

The photooxidation of acetaldehyde by hydroxyl radicals during daylight hours is considered the dominant atmospheric acetaldehyde removal mechanism because it produces the shortest lifetime for acetaldehyde

Table V-1

ATMOSPHERIC LIFETIME OF ACETALDEHYDE AND REMOVAL PROCESSES at 298°K

Oxidant	Atmospheric Concentration (mol cm^{-3})	Rate Constant ($cm^3 mol^{-1} sec^{-1}$)	Atmospheric Lifetime	References
Hydroxyl radical	1.5×10^6	1.58×10^{-11}	1 day[a]	Atkinson and Pitts 1978 Michael 1985 Niki et al. 1978 Prinn et al. 1987
Ozone	7×10^{11}	$< 1 \times 10^{-20}$	>4.5 yr.	Atkinson and Carter 1984 Logan 1985
Nitrate radical	2.4×10^8	2.7×10^{-15}	35 days	Dlugokencky and Howard 1989 Platt et al. 1984
Hydroperoxyl radical	$\sim 10^7$	1×10^{-15}	~3 yr.	Hard et al. 1984 Moortgat et al. 1987

a. Note that one day is equivalent to 12 hours of daylight. Hydroxyl reactions occur only during daylight hours.

(approximately one day). The short lifetime is due to the acetaldehyde-hydroxyl reaction rate constant and the concentration of hydroxyl radicals in the atmosphere

$$\tau = 1/k[OH] = 1 \text{ day.}$$

After evaluating the available data (Morris et al. 1971, Morris and Niki 1971, Niki et al. 1978, Atkinson and Pitts 1978, Kerr and Sheppard 1981, Semmes et al. 1985, and Michael et al. 1985) concerning the kinetics and mechanism of the reaction of the hydroxyl radical with acetaldehyde, Atkinson (1989) recommended a rate constant of:

$$k = 1.58 \times 10^{-11} cm^3 \text{ molecule}^{-1} \text{second}^{-1} \pm 20\% \text{ at } 298^oK.$$

Prinn et al. (1987) estimated the concentration of hydroxyl radicals in the atmosphere to be 1.5×10^6 molecules cm^{-3} x as a 12 hour daytime average.

While definite product and mechanistic data are not available, peroxyacetyl nitrate (PAN) has been observed as a product of the reaction of the hydroxyl radical with acetaldehyde in room temperature air when nitrogen oxides are present (Atkinson and Lloyd 1984). This shows that, at room temperature, this reaction must proceed via overall hydrogen atom abstraction from the -CHO group (hydrogen atom abstraction from the $-CH_3$ group is expected to be of minimal importance at room temperature) (Atkinson 1987). The initial hydrogen atom abstraction forms the acetyl radical which, exclusively under tropospheric conditions, combines with oxygen to yield the acetyl peroxy radical. The acetyl peroxy radical then reacts with nitrogen oxides to create PAN (Atkinson 1990) (see Section C, Fate of Atmospheric Acetaldehyde for the chemical reaction).

b. **Photolysis**

Photolysis of acetaldehyde is the chemical decomposition of atmospheric acetaldehyde induced by sunlight. The rate of photolysis depends on three variables which are, in turn, wave-length dependent:

absorption cross-section (σ)[1], photolysis quantum yield (ϕ)[2], and radiation intensity (J)[3].

$$1/\tau = k = \int_{\sim 290\ nm}^{\sim 800\ nm} \alpha_\lambda \phi_\lambda J_\lambda d\lambda = 6.6 \text{ days at zenith angle } 0.^{o} \quad [4]$$

Photolysis is of secondary importance as an atmospheric acetaldehyde removal mechanism (τ= 6.6 days) when compared to the acetaldehyde-hydroxyl radical reaction (τ= 1 day) (Horowitz and Calvert 1982, Meyrahn et al. 1982). The photodissociation is expected to proceed in the following manner:

$$CH_3CHO + h\nu \rightarrow CH_4 + CO$$

and

$$CH_3CHO + h\nu \rightarrow CH_3 + HCO$$

c. **Reaction with Ozone (O_3), Nitrate (NO_3) Radicals, and Hydroperoxyl (HO_2) Radicals**

The atmospheric lifetime of acetaldehyde resulting from oxidation by ozone, nitrate radicals, and hydroperoxyl radicals is estimated as >4.5 years, 35 days, and 3 years respectively. The ozone and hydroperoxyl radical reactions proceed during both day and night hours while the nitrate radical reaction occurs at night. These lifetimes were determined by the rate constants and concentration of reactants associated with each reaction (τ= k[B] where B is the atmospheric oxidant) (Atkinson 1989).

2. Physical Removal from the Atmosphere

Atkinson evaluated the limited available data on physical removal processes and found that dry and wet deposition are expected to only slightly increase the atmospheric removal of acetaldehyde above that of the acetaldehyde-hydroxyl reaction (Atkinson 1988 and 1989, Bidleman 1988).

Dry deposition removes organic gases by absorption or adsorption to snow or moist surfaces. Because dry deposition occurs only at ground surfaces, it plays a limited role in removing acetaldehyde from the atmosphere.

Since acetaldehyde dissolves in aqueous solutions, it is reasonable to assume that the compound is subject to wet deposition by incorporation into clouds, rain, and fog. However, the degree of acetaldehyde hydration calculated using the Henry's law coefficient ($H^* = 11.4 \pm 0.4$ mol atm^{-1} at 298^oK) of Betterton and Hoffmann (1988) is fairly small (1.4) when compared to that of formaldehyde (2.3×10^3). In addition, gas-phase organic compounds which are efficiently rained out have a washout ratio (concentration in rain/concentration in air) of 10^5 to 10^6. Atkinson (1989) calculated an acetaldehyde washout ratio of 28 at 298^oK using the H^* value of Betterton and Hoffmann (1988). This washout ratio compares favorably with the washout ratio of 37 reported earlier by Buttery et al. (1969). The episodic nature of precipitation events and the estimated low washout ratio of acetaldehyde indicate that wet deposition is not a significant removal mechanism (Atkinson 1989).

C. FATE

As mentioned in Section B, Persistence of Acetaldehyde, reaction with the hydroxyl radical and, to a lesser extent, photolysis are the major tropospheric chemical loss processes. The reaction with the hydroxyl radical and photolysis occur only during daytime hours with the acetaldehyde-hydroxyl radical reaction serving as the driving force for the estimated overall lifetime of acetaldehyde. Wet deposition may lead to a

shorter tropospheric lifetime, but wet deposition is episodic in nature and expected to be of minor importance due to the relatively low acetaldehyde washout ratio. The one-day lifetime calculated from the acetaldehyde-hydroxyl radical reaction can be regarded as the tropospheric lifetime of acetaldehyde with somewhat faster removal expected during rain or fog (Grosjean and Wright 1983).

The reactions subsequent to the hydroxyl radical reaction begin with hydrogen atom abstraction resulting in the formation of the acetyl radical (CH_3CO)

$$OH + CH_3CHO \rightarrow H_2O + CH_3CO.$$

Exclusively under tropospheric conditions, the acetyl radical is rapidly oxidized to the acetyl peroxy radical ($CH_3C(O)OO$)

$$CH_3CO + O_2 \rightarrow CH_3C(O)OO.$$

The acetyl peroxy radical reacts with nitric oxide and nitrogen dioxide, with the latter reaction forming peroxy acetyl nitrate ($CH_3C(O)OONO_2$) (PAN)

$$CH_3C(O)OO + NO \rightarrow CH_3C(O)O + NO_2$$
$$\downarrow$$
$$CH_3 + CO_2$$

$$CH_3C(O)OO + NO_2 \rightleftarrows \underset{(PAN)}{CH_3C(O)OONO_2}\ .$$

Additionally, in a "clean" troposphere with low levels of nitrogen oxides, the reactions of the acetyl peroxy radical with hydroperoxyl and methyl peroxy (CH_3O_2) radicals may result in end products of formaldehyde (HCHO) and acetic acid (CH_3COOH) (Atkinson 1989, 1990).

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APPENDIX A

PHOTOCHEMICALLY FORMED ACETALDEHYDE AS A PERCENT OF AMBIENT CONCENTRATION

State of California

M E M O R A N D U M

To : Beth Schwehr, Manager
Toxics Emission Inventory Section
Technical Support Division

Date : May 31, 1991

Subject : Estimates of Secondary Ambient Acetaldehyde

Dr. Kit Wagner, Manager
Control Strategy Modeling Section
Technical Support Division

From : **Air Resources Board**

This memo is to clarify certain portions of our estimates of secondary acetaldehyde in the South Coast Air Basin. All estimates of the secondary component of ambient acetaldehyde concentrations are for the South Coast Air Basin. These estimates are based on simulations for August 28, 1987 using the Urban Airshed Model with the Carbon Bond 4 chemistry with and without primary emissions of acetaldehyde. This day represents meteorological conditions conducive to high ozone concentrations over the South Coast Air Basin and thus probably represents an upper limit for secondary concentrations of acetaldehyde.

We selected 32 monitoring sites throughout the basin with the intent of focusing on areas of high population. The average daily concentrations of acetaldehyde were estimated for secondary, primary, and boundary/initial condition components. The boundary/initial condition component of the acetaldehyde concentrations are very small, averaging about 2 percent or less of the total concentration. The secondary fractions of the ground level acetaldehyde concentrations are shown in Table 1.

Table 1

Secondary Acetaldehyde
Percent of Ambient Concentration
Averaged Over 32 Sites

Daily	Daytime	Nighttime
55.6	67.0	41.1

These statistics were computed from the 32 sites shown in Attachment 1 to this memorandum. The daily ratio is based on the overall 24-hour acetaldehyde concentrations of secondary to total acetaldehyde concentrations. Daytime includes hours 6am through 7pm PDT (13 hours), while nighttime is for 7pm through 6am PDT (11 hours).

The daily average secondary acetaldehyde is 56% over the 32 sites we have considered. Because we used a summer high ozone day this is likely to significantly overpredict the annual average secondary acetaldehyde.

Table 2 shows the acetaldehyde concentrations averaged over the 32 sites for each case in Table 1.

Table 2

Acetaldehyde Concentrations (PPB) for August 28, 1987
(Averaged Over 32 Sites)

	Daylight	Nighttime	Daily
Secondary	5.31	2.98	4.24
Total	7.93	7.25	7.62

The Carbon Bond 4 mechanism represents the acetaldehyde mechanism and rate constants with the model species ALD2. Acetaldehyde and certain other higher carbonyls are grouped together as ALD2. Our results actually represent ALD2. These results should be considered approximate in terms of acetaldehyde. We also wish to point out that this model underpredicts ozone and hydrocarbons.

cc: Terry McGuire
Don McNerny
Linda Murchison
Joan Denton (SSD)
Chris Nguyen

PDA//B48092

ATTACHMENT 1

Site Specific Modeled Acetaldehyde Concentrations
August 28, 1987
South Coast Air Basin
(ppb)

SITE	PRIMARY	SECONDARY
Anaheim	3.2	3.0
Azusa	4.0	5.3
Beverly Hills	4.4	4.2
Burbank	4.1	6.1
Downtown LA	5.1	5.0
Claremont	3.4	6.0
Costa Mesa	1.8	1.7
El Monte	4.3	4.7
Fontana	3.2	7.5
Glendora	3.5	6.1
Hawthorne	2.0	1.5
La Habra	4.3	5.0
Lancaster	0.4	3.1
Long Beach	1.2	1.7
Los Alamitos	2.7	2.4
Lynnwood	2.7	2.6
Newhall	3.8	7.3
Norco	3.9	5.3
Pasadena	5.0	6.0
Pico Rivera	4.0	3.9
Palm Springs	1.0	3.4
Pomoma	3.6	5.8
Redlands	3.9	10.6
Reseda	4.6	7.4
Riverside	3.2	6.9
San Bernardino	4.3	10.3
Thousand Oaks	2.4	3.3
Torrance	9.1	2.5
Upland	2.7	6.1
Victorville	0.6	4.9
Whittier	4.0	4.3
West LA	2.1	3.0

2. CALCULATIONS TO ESTIMATE PHOTOCHEMICALLY FORMED ACETALDEHYDE

This section addresses the calculation the staff used to estimate the tons of acetaldehyde per year formed by photo-chemical oxidation.

The term "direct" or "primary" acetaldehyde refers to acetaldehyde that is a combustion product or directly emitted from a source. Examples of these emissions include acetaldehyde from tailpipes, smokestacks and burning fields. Table III-1 shows California direct and secondary acetaldehyde emissions in 1987. Direct emissions from mobile and stationary sources ranged from 11,444 to 23,902 tons per year.

Acetaldehyde can also be formed in the atmosphere by photochemical oxidation of certain hydrocarbons from these sources and is called "secondary" acetaldehyde. An air pollution model (Appendix A.1). predicts that an average 55.6 percent of acetaldehyde is secondarily formed during a 24 hour period on a hot summer day. Thus, if the photochemically formed acetaldehyde is 55.6 percent then the direct acetaldehyde would constitute 44.4 percent of the total acetaldehyde. The photo-oxidation acetaldehyde product can be calculated if formed in the same geographical location and time period.

To estimate the range of secondary acetaldehyde emissions the following calculations were used. The tonnage is not to be taken as concise numbers but rather is provided to put a perspective on the contribution of photochemical-oxidation to total acetaldehyde in ambient air.

EMS:	photochemical acetaldehyde product, tons/year
44.4:	percent of primary emissions of acetaldehyde
55.6:	percent of secondary emissions of acetaldehyde
11,444:	acetaldehyde low range direct emissions, tons/year
23,902:	acetaldehyde high range emissions, tons/year

Lower end of range: $\frac{44.4}{11,444} = \frac{55.6}{EMS}$;

EMS = 14,330 secondary acetaldehyde, tons/year (approximately 14,000 tons/year)

Upper end of range: $\frac{44.4}{23,902} = \frac{55.6}{EMS}$;

EMS = 29,931 secondary acetaldehyde, tons/year (approximately 30,000 tons/year)

APPENDIX B

EMISSION ESTIMATES

EMISSION ESTIMATES

I. Mobile Sources

1. On-Road Motor Vehicles

In general, the lower limit of acetaldehyde emissions from on-road motor vehicles is estimated as follows:

$$EMS = TOG * (THC/TOG) * F \quad (1)$$

Where:

- EMS : acetaldehyde emissions, tons/year.
- TOG : total organic gas emissions for specific vehicular classes, tons/year.
- THC : total hydrocarbon emissions, tons/year.
- F : fraction of acetaldehyde to total hydrocarbons, dimensionless.

Acetaldehyde emissions from all on-road motor vehicles along with the appropriate fractions of acetaldehyde to total hydrocarbons (THC) are tabulated in Table A-1. This Table lists the lower limits of acetaldehyde emissions for different classes of vehicles.

The methodology to estimate the upper limits of acetaldehyde emission from on-road motor vehicles is explained in the main text. Table A-2 lists the upper limits of acetaldehyde emissions along with the TOG emissions and the fractions of acetaldehyde to TOG from on-road vehicular exhaust.

2. Other Mobile Sources

The ARB has compiled volatile organic compound (VOC) profiles for a number of fuel oil combustion processes (ARB, 1989). Based on these profiles and the total organic gas (TOG) emissions from off-road vehicles, trains, ships, aircraft, utility and mobile equipment, estimates of acetaldehyde emissions from these sources are as follows:

$$EMS = TOG * FA \quad (2)$$

Where:

- EMS : acetaldehyde emissions, tons/year.
- TOG : total organic gas emissions for specific category, tons/year.
- FA : fraction of acetaldehyde to TOG, dimensionless.

Table A-3 lists acetaldehyde emissions along with TOG emissions for other mobile sources in California.

Table A-1

Lower Limits of Acetaldehyde Emissions from On-Road Motor Vehicles for 1987

	THC[1]		Acetaldehyde [1]
	(tons/yr)	(% of THC)	(tons/yr)
Light-Duty Passenger Cars			
Non Catalyst	113,281	0.44	498
Catalyst	125,324	0.31	389
Diesel	1,560	0.54	8
Light- and Medium-Duty Trucks			
Non Catalyst	40,122	0.44	177
Catalyst	53,365	0.31	165
Diesel	405	1.11	4
Heavy-Duty Trucks			
Non Catalyst	17,411	0.54	94
Catalyst	161	0.38	1
Diesel	25,143	1.11	279
Urban Buses	1,067	1.11	12
Motorcycles	5,060	0.44	22
Total			1,649

1. ARB, 1990a. Emissions have been rounded to the nearest whole number.

Table A-2
Upper Limits of Acetaldehyde Emissions from On-Road Motor Vehicles for 1987

	TOG[1] (tons/yr)	Acetaldehyde[2] Fraction	Acetaldehyde[1] (tons/yr)
Light-Duty Passenger Cars			
Non Catalyst	119,963	0.0190	2,280
Catalyst	139,046	0.0059	820
Diesel	1,810	0.0296	54
Light- and Medium-Duty Trucks			
Non Catalyst	42,488	0.0190	807
Catalyst	59,320	0.0059	350
Diesel	469	0.0296	14
Heavy-Duty Trucks			
Non Catalyst	20,250	0.0190	385
Catalyst	178	0.0059	1
Diesel	29,244	0.0296	865
Urban Buses	1,243	0.0296	37
Motorcycles	5,359	0.0190	102
Total			5,715

Table A-3
Acetaldehyde Emissions from Other Mobile Sources for 1987

	TOG[1] (tons/year)	Acetaldehyde[2] Fraction	Acetaldehyde[1] (tons/year)
Off-Road Vehicles			
Diesel Combustion	1,652	0.0296	49
Gasoline Combustion	38,407	0.0190	730
Trains	10,819	0.0296	320
Ships	2,533	0.0296	75[3]
Aircraft	1,622	0.0190	31
Mobile and Utility Equipment			
Diesel Combustion	9,971	0.0296	295
Gasoline & LPG Combustion	30,494	0.0190	579
Total			2,079

1. ARB, 1990b; and ARB, 1990c. Emissions have been rounded to the nearest whole number.
2. ARB, 1989.
3. Approximately 21 % of this estimate is for activities occurring in the Outer Continental Shelf area.

III. Stationary Area Sources

For stationary area sources, the staff has used a methodology similar to that used in estimating acetaldehyde emissions from fuel combustion sources. The staff has used the amount of material burned and the appropriate emission factors to estimate acetaldehyde emissions from stationary area sources. These estimates are reported in Table A-6 as follows:

Table A-6
Acetaldehyde Emissions from Stationary Area Sources

Material Burned	Process Rate[2]	Emission Factor	Emissions[1] (tons/year)
Wood	1.12×10^6 tons	0.20 lb/ton	110 - 660[3]
Diesel	6.29×10^6 gallons	Not applicable	43[4]
Oil[5]	1.21×10^6 tons	0.0016 - 0.0032 lb/ton	0.97 - 1.9
Natural Gas	8.38×10^{11} ft^3	$(1.7 - 3.4) \times 10^{-8}$ lb/ft^3	7 - 14
Ag. Burning	2.81×10^6tons	0.73 - 1.5 lb/ton	1,030 - 2,110
Manag't Burning	3.32×10^6 tons	0.73 - 1.5 lb/ton	1,210 - 2,490
Open Burning	2.38×10^5 tons	0.73 - 1.5 lb/ton	87 - 178
Wildfires	1.23×10^7 tons	0.73 - 1.5 lb/ton	4,490 - 9,220
Total			6,980 - 14,700

1. These numbers may not exactly equal the process rates time the emission factors due to rounding in the original calculations (at most three significant figures).

2. ARB (1990f) These process rates have been rounded off to at most three significant figures.

3. The upper number was estimated using TOG emissions and VOC speciation profile for residential wood combustion.

4. Calculated from TOG emissions and the fraction of acetaldehyde in TOG. A small portion (less than 1%) of this emission estimate represents emissions for activities occurring in the Outer Continental Shelf (OCS) area.

5. This category also includes 25% from unspecified liquid material combustion sources.

II. Stationary Point Sources

1. Fuel Combustion

In general, acetaldehyde emissions from all fuel combustion sources were estimated as follows:

$$EMS = PR * EF \quad (3)$$

Where:
EMS = acetaldehyde emissions, tons/year.
PR = amount of coal, oil, or gases burned; tons, gallons, or million cubic feet per year.
EF = emission factor; lbs per ton, gallon, or million cubic feet.

Acetaldehyde emissions for each of the fuel combustion types, along with the process rates and emission factors are tabulated in Table A-4 as follows:

Table A-4
Acetaldehyde Emissions from Fuel Combustion Sources

Fuel Type	Process Rate[1]	Emission Factor[2]	Emissions (tons/year)
Coal	1.6×10^6 tons	0.0014 - 0.0029 lb/ton	1 - 2
Diesel	3.24×10^6 gallons	Not Applicable	1[3]
Gasoline	4.53×10^6 gallons	Not Applicable	1000
Natural Gas	1.8×10^{12} ft^3	$(1.7 - 3.4) \times 10^{-8}$ lb/ft^3	15 - 31
Oil	1.26×10^7 tons	0.0016 - 0.0032 lb/ton	10 - 20
Wood	5.63×10^6 tons	0.20 lb/ton	563

1. ARB, 1990c.
2. MRI, 1987.
3. ARB, 1990h. Calculated from TOG emissions and the fraction of acetaldehyde in TOG.

2. Refineries - Processing

Based on the "Annual Refining Survey" of the Oil and Gas Journal, California refineries had a rated charge capacity of approximately 2.28 million barrels per calendar day of crude oil in 1988 (OGJ, 1989). Catalytic cracking units had a rated charge capacity of 645,500 bbls per stream day or 223,827 thousand bbls per calendar year and thermal operations (assuming coking operations) had a rated charge capacity of 503,200 bbls per stream day or 174,485 thousand bbls per calendar year in 1988 (OGJ, 1989). Estimates of acetaldehyde emissions for refineries are as follows:

$$EMS = RC * EF \qquad (4)$$

Where:

EMS = acetaldehyde emissions, tons/year.
RC = rated charge capacity, bbls/yr.
EF = acetaldehyde emission factor, lbs/1000 bbls.

Acetaldehyde emission factors are different depending on the refining processes; thus, acetaldehyde emissions are different from these processes. Table A-5 lists acetaldehyde emissions from each refining process, along with the charge capacities and the acetaldehyde emission factors.

Considering the possibility of additional acetaldehyde emissions from other operations such as catalytic reforming, catalytic hydrorefining and catalytic hydrotreating, a range of estimates includes acetaldehyde emissions from petroleum refining processes. To account for these other operations, the process rates for all catalytic units as reported in the OGJ have been added to estimate maximum process rates for catalytic cracking units. This process rate is then used to estimate the high end of the range shown in Table A-5 for acetaldehyde emissions from catalytic cracking units in refineries.

Table A-5

Acetaldehyde Emissions from Refinery Processing in California

Source	Charge capacity[1] (1000 bbls/yr)		EF (lbs/1000 bbls)	Acetaldehyde Emissions (tons/yr)	
	Low	High		Low	High
Catalytic Cracking	223,827	1,062,945[2]	1.40	157	744
Thermal Operations[3]	174,485	174,485	0.34	30	30
Total[4]				190	770

---

1. OGJ, 1989. Charge capacities are expressed as the volume of crude oil that the facility can process per calendar year. These numbers were estimated based on the rated charge capacities per stream day. The OGJ assumed that the capacity per calendar day equals approximately 95% of the capacity per stream day.

2. This number was estimated by adding all process rates for catalytic units as reported in the OGJ. Specifically, 223,827 thousand bbls of oil were processed in catalytic cracking units; 194,700 thousand bbls in catalytic reforming units; 133,499 thousand bbls in catalytic hydrorefining units, and 328,875 thousand bbls in catalytic hydrotreating units.

3. Assumed to be coking operations.

4. The totals have been rounded to at most two significant figures.

3. Coffee Roasting

In 1987, coffee makers in California roasted approximately 279,000 tons of green coffee beans. Most of these facilities use an after burner as control equipment (ARB, 1990). Acetaldehyde emissions from coffee bean roasting in California are estimated as follows:

$$EMS = PR * EF \tag{5}$$

Where:

EMS = acetaldehyde emissions, tons per year.
PR = amount of green beans roasted, tons/year.
EF = controlled emission factor, ton acetaldehyde per ton green beans.

$$EMS = 278{,}970 \text{ tons/yr} * 8.2 \times 10^{-6} \text{ ton/ton}$$

$$= 2.3 \text{ tons acetaldehyde per year.}$$

APPENDIX C

ANALYSIS OF ACETALDEHYDE

The following procedure is used to analyze acetaldehyde as well as formaldehyde.

State of California
Air Resources Board
Monitoring & Laboratory Division

Standard Operating Procedure
for the
Determination of Formaldehyde in Ambient Air

1.0 Scope

This is a high performance liquid chromatographic (HPLC) method for the determination of formaldehyde in the ambient air utilizing solid adsorbent. The method was developed from EPA Method TO11.

2.0 Summary of Method

2.1 Ambient air is drawn through Sep-Pak chromatographic grade silica gel cartridges. The cartridges are coated with acidified 2,4-dinitrophenylhydrazine (DNPH). Sampling rate is dependent upon carbonyl concentration but is estimated to be 0.7L per minute maximum for a 24-hour period. During sampling, formaldehyde reacts with the DNPH to form a DNPH-formaldehyde derivative (DNPH-HCHO).

2.2 The DNPH-HCHO is eluted from the sampling cartridges using acetonitrile (ACN) and is quanitified using reverse-phase HPLC with ultraviolet absorption detection at 360 nm.

3.0 Interferences/Limitations

3.1 Since this procedure is written for the sampling and analysis of formaldehyde, interferences resulting from certain isomeric aldehydes that may be unresolved by the HPLC system when analyzing for other aldehydes is not a factor.

3.2 Formaldehyde contamination of the DNPH reagent is a frequently encountered problem. The DNPH must be purified by multiple recrystallations in UV grade ACN. Recrystallization is accomplished at 40-60°C by slow evaporation of the solvent to maximize crystal size. The purified DNPH crystals are stored under UV grade acetonitrile until use. Impurity levels in the DNPH are determined by HPLC prior to use.

4.0 Apparatus

4.1 A gradient HPLC system consisting of a mobile phase reservoir; high pressure pumps; an injection valve or automatic sampler; a C-18 reverse phase column 3.9 mmx 30 cm; a variable wavelength UV detector operating at 360 nM; and a data system.

4.2 Sampling system - a XonTech Module 920 Multi-media sampler outfitted with a sampling head configured to hold the adsorbant Sep-Pak cartridges and capable of sampling at a flow rate of between 0.5 and 2.0 LPM.

4.3 Supelco 4 mL glass desorption vials with teflon lined screw caps. Sun brokers 1 mL autosampler "Sun Vial" with polyethylene cap septum.

4.4 Sample shaker/desorber and sample racks.

4.5 Gelman AcroPrep syringeless 0.45 nm PTFE membrane sample filter units.

4.6 Filtration and degassing system for mobile phase solvents such as Waters Part #85124.

4.7 Various volumetric pipets and flasks and graduated cylinders.

4.8 Special glass apparatus for rinsing, storing and dispensing saturated DNPH stock reagent (see Figure #_1_).

4.9 Hotplate.

4.10 Polyethylene gloves - used to handle the treated cartridges.

5.0 Reagents

5.1 2,4-Dinitrophenylhydrazine (DNPH) - Aldrich Chemical (Catalog #D19,930-3) or equivalent. Recrystallize at least twice with UV grade acetonitrile before use.

5.2 Acetonitrile and water mobile phase solvents, HPLC grade such as Burdick & Jackson Product #016 and Baker #4218-3, respectively.

5.3 Hydrochloric acid - analytical grade.

5.4 Formaldehyde - analytical grade.

5.5 Methanol or Ethanol - analytical grade.

5.6 Sep-Pak silica gel cartridges - Waters Associates, 34 Maple Street, Milford, MA - Product #51900

5.7 Calibration Standards are prepared in ACN from the DNPH-formaldehyde derivative. A stock solution of 100 mg/L is prepared by dissolving 10 mg of solid derivative in 100 mL of ACN. Calibration standards spanning the range of interest are prepared from the stock solution.

6.0 <u>Preparation of Reagents & Cartridges</u>

6.1 Purification of 2,4-Dinitrophenylhydrazine (DNPH) [<u>Note</u>: This procedure should be performed under a properly ventilated hood.]

6.1.1 Prepare a supersaturated solution of DNPH by boiling excess DNPH in 200 mL of acetonitrile for approximately one hour.

6.1.2 After one hour, remove and transfer the supernatant to a covered beaker on a hot plate and allow gradual cooling to 40-60°C.

6.1.3 Let covered beaker heat at this temperature range, allowing 95% of solvent to evaporate slowly.

6.1.4 Decant solution to waste, and rinse crystals twice with three times their apparent volume of acetonitrile. [CAUTION: Various health effects are resultant from the inhalation of acetonitrile. At 500 ppm in air, brief inhalation has produced nose and throat irritation. At 160 ppm, inhalation for 4 hours has caused flushing of the face (2 hour delay after exposure) and bronchial tightness (5 hour delay). Heavier exposures have produced systemic effects with symptoms ranging from headache, nausea, and lassitude to vomiting, chest or abdominal pain, respiratory depression, extreme weakness, stupor, convulsions and death (dependent upon concentration and time)].

6.1.5 Transfer crystals to another clean beaker, add 200 mL of acetonitrile, heat to boiling, and again let crystals grow slowly at 40-60°C until 95% of the solvent has evaporated.

6.1.6 Repeat rinsing process as described in Section 6.1.4.

6.1.7 Take an aliquot of the second rinse, dilute 10 times with acetonitrile, acidify with 1 mL of 3.8 M perchloric acid per 100 mL of DNPH solution, and analyze by HPLC. An ideal impurity level is shown in Figure 2.

6.1.8 The impurity level of DNPH should be below the sensitivity (ppb, v/v) level indicated in Table 1 for the anticipated sample volume. If the impurity level is not acceptable for intended sampling application, repeat recrystallization.

6.1.9 Transfer the purified crystals to an all-glass reagent bottle, add 200 mL of ACN, stopper, shake gently, and let stand overnight. Analyze supernatant by HPLC. The purity level should be comparable to that shown in Figure #__2__.

6.2 Preparation of DNPH-Formaldehyde Derivative

6.2.1 Titrate a saturated solution of DNPH in 2N HCl with formaldehyde (other aldehydes may be used if their detection is desirable, see Fig.3 for a typical chromatagram of the various DNPH-Carbonyl derivatives.).

6.2.2 Filter the colored precipitate, wash with 2N HCl and water and let precipitate air dry.

6.2.3 Check the purity of the DNPH-formaldehyde derivative by melting point determination table or HPLC analysis.

6.3 Preparation of DNPH-formaldehyde Standards

6.3.1 Prepare a standard stock solution of the DNPH-formaldehyde derivative by dissolving accurately weighed amounts in acetonitrile.

6.3.2 Prepare a working calibration standard mix from the standard stock solution. The concentration of the DNPH-formaldehyde compound in the standard mix solutions should be adjusted to reflect relative distribution in a real sample. [Note: Individual stock solutions of approximately 100 mg/L are prepared by dissolving 10 mg of the solid derivative in 100 mL of acetonitrile. The individual solution is used to prepare calibration standards containing the derivative of interest at concentrations of 0.1-10 mg/L, which spans the concentration of interest for most ambient air work.]

6.3.3 Store all standard solutions in a refrigerator. They are stable for several months.

6.4 Preparation of DNPH-Coated Cartridges

[Note: This procedure must be performed in an atmosphere with a very low aldehyde background. All glassware and plastic ware must be scrupulously cleaned and rinsed with deionized water and aldehyde free acetonitrile. Contact of reagents with laboratory air must be minimized. Polyethylene gloves must be worn when handling the cartridges.]

6.4.1 DNPH Coating Solution

6.4.1.1 Dilute 25 mL of saturated DNPH stock solution to 100 mL with acetonitrile in a reagent bottle equipped with a positive displacement dispenser.

6.4.1.2 Acidify with 1.0 mL of concentrated HCl. [Note: The atmosphere above the acidified solution should preferably be filtered through a DNPH-coated silica gel cartridge to minimize contamination from laboratory air.]

6.4.1.3 Prime the dispenser and slowly dispense 10-20 mL to waste.

6.4.1.4 The impurity level should be similar to that shown in Figure 2.

6.4.2 Coating of Sep-Pak Cartridges

6.4.2.1 Open the Sep-PAk package, connect the short end to a 10-mL syringe, and place it in the syringe rack. [Note: Prepare as many cartridges and syringes as possible.]

6.4.2.2 Using a positive displacement repetitive pipet, add 10 mL of acetonitrile to each of the syringes.

6.4.2.3 Let liquid drain to waste by gravity. [Note: Remove any air bubbles that may be trapped between the syringe and the silica cartridge by displacing them with the acetonitrile in the syringe.]

6.4.2.4 Set the repetitive dispenser containing the acidified DNPH coating solution to dispense 10mL into the cartridges.

6.4.2.5 Once the effluent flow at the outlet of the cartridge has stopped, dispense 10mL of the DNPH coating reagent into each of the syringes.

6.4.2.6 Let the coating reagent drain by gravity through the cartridge until flow at the other end of the cartridge stops.

6.4.2.7 Wipe the excess liquid at the outlet of each of the cartridges with clean tissue paper.

6.4.2.8 Remove the cartridges from the syringes and connect the short ends to the Luer ports of the drying manifold.

6.4.2.9 Connect a DNPH-coated Sep-Pak cartridge to the outlet port of the drying manifold. This "guard cartridge" will serve to remove any trace of formaldehyde in the nitrogen gas supply.

6.4.2.10 Pass nitrogen through each of the cartridges at about 300-400 mL/min for 5-10 minutes.

6.4.2.11 After drying, arrange the Sep-Paks in pairs using a one inch piece of 3/16" ID Tygon tubing. Make sure the Sep-Pak cartridge ends butt together. The first cartridge is the primary (sampling cartridge) while the second is used to detect sample breakthrough. Cap the two exposed cartridge ends with 3/16" ID column caps.

6.4.2.12 Store cartridges in a screw cap glass culture tube in a refrigerator until use.

6.4.2.13 Before transport, remove the screw-capped glass culture tubes containing the adsorbent tube pairs from the refrigerator and place the tubes in a friction-top metal tube and the metal tube in fiberboard screw cap mailing case.

7.0 Sampling

7.1 A XonTech Model 920 sampler is used to draw the ambient sample through the cartridges.

7.2 Remove the Sep-Pak pair from the transport containers. Uncap and place the cartridges in the metal cartridge holder making sure the short ends of the cartridges point up. Also make sure the primary Sep-Pak cartridge end fits through the 3/16" hole in the septum seal located in the XonTech sampling head receptacle, thus ensuring a leak free system once the cartridge holder is snugged up into the head receptacle.

7.3 Expose the Sep-Pak cartridges to 0.7 LPM ambient air for 24 hours. After the run remove the Sep-Pak cartridge pair, recap the ends and put back in the respective transport containers along with the 920 "printout" for the sampling period.

7.4 The formaldeyde sampling is to be done on the same schedule as that for "Toxics" and therefore the transport container can be placed in the air bag carton for shipment back to the lab.

7.5 Upon receipt at the lab the Sep-Paks are placed in cold storage until desorbtion.

8.0 Sample Analysis

8.1 Sample Desorption

8.1.1 Remove the Sep-Pak cartridges from the culture tube and connect each (outlet or long end during sampling) to a clean syringe.

8.1.2 Place the cartridge/syringe in the syringe rack and backflush the cartridge (gravity feed) with 6 mL of acetonitrile to a 5 mL volumetric flask.

8.1.3 Dilute to the 5 mL mark with ACN. Label the flask with sample ID.

8.2 HPLC Analysis

8.2.1 The operating parameters are as follows:

Column: BondaPak c-18 (3.9 mm x 30 cm) operated @ 30°C

Mobile Phase: Isocratic 40/60 ACN/H_2O

Detector: Model 490 UV/Vis at 360 nM. Sample rate 1 point/sec and 1.00 AUFS.

Flow Rate/Run Time: 1.0 mL/min.; 25 minute run

Retention Time: Formaldehyde ~ 13.5 minutes
Acetaldehyde ~ 19.5 minutes

Injection Volume: 25 uL

8.2.2 Equilibrate the column for 30 minutes before first analysis. Analyze a blank to check for method interferences.

8.2.3 Calibrate the instrument using five standard concentrations each analyzed in triplicate. The results are used to prepare a calibration curve. Linear response is indicated when an r of at least 0.995 for a linear least squares fit of the data is obtained. The retention times for each analyte should agree within 2%.

8.2.4 Check the calibration of the instrument for each run by analyzing a control sample. The concentration given must fall within the UWL and LWL of the control sample value (± 2 S.D.) Plot all results on the method control chart. The day to day response for the various standards should be within 10%.

8.2.5 Prepare a multimethod routine to control the automatic sampler. Run two injections per sample and a control for every ten samples.

9.0 Calculations

$$ug/M^3 = \frac{(ug/mL)(mL\ of\ extract)(1000)}{(minutes\ sampled)(LPM\ air\ flow)}$$

10.0 Method Sensitivity and Precision

Formaldehyde conc.(ug/5mL)	0.4	0.7	1.8	3.6	7.2
Peak Area (M)	55	112	262	566	1098
Std Deviation	4	1	9	36	60
Coeff. of Variation (%)	7.2	0.9	3.4	6.4	5.5

Correlation Coefficient: 0.997

Slope: 0.99996

Intercept: 0.0002 ug/mL

MLD: 0.1 ug/5mL ("X" intercept + 3 S.D. of 0.4 std.)

n=3/conc.

TABLE 1. SENSITIVITY (PPB,V/V) OF SAMPLING/ANALYSIS FOR ALDEHYDES AND KETONES IN AMBIENT AIR USING ADSORBENT CARTRIDGE FOLLOWED BY GRADIENT HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Sample Volume, L	10	20	30	40	50	60	100	200	300	400	500	1000
Compound	Sensitivity (ppb, v/v) of DNPH/HPLC Method for Carbonyls in Ambient Air											
Formaldehyde	1.45	0.73	0.48	0.36	0.29	0.24	0.15	0.07	0.05	0.04	0.03	0.01
Acetaldehyde	1.36	0.68	0.45	0.34	0.27	0.23	0.14	0.07	0.05	0.03	0.03	0.01
Acrolein	1.29	0.65	0.43	0.32	0.26	0.22	0.13	0.06	0.04	0.03	0.03	0.01
Acetone	1.28	0.64	0.43	0.32	0.26	0.21	0.13	0.06	0.04	0.03	0.03	0.01
Propionaldehyde	1.28	0.64	0.43	0.32	0.26	0.21	0.13	0.06	0.04	0.03	0.03	0.01
Crotonaldehyde	1.22	0.61	0.41	0.31	0.24	0.20	0.12	0.06	0.04	0.03	0.02	0.01
Butyraldehyde	1.21	0.61	0.40	0.30	0.24	0.20	0.12	0.06	0.04	0.03	0.02	0.01
Benzaldehyde	1.07	0.53	0.36	0.27	0.21	0.18	0.11	0.05	0.04	0.03	0.02	0.01
Isovaleraldehyde	1.15	0.57	0.38	0.29	0.23	0.19	0.11	0.06	0.04	0.03	0.02	0.01
Valeraldehyde	1.15	0.57	0.38	0.29	0.23	0.19	0.11	0.06	0.04	0.03	0.02	0.01
o-tolualdehyde	1.02	0.51	0.34	0.25	0.20	0.17	0.10	0.05	0.03	0.03	0.02	0.01
m-tolualdehyde	1.02	0.51	0.34	0.25	0.20	0.17	0.10	0.05	0.03	0.03	0.02	0.01
p-tolualdehyde	1.02	0.51	0.34	0.25	0.20	0.17	0.10	0.05	0.03	0.03	0.02	0.01
Hexanaldehyde	1.09	0.55	0.36	0.27	0.22	0.18	0.11	0.05	0.04	0.03	0.02	0.01
2,5-Dimethylbenzaldehyde	0.97	0.49	0.32	0.24	0.19	0.16	0.10	0.05	0.03	0.02	0.02	0.01

[Note: Ppb values are measured at 1 atm and 25°C; sample cartridge is eluted with 5 mL acetonitrile, and 25 μL are injected onto HPLC column.]

[Note: Maximum sampling flow through a DNPH-coated SEP-PAK is about 1.5 L per minute.]

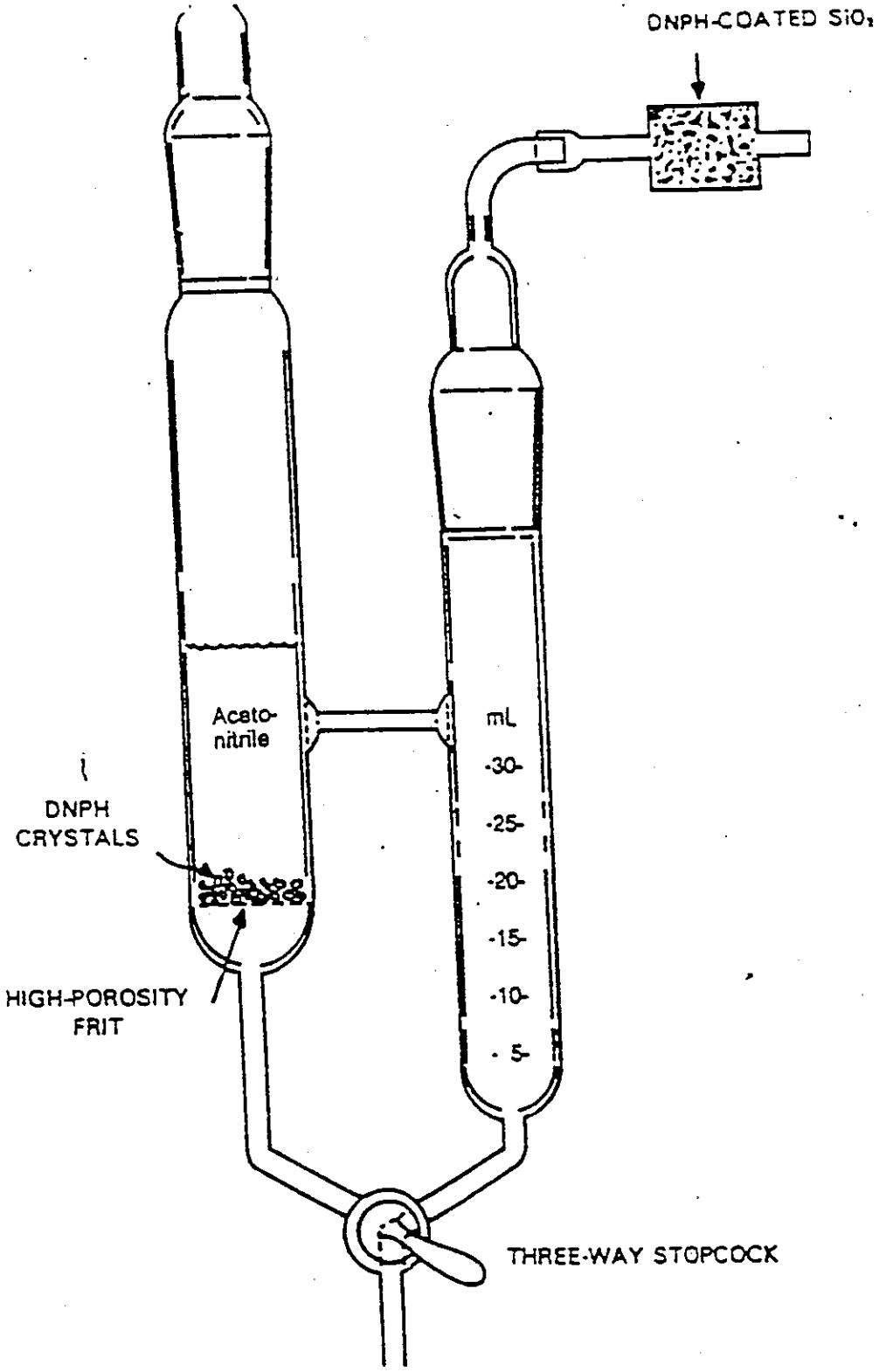


FIGURE 1 SPECIAL GLASS APPARATUS FOR RINSING, STORING, AND DISPENSING SATURATED DNPH STOCK SOLUTION

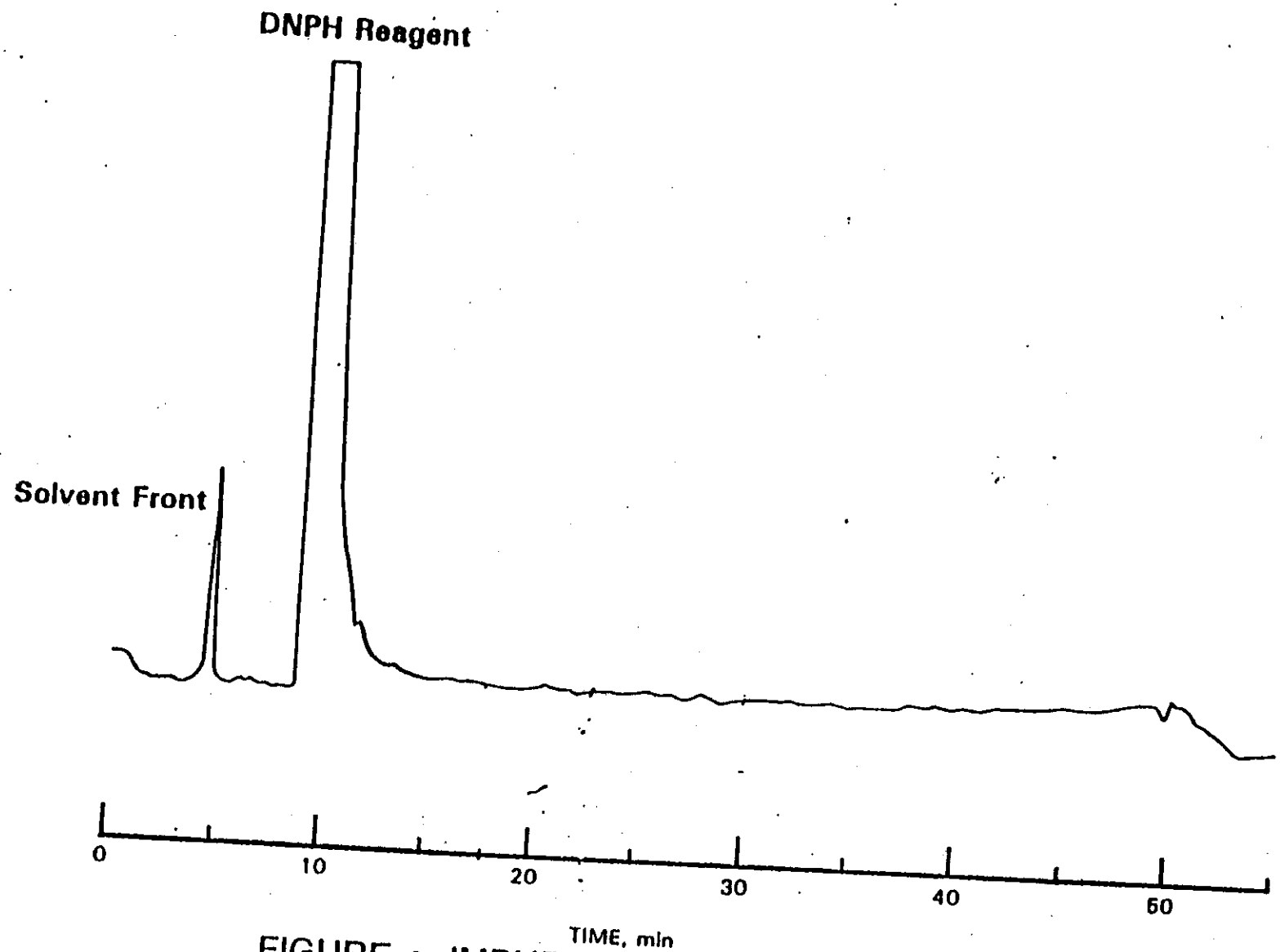
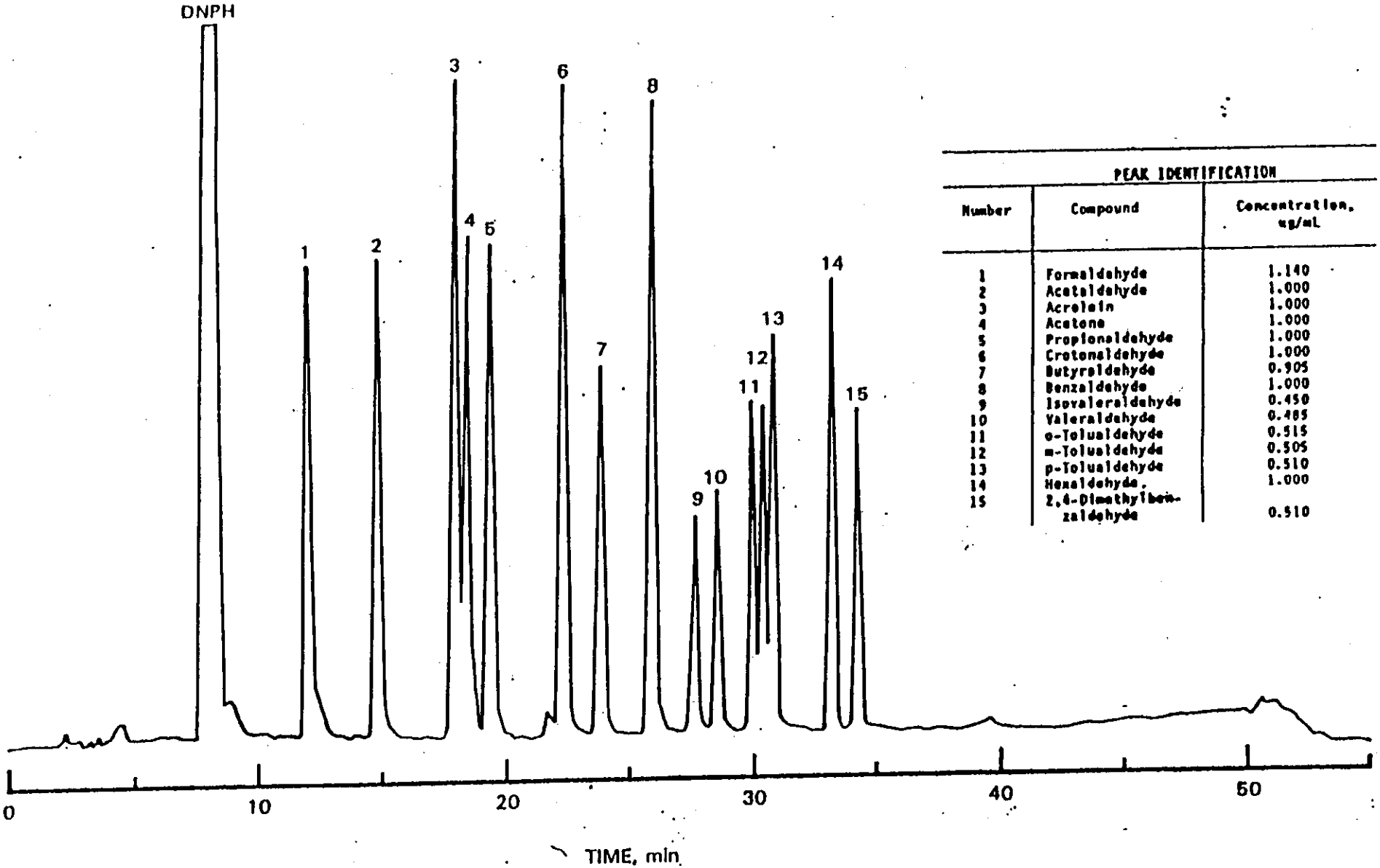


FIGURE 2. IMPURITY LEVEL OF DNPH AFTER RECRYSTALLIZATION



PEAK IDENTIFICATION

Number	Compound	Concentration, µg/mL
1	Formaldehyde	1.140
2	Acetaldehyde	1.000
3	Acrolein	1.000
4	Acetone	1.000
5	Propionaldehyde	1.000
6	Crotonaldehyde	1.000
7	Butyraldehyde	0.905
8	Benzaldehyde	1.000
9	Isovaleraldehyde	0.450
10	Valeraldehyde	0.485
11	o-Tolualdehyde	0.515
12	m-Tolualdehyde	0.505
13	p-Tolualdehyde	0.510
14	Hexaldehyde	1.000
15	2,4-Dimethylbenzaldehyde	0.510

FIGURE 3 CHROMATOGRAPHIC SEPARATION OF DNPH DERIVATIVES OF 15 CARBONYL STANDARDS

APPENDIX D

BOOTSTRAP STATISTICAL METHODS

Statistical Science
1986, Vol. 1, No. 1, 54–77

Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy

B. Efron and R. Tibshirani

Abstract. This is a review of bootstrap methods, concentrating on basic ideas and applications rather than theoretical considerations. It begins with an exposition of the bootstrap estimate of standard error for one-sample situations. Several examples, some involving quite complicated statistical procedures, are given. The bootstrap is then extended to other measures of statistical accuracy such as bias and prediction error, and to complicated data structures such as time series, censored data, and regression models. Several more examples are presented illustrating these ideas. The last third of the paper deals mainly with bootstrap confidence intervals.

Key words: Bootstrap method, estimated standard errors, approximate confidence intervals, nonparametric methods.

1. INTRODUCTION

A typical problem in applied statistics involves the estimation of an unknown parameter θ. The two main questions asked are (1) what estimator $\hat{\theta}$ should be used? (2) Having chosen to use a particular $\hat{\theta}$, how accurate is it as an estimator of θ? The bootstrap is a general methodology for answering the second question. It is a computer-based method, which substitutes considerable amounts of computation in place of theoretical analysis. As we shall see, the bootstrap can routinely answer questions which are far too complicated for traditional statistical analysis. Even for relatively simple problems computer-intensive methods like the bootstrap are an increasingly good data analytic bargain in an era of exponentially declining computational costs.

This paper describes the basis of the bootstrap theory, which is very simple, and gives several examples of its use. Related ideas like the jackknife, the delta method, and Fisher's information bound are also discussed. Most of the proofs and technical details are omitted. These can be found in the references given, particularly Efron (1982a). Some of the discussion here is abridged from Efron and Gong (1983) and also from Efron (1984).

Before beginning the main exposition, we will describe how the bootstrap works in terms of a problem where it is not needed, assessing the accuracy of the sample mean. Suppose that our data consists of a random sample from an unknown probability distribution F on the real line,

$$X_1, X_2, \cdots, X_n \sim F. \tag{1.1}$$

Having observed $X_1 = x_1, X_2 = x_2, \cdots, X_n = x_n$, we compute the sample mean $\bar{x} = \sum_1^n x_n/n$, and wonder how accurate it is as an estimate of the true mean $\theta = E_F\{X\}$.

If the second central moment of F is $\mu_2(F) = E_F X^2 - (E_F X)^2$, then the standard error $\sigma(F; n, \bar{x})$, that is the standard deviation of $\bar{x}$ for a sample of size n from distribution F, is

$$\sigma(F) = \{\mu_2(F)/n\}^{1/2}. \tag{1.2}$$

The shortened notation $\sigma(F) = \sigma(F; n, \bar{x})$ is allowable because the sample size n and statistic of interest $\bar{x}$ are known, only F being unknown. The standard error is the traditional measure of $\bar{x}$'s accuracy. Unfortunately, we cannot actually use (1.2) to assess the accuracy of $\bar{x}$, since we do not know $\mu_2(F)$, but we can use the *estimated standard error*

$$\hat{\sigma} = \{\hat{\mu}_2/n\}^{1/2}. \tag{1.3}$$

where $\hat{\mu}_2 = \sum_{i=1}^n (x_i - \bar{x})^2/(n-1)$, the unbiased estimate of $\mu_2(F)$.

There is a more obvious way to estimate $\sigma(F)$. Let

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$\hat{F}$ indicate the empirical probability distribution.

(1.4) $\hat{F}$: probability mass $1/n$ on $x_1, x_2, \cdots, x_n$.

Then we can simply replace F by $\hat{F}$ in (1.2), obtaining

$$\hat{\sigma} = \sigma(\hat{F}) = [\mu_2(\hat{F})/n]^{1/2}, \tag{1.5}$$

is the estimated standard error for $\bar{x}$. This is the *bootstrap estimate*. The reason for the name "bootstrap" will be apparent in Section 2, when we evaluate $\sigma(\hat{F})$ for statistics more complicated than $\bar{x}$. Since

$$\hat{\mu}_2 = \mu_2(\hat{F}) = \sum_{i=1}^{n} \frac{(x_i - \bar{x})^2}{n}, \tag{1.6}$$

$\hat{\sigma}$ is not quite the same as $\tilde{\sigma}$, but the difference is too small to be important in most applications.

Of course we do not really need an alternative formula to (1.3) in this case. The trouble begins when we want a standard error for estimators more complicated than $\bar{x}$, for example, a median or a correlation or a slope coefficient from a robust regression. In most cases there is no equivalent to formula (1.2), which expresses the standard error $\sigma(F)$ as a simple function of the sampling distribution F. As a result, formulas like (1.3) do not exist for most statistics.

This is where the computer comes in. It turns out that we can always numerically evaluate the bootstrap estimate $\hat{\sigma} = \sigma(\hat{F})$, without knowing a simple expression for $\sigma(F)$. The evaluation of $\hat{\sigma}$ is a straightforward Monte Carlo exercise described in the next section. In a good computing environment, as described in the remarks in Section 2, the bootstrap effectively gives the statistician a simple formula like (1.3) for any statistic, no matter how complicated.

Standard errors are crude but useful measures of statistical accuracy. They are frequently used to give approximate confidence intervals for an unknown parameter θ

$$\theta \in \hat{\theta} \pm \hat{\sigma} z^{(\alpha)}, \tag{1.7}$$

where $z^{(\alpha)}$ is the $100 \cdot \alpha$ percentile point of a standard normal variate, e.g., $z^{(.95)} = 1.645$. Interval (1.7) is sometimes good, and sometimes not so good. Sections 7 and 8 discuss a more sophisticated use of the bootstrap, which gives better approximate confidence intervals than (1.7).

The standard interval (1.7) is based on taking literally the large sample normal approximation $(\hat{\theta} - \theta)/\hat{\sigma} \sim N(0, 1)$. Applied statisticians use a variety of tricks to improve this approximation. For instance if θ is the correlation coefficient and $\hat{\theta}$ the sample correlation, then the transformation $\phi = \tanh^{-1}(\theta)$, $\hat{\phi} = \tanh^{-1}(\hat{\theta})$ greatly improves the normal approximation, at least in those cases where the underlying sampling distribution is bivariate normal. The correct tactic then is to transform, compute the interval (1.7) for ϕ, and transform this interval back to the θ scale.

We will see that bootstrap confidence intervals can automatically incorporate tricks like this, without requiring the data analyst to produce special techniques, like the $\tanh^{-1}$ transformation, for each new situation. An important theme of what follows is the substitution of raw computing power for theoretical analysis. This is not an argument against theory, of course, only against unnecessary theory. Most common statistical methods were developed in the 1920s and 1930s, when computation was slow and expensive. Now that computation is fast and cheap we can hope for and expect changes in statistical methodology. This paper discusses one such potential change, Efron (1979b) discusses several others.

2. THE BOOTSTRAP ESTIMATE OF STANDARD ERROR

This section presents a more careful description of the bootstrap estimate of standard error. For now we will assume that the observed data $\mathbf{y} = (x_1, x_2, \cdots, x_n)$ consists of independent and identically distributed (iid) observations $X_1, X_2, \cdots, X_n \sim_{\text{iid}} F$, as in (1.1). Here F represents an unknown probability distribution on $\mathscr{X}$, the common sample space of the observations. We have a statistic of interest, say $\hat{\theta}(\mathbf{y})$, to which we wish to assign an estimated standard error.

Fig. 1 shows an example. The sample space $\mathscr{X}$ is $\mathbb{R}^{2+}$, the positive quadrant of the plane. We have observed $n = 15$ bivariate data points, each corresponding to an American law school. Each point x_i consists of two summary statistics for the 1973 entering class at law school i

$$x_i = (\text{LSAT}_i, \text{GPA}_i); \tag{2.1}$$

LSAT_i is the class' average score on a nationwide exam called "LSAT"; GPA_i is the class' average undergraduate grades. The observed Pearson correlation

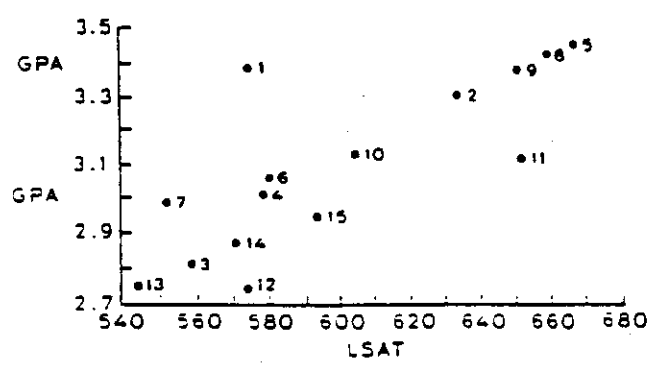

FIG. 1. *The law school data (Efron, 1979b). The data points, beginning with School 1, are* (576, 3.39), (635, 3.30), (558, 2.81), (578, 3.03), (666, 3.44), (580, 3.07), (555, 3.00), (661, 3.43), (651, 3.36), (605, 3.13), (653, 3.12), (575, 2.74), (545, 2.76), (572, 2.88), (594, 2.96).

coefficient for these 15 points is $\hat{\theta} = .776$. We wish to assign a standard error to this estimate.

Let $\sigma(F)$ indicate the standard error of $\hat{\theta}$, as a function of the unknown sampling distribution F,

$$\sigma(F) = [\mathrm{Var}_F\{\hat{\theta}(\mathbf{y})\}]^{1/2}. \tag{2.2}$$

Of cou[illegible] a function of the sample size n and the form of the statistic $\hat{\theta}(\mathbf{y})$, but since both of these are known they need not be indicated in the notat[illegible] bootstrap estimate of standard error is

$$\hat{\sigma} = \sigma(\hat{F}), \tag{2.3}$$

wher[illegible] empirical distribution (1.4), putting [illegible] data point x_i. In the [illegible] ution putting mass $1/15$ on each point in Fig. 1, and $\hat{\sigma}$ is the standard devia[illegible] of the correlation coefficient for 15 iid points draw[illegible]

In most cases, including that of the correlation coefficient, there is no simple expression for the function $\sigma(F)$ in (2.2). Nevertheless, it is easy to numerically evaluate $\hat{\sigma} = \sigma(\hat{F})$ by means of a Monte Carlo algorithm, which depends on the following notation: $\mathbf{y}^* = (x_1^*, \ldots, x_n^*)$ indicates n independent draws from $\hat{F}$, called a *bootstrap sample*. Because $\hat{F}$ is the empirical distribution of the data, a bootstrap sample turn[illegible] same as a random sample of size n d[illegible] *replacement* from the actual sample $\{x_1, \ldots, x_n\}$.

The Monte Carlo algorithm proceeds in three steps: (i) using a random number generator, independently draw a large number of bootstrap samples, say $\mathbf{y}^*(1)$, $\mathbf{y}^*(2)$, [illegible] $\mathbf{y}^*(B)$; (ii) for each bootstrap sample $\mathbf{y}^*(b)$, evaluate the statistic of interest, say $\hat{\theta}^*(b) = \hat{\theta}(\mathbf{y}^*(b))$, $b = 1, 2, \ldots, B$, and (iii) calculate the sample standard de[illegible] values

$$\hat{\sigma}_B = \left(\frac{\sum_{b=1}^{B} \{\hat{\theta}^*(b) - \hat{\theta}^*(\cdot)\}^2}{B-1}\right)^{1/2}, \tag{2.4}$$

$$\hat{\theta}^*(\cdot) = \frac{\sum_{b=1}^{B} \hat{\theta}^*(b)}{B}.$$

It is easy to see that as $B \to \infty$, $\hat{\sigma}_B$ will approach $\hat{\sigma} = \sigma(\hat{F})$, the bootstrap estimate of standard error. All we are doing is evaluating a standard deviation by Monte Carlo sampling. Later, in Section 9, we will discuss how large B need be taken. For most [illegible] range 50 to 200 is quite adequate. In what follows we will usually ignore the difference between $\hat{\sigma}$ and $\hat{\sigma}_B$, calling both simply "$\hat{\sigma}$."

[illegible] bootstrap sample taken with the same sample size n as the original data set? Remember that $\sigma(F)$ is actually $\sigma(F, n, \theta)$, the standard error for the statistic $\hat{\theta}$ based on a random sample of size n from [illegible] The bootstrap estimate $\hat{\sigma}$ is actually $\sigma(\hat{F}, n, \hat{\theta})$ evaluated at $F = \hat{F}$. The Monte Carlo algorithm will not converge to $\hat{\sigma}$ if the bootstrap sample size differs from the true n. Bickel and Freedman (1981) show how to correct the algorithm to give $\hat{\sigma}$ if in fact the bootstrap sample size is taken different than n, but so far there does not seem to be any practical advantage to be gained in this way.

Fig. 2 shows the histogram of $B = 1000$ bootstrap replications of the correlation coefficient from the law school data. For convenient reference the abscissa is plotted in terms of $\hat{\theta}^* - \hat{\theta} = \hat{\theta}^* - .776$. Formula (2.4) gives $\hat{\sigma} = .127$ as the bootstrap estimate of standard error. This can be compared with the usual normal theory estimate of standard error for $\hat{\theta}$,

$$\hat{\sigma}_{\mathrm{NORM}} = (1 - \hat{\theta}^2)/(n-3)^{1/2} = .115, \tag{2.5}$$

[Johnson and Kotz (1970, p. 229)].

REMARK. The Monte Carlo algorithm leading to $\hat{\sigma}_B$ (2.4) is simple to program. On the Stanford version of the statistical computing language S, Professor Arthur Owen has introduced a single command which bootstraps any statistic in the S catalog. For instance the bootstrap results in Fig. 2 are obtained simply by typing

```
tboot(lawdata, correlation, B = 1000).
```

The execution time is about a factor of B greater than that for the original computation.

There is another way to describe the bootstrap standard error: $\hat{F}$ is the nonparametric maximum likelihood estimate (MLE) of the unknown distribution F (Kiefer and Wolfowitz, 1956). This means that the bootstrap estimate $\hat{\sigma} = \sigma(\hat{F})$ is the nonparametric MLE of $\sigma(F)$, the true standard error.

In fact there is nothing which says that the bootstrap must be carried out nonparametrically. Suppose for instance that in the law school example we believe the true sampling distribution F must be bivariate normal. Then we could estimate F with its *parametric* MLE $\hat{F}_{\mathrm{NORM}}$, the bivariate normal distribution having the same mean vector and covariance matrix as the

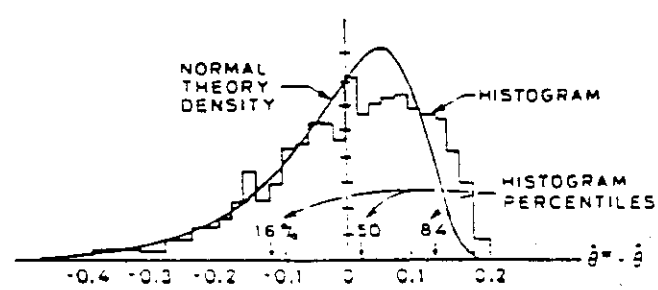

FIG. 2. *Histogram of $B = 1000$ bootstrap replications of $\hat{\theta}^*$ for the law school data. The normal theory density curve has a similar shape, but falls off more quickly at the upper tail.*

data. The bootstrap samples at step (i) of the algorithm could then be drawn from $\hat{F}_{\text{NORM}}$ instead of $\hat{F}$, and steps (ii) and (iii) carried out as before.

The smooth curve in Fig. 2 shows the results of carrying out this "normal theory bootstrap" on the law school data. Actually there is no need to do the bootstrap sampling in this case, because of Fisher's formula for the sampling density of a correlation coefficient in the bivariate normal situation (see Chapter 32 of [illegible] and Kotz, 1970). This density can be thought of as the bootstrap distribution for $B = \infty$. Expression (2.5) is a close approximation to $\hat{\sigma}_{\text{NORM}} = \sigma(\hat{F}_{\text{NORM}})$, the parametric bootstrap estimate of standard [illegible]

[illegible] of the bootstrap, [illegible] remembering that all of the usual formulas for estimating standard errors, like $\hat{\mathcal{I}}^{-1/2}$ where [illegible] is the observed Fisher information, are essentially bootstrap estimates carried out in a parametric framework. This point is carefully explained in Section 5 of Efron (1982c). The straightforward nonparametric algorithm (i)–(iii) has the virtues of avoiding all parametric assumptions, all approximations (such as those involved with the Fisher information expression for the standard error of an MLE), and in fact all analytic difficulties of any kind. The data analyst is free to obtain standard errors for enormously complicated estimators, subject only to the constraints of computer time. Sections 3 and 6 discuss some interesting applied problems which are far too complicated for standard analyses.

How well does the bootstrap work? Table 1 shows the answer in one situation. Here $\mathcal{X}$ is the real line, $n = 15$, and the statistic $\hat{\theta}$ of interest is the 25% trimmed mean. If the true sampling distribution F is $N(0, 1)$, then the true standard error is $\sigma(F) = .286$. The bootstrap estimate $\hat{\sigma}$ is nearly unbiased, averaging .287 in a large sampling experiment. The standard deviation of the bootstrap estimate $\hat{\sigma}$ is itself .071 in this case, with coefficient of variation .071/.287 = .25. (Notice that there are two levels of Monte Carlo involved in Table 1: first drawing the actual samples $\mathbf{y} = (x_1, x_2, \cdots, x_{15})$ from F, and then drawing bootstrap samples $(x_1^*, x_2^*, \cdots, x_{15}^*)$ with $\mathbf{y}$ held fixed. The bootstrap samples evaluate $\hat{\sigma}$ for a fixed value of $\mathbf{y}$. The standard deviation .071 refers to the variability of $\hat{\sigma}$ due to the random choice of $\mathbf{y}$.)

The jackknife, another common method of assigning nonparametric standard errors, is discussed in Section 10. The jackknife estimate $\hat{\sigma}_J$ is also nearly unbiased for $\sigma(F)$, but has higher coefficient of variation (CV). The minimum possible CV for a scale-invariant estimate of $\sigma(F)$, assuming full knowledge of the parametric model, is shown in brackets. The nonparametric bootstrap is seen to be moderately efficient in both cases considered in Table 1.

Table 2 returns to the case of $\hat{\theta}$ the correlation coefficient. Instead of real data we have a sampling experiment in which the true F is bivariate normal, true correlation $\theta = .50$, sample size $n = 14$. Table 2 is abstracted from a larger table in Efron (1981b), in

TABLE 1

A sampl[illegible] bootstrap and jackknife estim[illegible] for the 25% trimmed mean, sample size $n = 15$

	F standard normal			F negative exponential		
	Ave	SD	CV	Ave	SD	CV
Bootstrap $\hat{\sigma}$ ($B = 200$)	.287	.071	.25	.242	.078	.32
Jackknife	.280	.084	.30	.224	.085	.38
True [illegible]	[illegible]		(.19)	.232		(.27)

TABLE 2

Estimates of standard error for the correlation coefficient $\hat{\theta}$ and for $\hat{\phi} = \tanh^{-1}\hat{\theta}$; sample size $n = 14$, distribution F bivariate normal with true correlation $\rho = .5$ (from a larger table in Efron, 1981b)

	Summary statistics for 200 trials							
	Standard error estimates for $\hat{\theta}$				Standard error estimates for $\hat{\phi}$			
	Ave	SD	CV	$\sqrt{\text{MSE}}$	Ave	SD	CV	$\sqrt{\text{MSE}}$
1. Bootstrap $B = 128$	.206	.066	.32	.067	.301	.065	.22	.065
2. Bootstrap $B = 512$	.206	.063	.31	.064	.301	.062	.21	.062
3. Normal smoothed bootstrap $B = 128$	.200	.060	.30	.063	.296	.041	.14	.041
4. Unsmoothed bootstrap $B = 128$	.205	.061	.30	.062	.298	.058	.19	.058
5. Unsmoothed bootstrap $B = 512$	.205	.059	.29	.060	.296	.052	.18	.052
6. Jackknife	.223	.085	.38	.085	.314	.090	.29	.091
7. Delta method (Infinitesimal jackknife)	.175	.058	.33	.072	.244	.052	.21	.076
8. Normal theory	.217	.056	.26	.056	.302	0	0	.003
True standard error	.218				.299			

which some of the methods for estimating a standard error required the sample size to be even.

The left side of Table 2 refers to $\hat{\theta}$, while the right side refers to $\hat{\phi} = \tanh^{-1}(\hat{\theta}) = .5 \log(1 + \hat{\theta})/(1 - \hat{\theta})$. For each estimator of standard error, the root mean squared error of estimation $[E(\hat{\sigma} - \sigma)^2]^{1/2}$ is given in the column headed $\sqrt{\text{MSE}}$.

The bootstrap was run with $B = 128$ and also with $B = 512$, the latter value yielding only slightly better estimates in accordance with the results of Section 9. Further increasing B would be pointless. It can be shown that $B = \infty$ gives $\sqrt{\text{MSE}} = .063$ for $\hat{\theta}$, only .001 less than $B = 512$. The normal theory estimate (2.5), which we know to be ideal for this sampling experiment, has $\sqrt{\text{MSE}} = .056$.

We can compromise between the totally nonparametric bootstrap estimate $\hat{\sigma}$ and the totally parametric bootstrap estimate $\hat{\sigma}_{\text{NORM}}$. This is done in lines 3, 4, and 5 of Table 2. Let $\hat{\Sigma} = \sum_{i=1}^{n} (x_i - \bar{x})(x_i - \bar{x})'/n$ be the sample covariance matrix of the observed data. The *normal smoothed bootstrap* draws the bootstrap sample from $\hat{F} \oplus N_2(0, .25\hat{\Sigma})$, $\oplus$ indicating convolution. This amounts to estimating F by an equal mixture of the n distributions $N_2(x_i, .25\hat{\Sigma})$, that is by a normal window estimate. Each point x_i^* in a smoothed bootstrap sample is the sum of a randomly selected original data point x_j, plus an independent bivariate normal point $z_i \sim N_2(0, .25\hat{\Sigma})$. Smoothing makes little difference on the left side of the table, but is spectacularly effective in the $\hat{\phi}$ case. The latter result is suspect since the true sampling distribution is bivariate normal, and the function $\hat{\phi} = \tanh^{-1}\hat{\theta}$ is specifically chosen to have nearly constant standard error in the bivariate normal family. The *uniform smoothed bootstrap* samples from $\hat{F} \oplus \mathcal{U}(0, .25\hat{\Sigma})$, where $\mathcal{U}(0, .25\hat{\Sigma})$ is the uniform distribution on a rhombus selected so $\mathcal{U}$ has mean vector 0 and covariance matrix $.25\hat{\Sigma}$. It yields moderate reductions in $\sqrt{\text{MSE}}$ for both sides of the table.

Line 6 of Table 2 refers to the *delta method*, which is the most common method of assigning nonparametric standard error. Surprisingly enough, it is badly biased downward on both sides of the table. The delta method, also known as the method of statistical differentials, the Taylor series method, and the infinitesimal jackknife, is discussed in Section 10.

3. EXAMPLES

Example 1. Cox's Proportional Hazards Model

In this section we apply bootstrap standard error estimation to some complicated statistics.

The data for this example come from a study of leukemia remission times in mice, taken from Cox (1972). They consist of measurements of remission time (y) in weeks for two groups, treatment ($x = 0$) and control ($x = 1$), and a 0–1 variable (δ_i) indicating whether or not the remission time is censored (0) or complete (1). There are 21 mice in each group.

The standard regression model for censored data is Cox's proportional hazards model (Cox, 1972). It assumes that the hazard function $h(t \mid x)$, the probability of going into remission in next instant given no remission up to time t for a mouse with covariate x, is of the form

$$h(t \mid x) = h_0(t)e^{\beta x}. \tag{3.1}$$

Here $h_0(t)$ is an arbitrary unspecified function. Since x here is a group indicator, this means simply that the hazard for the control group is e^{β} times the hazard for the treatment group. The regression parameter β is estimated independently of $h_0(t)$ through maximization of the so called "partial likelihood"

$$\text{PL} = \prod_{i \in D} \frac{e^{\beta x_i}}{\sum_{j \in R_i} e^{\beta x_j}}, \tag{3.2}$$

where D is the set of indices of the failure times and R_i is the set of indices of those at risk at time y_i. This maximization requires an iterative computer search.

The estimate $\hat{\beta}$ for these data turns out to be 1.51. Taken literally, this says that the hazard rate is $e^{1.51} = 4.33$ times higher in the control group than in the treatment group, so the treatment is very effective. What is the standard error of $\hat{\beta}$? The usual asymptotic maximum likelihood theory, one over the square root of the observed Fisher information, gives an estimate of .41. Despite the complicated nature of the estimation procedure, we can also estimate the standard error using the bootstrap. We sample with replacement from the triples $\{(y_1, x_1, \delta_1), \cdots, (y_{42}, x_{42}, \delta_{42})\}$. For each bootstrap sample $\{(y_1^*, x_1^*, \delta_1^*), \cdots, (y_{42}^*, x_{42}^*, \delta_{42}^*)\}$ we form the partial likelihood and numerically maximize it to produce the bootstrap estimate $\hat{\beta}^*$. A histogram of 1000 bootstrap values is shown in Fig. 3.

The bootstrap estimate of the standard error of $\hat{\beta}$ based on these 1000 numbers is .42. Although the bootstrap and standard estimates agree, it is interesting to note that the bootstrap distribution is skewed to the right. This leads us to ask: is there other information that we can extract from the bootstrap distribution other than a standard error estimate? The answer is yes—in particular, the bootstrap distribution can be used to form a confidence interval for β, as we will see in Section 9. The shape of the bootstrap distribution will help determine the shape of the confidence interval.

In this example our resampling unit was the triple (y_i, x_i, δ_i), and we ignored the unique elements of the problem, i.e., the censoring, and the particular model being used. In fact, there are other ways to bootstrap

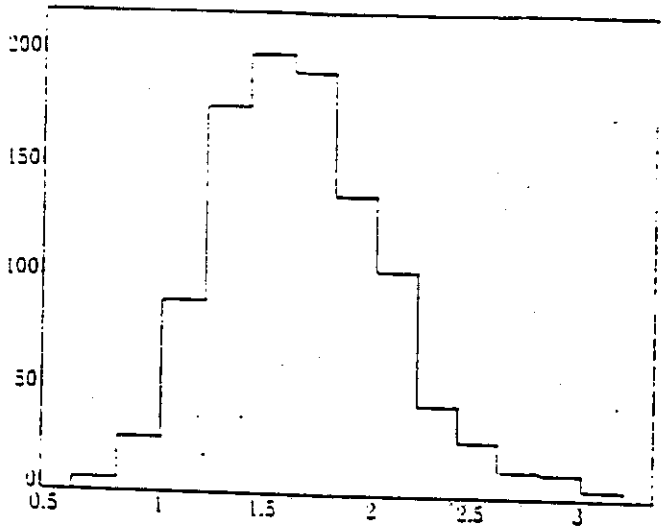

FIG. 3. *Histogram of 1000 bootstrap replications for the mouse leukemia data.*

this problem. We will see this when we discuss bootstrapping censored data in Section 5.

Example 2: Linear and Projection Pursuit Regression

We illustrate an application of the bootstrap to standard linear least squares regression as well as to a nonparametric regression technique.

Consider the standard regression setup. We have n observations on a response Y and covariates $(X_1, X_2, \cdots, X_p)$. Denote the ith observed vector of covariates by $x_i = (x_{i1}, x_{i2}, \cdots, x_{ip})'$. The usual linear regression model assumes

$$E(Y_i) = \alpha + \sum_{j=1}^{p} \beta_j x_{ij}. \tag{3.3}$$

Friedman and Stuetzle (1981) introduced a more general model, the *projection pursuit* regression model

$$E(Y_i) = \sum_{j=1}^{m} s_j(a_j \cdot x_i). \tag{3.4}$$

The p vectors a_j are unit vectors ("directions"), and the functions $s_j(\cdot)$ are unspecified.

Estimation of $\{a_1, s_1(\cdot)\}, \cdots, \{a_m, s_m(\cdot)\}$ is performed in a forward stepwise manner as follows. Consider $\{a_1, s_1(\cdot)\}$. Given a direction a_1, $s_1(\cdot)$ is estimated by a nonparametric smoother (e.g., running mean) of y on $a_1 \cdot x$. The projection pursuit regression algorithm searches over all unit directions to find the direction $\hat{a}_1$ and associated function $\hat{s}_1(\cdot)$ that minimize $\sum_i (y_i - \hat{s}_1(\hat{a} \cdot x_i))^2$. Then residuals are taken and the next direction and function are determined. This process is continued until no additional term significantly reduces the residual sum of squares.

Notice the relation of the projection pursuit regression model to the standard linear regression model. When the function $s_1(\cdot)$ is forced to be linear and is estimated by the usual least squares method, a one-term projection pursuit model is exactly the same as the standard linear regression model. That is to say, the fitted model $\hat{s}_1(\hat{a}_1 \cdot x_i)$ exactly equals the least squares fit $\hat{\alpha} + \sum_{j=1}^{p} \hat{\beta}_j x_{ij}$. This is because the least squares fit, by definition, finds the best direction and the best linear function of that direction. Note also that adding another linear term $\hat{s}_2(\hat{a}_2 \cdot x_2)$ would not change the fitted model since the sum of two linear functions is another linear function.

Hastie and Tibshirani (1984) applied the bootstrap to the linear and projection pursuit regression models to assess the variability of the coefficients in each. The data they considered are taken from Breiman and Friedman (1985). The response Y is Upland atmospheric ozone concentration (ppm); the covariates X_1 = Sandburg Air Force base temperature (C°), X_2 = inversion base height (ft), X_3 = Daggot pressure gradient (mm Hg), X_4 = visibility (miles), and X_5 = day of the year. There are 330 observations. The number of terms (m) in the model (3.4) is taken to be two. The projection pursuit algorithm chose directions $\hat{a}_1 = (.80, -.38, .37, -.24, -.14)'$ and $\hat{a}_2 = (.07, .16, .04, -.05, -.98)'$. These directions consist mostly of Sandburg Air Force temperature and day of the year, respec-

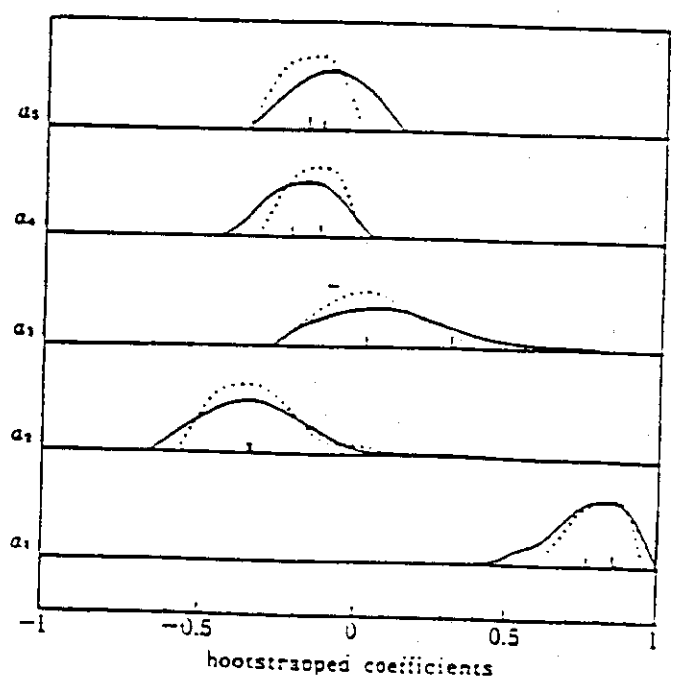

FIG. 4. *Smoothed histograms of the bootstrapped coefficients for the first term in the projection pursuit regression model. Solid histograms are for the usual projection pursuit model; the dotted histograms are for linear $s(\cdot)$.*

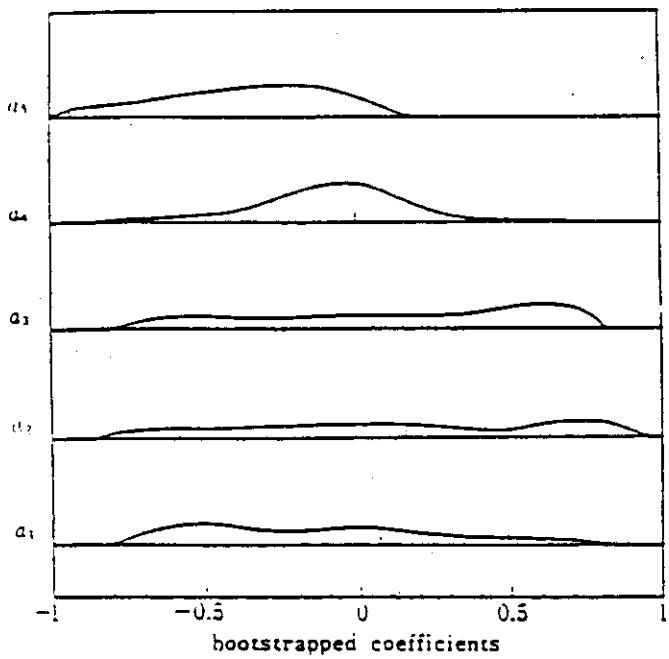

FIG. 5. *Smoothed histograms of the bootstrapped coefficients for the second term in the projection pursuit model.*

tively. (We do not show graphs of the estimated functions $\hat{s}_1(\cdot)$ and $\hat{s}_2(\cdot)$ although in a full analysis of the data they would also be of interest.) Forcing $\hat{s}_1(\cdot)$ to be linear results in the direction $\hat{a}_1 = (.90, -.37, .03, -.14, -.19)'$. These are just the usual least squares estimates $\hat{\beta}_1, \cdots, \hat{\beta}_p$ scaled so that $\sum_1^p \hat{\beta}_j^2 = 1$.

To assess the variability of the directions, a bootstrap sample is drawn with replacement from $(y_1, x_{11}, \cdots, x_{15}), \cdots, (y_{330}, x_{3301}, \cdots, x_{3305})$ and the projection pursuit algorithm is applied. Figs. 4 and 5 show histograms of the directions $\hat{a}_1^*$ and $\hat{a}_2^*$ for 200 bootstrap replications. Also shown in Fig. 4 (broken histogram) are the bootstrap replications of $\hat{a}_1$ with $\hat{s}_1(\cdot)$ forced to be linear.

The first direction of the projection pursuit model is quite stable and only slightly more variable than the corresponding linear regression direction. But the second direction is extremely unstable! It is clearly unwise to put any faith in the second direction of the original projection pursuit model.

Example 3: Cox's Model and Local Likelihood Estimation

In this example, we return to Cox's proportional hazards model described in Example 1, but with a few added twists.

The data that we will discuss come from the Stanford heart transplant program and are given in Miller and Halpern (1982). The response y is survival time in weeks after a heart transplant, the covariate x is age at transplant, and the 0–1 variable δ indicates whether the survival time is censored (0) or complete (1). There are measurements on 157 patients. A proportional hazards model was fit to these data, with a quadratic term, i.e. $h(t \mid x) = h_0(t)e^{\hat{\beta}_1 x + \hat{\beta}_2 x^2}$. Both $\hat{\beta}_1$ and $\hat{\beta}_2$ are highly significant; the broken curve in Fig. 6 is $\hat{\beta}_1 x + \hat{\beta}_2 x^2$ as a function of x.

For comparison, Fig. 6 shows (solid line) another estimate. This was computed using *local likelihood estimation* (Tibshirani and Hastie, 1984). Given a general proportional hazards model of the form $h(t \mid x) = h_0(t)e^{s(x)}$, the local likelihood technique assumes nothing about the parametric form of $s(x)$; instead it estimates $s(x)$ nonparametrically using a kind of local averaging. The algorithm is very computationally intensive, and standard maximum likelihood theory cannot be applied.

A comparison of the two functions reveals an important qualitative difference: the parametric estimate suggests that the hazard decreases sharply up to age 34, then rises; the local likelihood estimate stays approximately constant up to age 45 then rises. Has the forced fitting of a quadratic function produced a misleading result? To answer this question, we can bootstrap the local likelihood estimate. We sample with replacement from the triples $\{(y_1, x_1, \delta_1) \cdots (y_{157}, x_{157}, \delta_{157})\}$ and apply the local likelihood algorithm to each bootstrap sample. Fig. 7 shows estimated curves from 20 bootstrap samples.

Some of the curves are flat up to age 45, others are decreasing. Hence the original local likelihood estimate is highly variable in this region and on the basis of these data we cannot determine the true behavior of the function there. A look back at the original data shows that while half of the patients were under 45, only 13% of the patients were under 30. Fig. 7 also shows that the estimate is stable near the middle ages but unstable for the older patients.

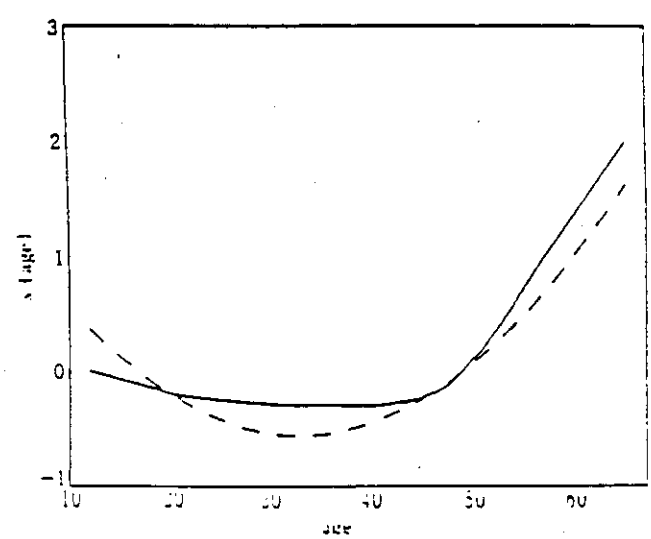

FIG. 6. *Estimates of log relative risk for the Stanford heart transplant data. Broken curve: parametric estimate. Solid curve: local likelihood estimate.*

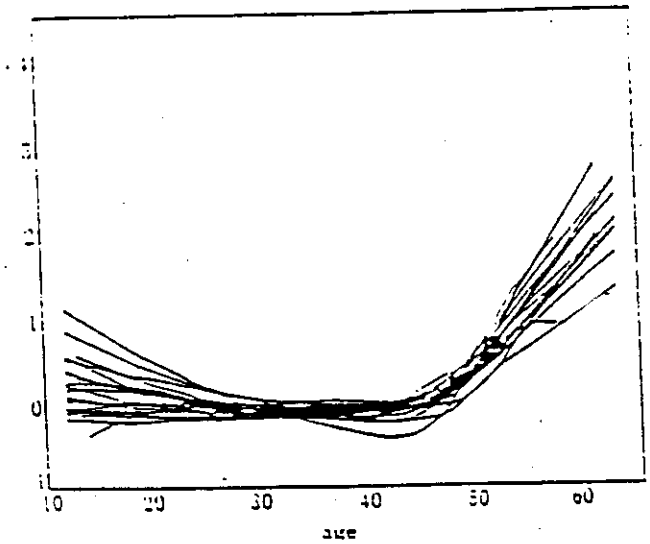

FIG. 7. 20 bootstraps of the local likelihood estimate for the Stanford heart transplant data.

4. OTHER MEASURES OF STATISTICAL ERROR

So far we have discussed statistical error, or accuracy, in terms of the standard error. It is easy to assess other measures of statistical error, such as bias or prediction error, using the bootstrap.

Consider the estimation of bias. For a given statistic $\hat{\theta}(\mathbf{y})$, and a given parameter $\mu(F)$, let

$$R(\mathbf{y}, F) = \hat{\theta}(\mathbf{y}) - \mu(F). \tag{4.1}$$

(It will help keep our notation clear to call the parameter of interest μ rather than θ.) For example, μ might be the mean of the distribution F, assuming the sample space $\mathcal{X}$ is the real line, and $\hat{\theta}$ the 25% trimmed mean. The bias of $\hat{\theta}$ for estimating μ is

$$\beta(F) = E_F R(\mathbf{y}, F) = E_F\{\hat{\theta}(\mathbf{y})\} - \mu(F). \tag{4.2}$$

The notation E_F indicates expectation with respect to the probability mechanism appropriate to F, in this case $\mathbf{y} = (x_1, x_2, \cdots, x_n)$ a random sample from F.

The bootstrap estimate of bias is

$$\hat{\beta} = \beta(\hat{F}) = E_{\hat{F}} R(\mathbf{y}^*, \hat{F}) = E_{\hat{F}}\{\hat{\theta}(\mathbf{y}^*)\} - \mu(\hat{F}). \tag{4.3}$$

As in Section 2, $\mathbf{y}^*$ denotes a random sample $(x_1^*, x_2^*, \cdots, x_n^*)$ from $\hat{F}$, i.e., a bootstrap sample. To numerically evaluate $\hat{\beta}$, all we do is change step (iii) of the bootstrap algorithm in Section 2 to

$$\begin{aligned} \hat{\beta}_B &= \frac{1}{B}\sum_{b=1}^{B} R(\mathbf{y}^*(b), \hat{F}) \\ &= \frac{\sum_{b=1}^{B} \hat{\theta}^*(b)}{B} - \mu(\hat{F}) \\ &= \hat{\theta}^*(\cdot) - \mu(\hat{F}). \end{aligned} \tag{4.4}$$

As $B \to \infty$, $\hat{\beta}_B$ goes to $\hat{\beta}$ (4.3).

TABLE 3

BHCG blood serum levels for 54 patients having metastasized breast cancer in ascending order

0.1.	0.1.	0.2.	0.4.	0.4.	0.6.	0.8.	0.8.	0.9.	0.9.	1.2.	1.3.	1.4.	1.5.	1.6.	1.6.	1.7.	1.7.	1.7.	1.8.	2.0.	2.0.	2.2.	2.2.	2.2.	2.3.	2.3.	2.4.	2.4.	2.4.	2.4.	2.4.	2.5.	2.5.	2.5.	2.7.	2.7.	2.8.	2.9.	2.9.	2.9.	3.0.	3.1.	3.1.	3.2.	3.2.	3.3.	3.3.	3.5.	4.4.	4.5.	6.4.	9.4

As an example consider the blood serum data of Table 3. Suppose we wish to estimate the true mean $\mu = E_F\{X\}$ of this population using $\hat{\theta}$, the 25% trimmed mean. We calculate $\hat{\mu} = \mu(\hat{F}) = 2.32$, the sample mean of the 54 observations, and $\hat{\theta} = 2.24$, the trimmed mean. The trimmed mean is lower because it discounts the effect of the large observations 6.4 and 9.4. It looks like the trimmed mean might be more robust for this type of data, and as a matter of fact a bootstrap analysis, $B = 1000$, gave estimated standard error $\hat{\sigma} = .16$ for $\hat{\theta}$, compared to .21 for the sample mean. But what about bias?

The same 1000 bootstrap replications which gave $\hat{\sigma} = .16$ also gave $\hat{\theta}^*(\cdot) = 2.29$, so

$$\hat{\beta} = 2.29 - 2.32 = -0.03. \tag{4.5}$$

according to (4.4). (The estimated standard deviation of $\hat{\beta}_B - \hat{\beta}$ due to the limitations of having $B = 1000$ bootstraps is only 0.005 in this case, so we can ignore the difference between $\hat{\beta}_B$ and $\hat{\beta}$.) Whether or not a bias of magnitude -0.03 is too large depends on the context of the problem. If we attempt to remove the bias by subtraction, we get $\hat{\theta} - \hat{\beta} = 2.24 - (-0.03) = 2.27$. Removing bias in this way is frequently a bad idea (see Hinkley, 1978), but at least the bootstrap analysis has given us a reasonable picture of the bias and standard error of $\hat{\theta}$.

Here is another measure of statistical accuracy, different from either bias or standard error. Let $\hat{\theta}(\mathbf{y})$ be the 25% trimmed mean and $\mu(F)$ be the mean of F, as in the serum example, and also let $\hat{\iota}(\mathbf{y})$ be the interquartile range, the distance between the 25th and 75th percentiles of the sample $\mathbf{y} = (x_1, x_2, \cdots, x_n)$. Define

$$R(\mathbf{y}, F) = \frac{\hat{\theta}(\mathbf{y}) - \mu(F)}{\hat{\iota}(\mathbf{y})}. \tag{4.6}$$

R is like a Student's t statistic, except that we have substituted the 25% trimmed mean for the sample mean and the interquartile range for the standard deviation.

Suppose we know the 5th and 95th percentiles of $R(\mathbf{y}, F)$, say $\rho^{(.05)}(F)$ and $\rho^{(.95)}(F)$, where the definition of $\rho^{(.05)}(F)$ is

$$\text{Prob}_F\{R(\mathbf{y}, F) < \rho^{(.05)}(F)\} = .05, \tag{4.7}$$

and similarly for $\rho^{(.95)}(F)$. The relationship $\text{Prob}_F\{\rho^{(.05)} \le R < \rho^{(.95)}\} = .90$ combines with definition (4.6) to

give a central 90% "t interval" for the mean $\mu(F)$,

$$\mu \in [\hat{\theta} - \hat{\iota}\rho^{(.95)}, \hat{\theta} - \hat{\iota}\rho^{(.05)}]. \tag{4.8}$$

Of course we do not know $\rho^{(.05)}(F)$ and $\rho^{(.95)}(F)$, but we can approximate them by their bootstrap estimates $\rho^{(.05)}(\hat{F})$ and $\rho^{(.95)}(\hat{F})$. A bootstrap sample $\mathbf{y}^*$ g[illegible] [illegible] value of (4.6), $R(\mathbf{y}^*, \hat{F}) = (\hat{\theta}(\mathbf{y}^*) - \mu(\hat{F}))/\hat{\iota}(\mathbf{y}^*)$, where $\hat{\iota}(\mathbf{y}^*)$ is the interquartile range of the bootstrap data $x_1^*, x_2^*, \cdots, x_n^*$. For any [illegible] number ρ, the bootstrap estimate of Pro[illegible] [illegible] B bootstrap samples is

$$\#\{R(\mathbf{y}^*(b), \hat{F}) < \rho\}/B. \tag{4.9}$$

B[illegible] [illegible] empirical distribution of [illegible] the values of ρ which make (4.9) equal .05 and .95. These approach $\rho^{(.05)}(\hat{F})$ and [illegible] as $B \to \infty$.

For [illegible] data, $B = 1000$ bootstrap replications gave $\rho^{(.05)}(\hat{F}) = -.303$ and $\rho^{(.95)}(\hat{F}) = .078$. Substituting these values into (4.9), and using the observed estimates $\hat{\theta} = 2.24$, $\hat{\iota} = 1.40$, gives

$$\mu \in [2.13, 2.66] \tag{4.10}$$

as a [illegible] 90% "bootstrap t interval" for the true mean $\mu(F)$. This is considerably shorter than the stand[illegible] interval for μ based on 53 degrees of freedom [illegible] 2.67]. Here $\hat{\sigma} = .21$ is the usual estimate of standard error (1.3).

Bootstrap confidence intervals are discussed further in Sections [illegible] and 8. They require more bootstrap replications than do bootstrap standard errors, on the order of $B = 1000$ rather than $B = 50$ or 100. This point is discussed briefly in Section 9.

By now it should be clear that we can use any random variable $R(\mathbf{y}, F)$ to measure accuracy, not just (4.[illegible]). [illegible] then estimate $E_F\{R(\mathbf{y}, F)\}$ by its [illegible] $\hat{F})\} \doteq \sum_{b=1}^{B} R(\mathbf{y}^*(b), \hat{F})/B$. Si[illegible] we can estimate $E_F R(\mathbf{y}, F)^2$ by $E_{\hat{F}} R(\mathbf{y}^*, \hat{F})^2$, etc. Efron (1983) considers the prediction problem, in [illegible] data is used to construct a pr[illegible] [illegible] naive estimate of the prediction rule's accuracy is the proportion of correct guesses it makes on its own training set, but this can be greatly [illegible] since the prediction rule is explicitly co[illegible] to minimize errors on the training set. In this case, a natural choice of $R(\mathbf{y}, F)$ is the over optimism, the difference between the naive estimate and [illegible] success rate of the prediction rule for new data. Efron (1983) gives the bootstrap estimate of over optimism and shows that it is closely related to [illegible] cross-validation, the usual method of estimating over optimism. The paper goes on to show that some modifications of the bootstrap estimate greatly outperform both cross-validation and the bootstrap.

5. MORE COMPLICATED DATA SETS

The bootstrap is not restricted to situations where the data is a simple random sample from a single distribution. Suppose for instance that the data consists of two independent random samples,

$$\begin{aligned} &U_1, U_2, \cdots, U_m \sim F \quad \text{and} \\ &V_1, V_2, \cdots, V_n \sim G, \end{aligned} \tag{5.1}$$

where F and G are possibly different distributions on the real line. Suppose also that the statistic of interest is the Hodges–Lehmann shift estimate

$$\hat{\theta} = \text{median}\{V_j - U_i, i = 1, 2, \cdots, m, j = 1, 2, \cdots, n\}. \tag{5.2}$$

Having observed $U_1 = u_1$, $U_2 = u_2$, $\cdots$, $V_n = v_n$, we desire an estimate for $\sigma(F, G)$, the standard error of $\hat{\theta}$.

The bootstrap estimate of $\sigma(F, G)$ is $\hat{\sigma} = \sigma(\hat{F}, \hat{G})$, where $\hat{F}$ is the empirical distribution of $u_1, u_2, \cdots, u_m$, and $\hat{G}$ is the empirical distribution of $v_1, v_2, \cdots, v_n$. It is easy to modify the Monte Carlo algorithm of Section 2 to numerically evaluate $\hat{\sigma}$. Let $\mathbf{y} = (u_1, u_2, \cdots, v_n)$ be the observed data vector. A bootstrap sample $\mathbf{y}^* = (u_1^*, u_2^*, \cdots, u_m^*, v_1^*, v_2^*, \cdots, v_n^*)$ consists of a random sample $U_1^*, \cdots, U_m^*$ from $\hat{F}$ and an independent random sample $V_1^*, \cdots, V_n^*$ from $\hat{G}$. With only this modification, steps (i) through (iii) of the Monte Carlo algorithm produce $\hat{\sigma}_B$, (2.4), approaching $\hat{\sigma}$ as $B \to \infty$.

Table 4 reports on a simulation experiment investigating how well the bootstrap works on this problem. 100 trials of situation (5.1) were run, with $m = 6$, $n = 9$, F and G both Uniform [0, 1]. For each trial, both $B = 100$ and $B = 200$ bootstrap replications were generated. The bootstrap estimate $\hat{\sigma}_B$ was nearly unbiased for the true standard error $\sigma(F, G) = .167$ for either $B = 100$ or $B = 200$, with a quite small standard deviation from trial to trial. The improvement in going from $B = 100$ to $B = 200$ is too small to show up in this experiment.

In practice, statisticians must often consider quite complicated data structures: time series models, mul-

TABLE 4

Bootstrap estimate of standard error for the Hodges–Lehmann two-sample shift estimate; 100 trials

	Summary statistics for $\hat{\sigma}_B$		
	Ave	SD	CV
$B = 100$	.165	.030	.18
$B = 200$	.166	.031	.19
True σ	.167		

Note: $m = 6$, $n = 9$; true distributions F and G both uniform [0, 1].

tifactor layouts, sequential sampling, censored and missing data, etc. Fig. 8 illustrates how the bootstrap estimation process proceeds in a general situation. The actual probability mechanism P which generates the observed data $\mathbf{y}$ belongs to some family $\mathcal{P}$ of possible probability mechanism. In the Hodges–Lehmann example, $\mathcal{P} = (F, G)$, a pair of distributions on the real line, P equals the family of all such pairs, and $\mathbf{y} = (u_1, u_2, \cdots, u_m, v_1, v_2, \cdots, v_n)$ is generated by random sampling m times from F and n times from G.

We have a random variable of interest $R(\mathbf{y}, P)$, which depends on both $\mathbf{y}$ and the unknown model P, and we wish to estimate some aspect of the dis- [illegible] the Hodges–Lehmann example, $R(\mathbf{y}, P) = \hat{\theta}(\mathbf{y}) - E_P\{\hat{\theta}\}$, and we estimated $\sigma(P) = \{E_P R(\mathbf{y}, P)^2\}^{1/2}$, the standard error of $\hat{\theta}$. As before, the notation E_P indicates expectation when $\mathbf{y}$ is generated according to mechanism P.

We assume that we have some way of estimating the entire probability model P from the data $\mathbf{y}$, producing the estimate called $\hat{P}$ in Fig. 8. (In the two-sample problem, $\hat{P} = (\hat{F}, \hat{G})$, the pair of empirical distributions.) *This is the crucial step for the bootstrap.* It can be carried out either parametrically or nonparametrically, by maximum likelihood or by some other estimation technique.

Once we have $\hat{P}$, we can use Monte Carlo methods to generate bootstrap data sets $\mathbf{y}^*$, according to the same rules by which $\mathbf{y}$ is generated from P. The bootstrap random variable $R(\mathbf{y}^*, \hat{P})$ is observable, since we know $\hat{P}$ as well as $\mathbf{y}^*$, so the distribution of $R(\mathbf{y}^*, \hat{P})$ can be found by Monte Carlo sampling. The bootstrap estimate of $E_P R(\mathbf{y}, P)$ is then $E_{\hat{P}} R(\mathbf{y}^*, \hat{P})$, and likewise for estimating any other aspect of $R(\mathbf{y}, P)$'s distribution.

A regression model is a familiar example of a complicated data structure. We observe $\mathbf{y} = (y_1, y_2, \cdots, y_n)$, where

$$(5.3) \qquad y_i = g(\beta, t_i) + \epsilon_i \quad i = 1, 2, \cdots, n.$$

Here β is a vector of unknown parameters we wish to estimate: for each i, t_i is an observed vector of covariates: and g is a known function of β and t_i, for instance $e^{\beta' t_i}$. The ϵ_i are an iid sample from some unknown distribution F on the real line.

$$(5.4) \qquad \epsilon_1, \epsilon_2, \cdots, \epsilon_n \sim F,$$

where F is usually assumed to be centered at 0 in some sense, perhaps $E\{\epsilon\} = 0$ or $\text{Prob}\{\epsilon < 0\} = .5$. The probability model is $P = (\beta, F)$; (5.3) and (5.4) describe the step $P \to \mathbf{y}$ in Fig. 8. The covariates $t_1, t_2, \cdots, t_n$, like the sample size n in the simple problem (1.1), are considered fixed at their observed values.

For every choice of β we have a vector $\mathbf{g}(\beta) = (g(\beta, t_1), g(\beta, t_2), \cdots, g(\beta, t_n))$ of predicted values for $\mathbf{y}$. Having observed $\mathbf{y}$, we estimate β by minimizing some measure of distance between $\mathbf{g}(\beta)$ and $\mathbf{y}$,

$$(5.5) \qquad \hat{\beta}: \min_{\beta} D(\mathbf{y}, \mathbf{g}(\beta)).$$

The most common choice of D is $D(\mathbf{y}, \mathbf{g}) = \sum_{i=1}^n \{y_i - g(\beta, t_i)\}^2$.

How accurate is $\hat{\beta}$ as an estimate of β? Let $R(\mathbf{y}, P)$ equal the vector $\hat{\beta} - \beta$. A familiar measure of accuracy is the mean square error matrix

$$(5.6) \qquad \begin{aligned} \Sigma(P) &= E_P(\hat{\beta} - \beta)(\hat{\beta} - \beta)' \\ &= E_P R(\mathbf{y}, P) R(\mathbf{y}, P)'. \end{aligned}$$

The bootstrap estimate of accuracy $\hat{\Sigma} = \Sigma(\hat{P})$ is obtained by following through Fig. 8.

There is an obvious choice for $\hat{P} = (\hat{\beta}, \hat{F})$ in this case. The estimate $\hat{\beta}$ is obtained from (5.5). Then $\hat{F}$ is the empirical distribution of the residuals,

$$(5.7) \qquad \hat{F}: \text{mass}(1/n) \quad \text{on} \quad \hat{\epsilon}_i = y_i - g(\hat{\beta}, t_i), \quad i = 1, \cdots, n.$$

A bootstrap sample $\mathbf{y}^*$ is obtained by following rules (5.3) and (5.4),

$$(5.8) \qquad y_i^* = g(\hat{\beta}, t_i) + \epsilon_i^*, \quad i = 1, 2, \cdots, n,$$

where $\epsilon_1^*, \epsilon_2^*, \cdots, \epsilon_n^*$ is an iid sample from $\hat{F}$. Notice that the ϵ_i^* are independent bootstrap variates, even though the $\hat{\epsilon}_i$ are not independent variates in the usual sense.

Each bootstrap sample $\mathbf{y}^*(b)$ gives a bootstrap value $\hat{\beta}^*(b)$,

$$(5.9) \qquad \hat{\beta}^*(b): \min_{\beta} D(\mathbf{y}^*(b), \mathbf{g}(\beta)),$$

as in (5.5). The estimate

$$(5.10) \qquad \hat{\Sigma}_B = \frac{\sum_{b=1}^B \{\hat{\beta}^*(b) - \hat{\beta}^*(\cdot)\}\{\hat{\beta}^*(b) - \hat{\beta}^*(\cdot)\}'}{B}$$

approaches the bootstrap estimate $\hat{\Sigma}$ as $B \to \infty$. (We could just as well divide by $B - 1$ in (5.10).)

In the case of ordinary least squares regression, where $g(\beta, t_i) = \beta' t_i$ and $D(\mathbf{y}, \mathbf{g}) = \sum_{i=1}^n (y_i - g_i)^2$,

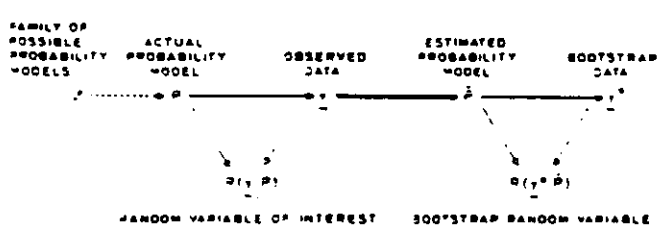

FIG. 8. *A schematic illustration of the bootstrap process for a general probability model P. The expectation of R(y, P) is estimated by the bootstrap expectation of R(y*, P̂). The double arrow indicates the crucial step in applying the bootstrap.*

Section 7 of Efron (1979a) shows that the bootstrap estimate, $B = \infty$, can be calculated without Monte Carlo sampling, and is

$$(5.11) \qquad \hat{\Sigma} = \hat{\sigma}^2\left(\sum_{i=1}^{n} t_i t_i'\right)^{-1} \quad \left[\hat{\sigma}^2 = \sum_{1}^{n} \frac{\hat{\varepsilon}_n^2}{n}\right].$$

This is the usual Gauss–Markov answer, except for the divisor n in the definition of $\hat{\sigma}^2$.

There is another, simpler way to bootstrap a regression problem. We can consider each covariate-response pair $x_i = (t_i, y_i)$ to be a single data point obtained by simple random sampling from a distribution F. If the covariate vector t_i is p-dimensional, F is a distribution on $p + 1$ dimensions. Then we apply the bootstrap as described originally in Section 2 to the data set $x_1, x_2, \cdots, x_n \sim_{\text{iid}} F$.

The two bootstrap methods for the regression problem are asymptotically equivalent, but can perform quite differently in small sample situations. The class of possible probability models P is different for the two methods. The simple method, described last, takes less advantage of the special structure of the regression problem. It does *not* give answer (5.11) in the case of ordinary least squares. On the other hand the simple method gives a trustworthy estimate of $\hat{\beta}$'s variability *even if the regression model* (5.3) *is not correct*. The bootstrap, as outlined in Fig. 5, is very general, but because of this generality there will often be more than one bootstrap solution for a given problem.

As the final example of this section, we discuss *censored data*. The ages of 97 men at a California retirement center, Channing House, were observed either at death (an uncensored observation) or at the time the study ended (a censored observation). The data set $\mathbf{y} = \{(x_1, d_1), (x_2, d_2), \cdots, (x_{97}, d_{97})\}$, where x_i was the age of the ith man observed, and

$$d_i = \begin{cases} 1 & \text{if } x_i \text{ uncensored} \\ 0 & \text{if } x_i \text{ censored.} \end{cases}$$

Thus (777, 1) represents a Channing House man observed to die at age 777 months, while (843, 0) represents a man 843 months old when the study ended. His observation could be written as "843+," and in fact d_i is just an indicator for the absence or presence of "+." A full description of the Channing House data appears in Hyde (1980).

A typical data point (X_i, D_i) can be thought of as generated in the following way: a real lifetime X_i^0 is selected randomly according to a survival curve

$$(5.12) \qquad S^0(t) \equiv \text{Prob}\{X_i^0 > t\}, \quad (0 \le t < \infty)$$

and a censoring time W_i is independently selected according to another survival curve

$$(5.13) \qquad R(t) \equiv \text{Prob}\{W_i > t\}, \quad (0 \le t < \infty).$$

The statistician gets to observe

$$(5.14) \qquad X_i = \min\{X_i^0, W_i\}$$

and

$$(5.15) \qquad D_i = \begin{cases} 1 & \text{if } X_i = X_i^0 \\ 0 & \text{if } X_i = W_i. \end{cases}$$

Note: $1 - S^0(t)$ and $1 - R(t)$ are the cumulative distribution functions (cdf) for X_i^0 and W_i, respectively; with censored data it is more convenient to consider survival curves than cdf.

Under assumptions (5.12)–(5.15) there is a simple formula for the nonparametric MLE of $S^0(t)$, called the *Kaplan–Meier estimator* (Kaplan and Meier, 1958). For convenience suppose $x_1 < x_2 < x_3 < \cdots < x_n$, $n = 97$. Then the Kaplan–Meier estimate is

$$(5.16) \qquad \hat{S}^0(t) = \prod_{j=1}^{k_t} \left(\frac{n-i}{n-i+1}\right)^{d_i},$$

where k_t is the value of k such that $t \in [x_k, x_{k+1})$. In the case of no censoring, $\hat{S}^0(t)$ is equivalent to the observed empirical distribution of $x_1, x_2, \cdots, x_n$, but otherwise (5.16) corrects the empirical distribution to account for censoring. Likewise

$$(5.17) \qquad \hat{R}(t) = \prod_{j=1}^{k_t} \left(\frac{n-i}{n-i+1}\right)^{1-d_i}$$

is the Kaplan–Meier estimate of the censoring curve $R(t)$.

Fig. 9 shows $\hat{S}^0(t)$ for the Channing House men. It crosses the 50% survival level at $\hat{\theta} = 1044$ months. Call this value the observed median lifetime. We can use the bootstrap to assign a standard error to the observed median.

The probability mechanism is $P = (S^0, R)$; P produces (X_i^0, D_i) according to (5.12)–(5.15), and $\mathbf{y} = \{(x_1, d_1), \cdots, (x_n, d_n)\}$ by $n = 97$ independent repetitions of this process. An obvious choice of the estimate $\hat{P}$ in Fig. 8 is $(\hat{S}^0, \hat{R})$, (5.14), (5.15). The rest of

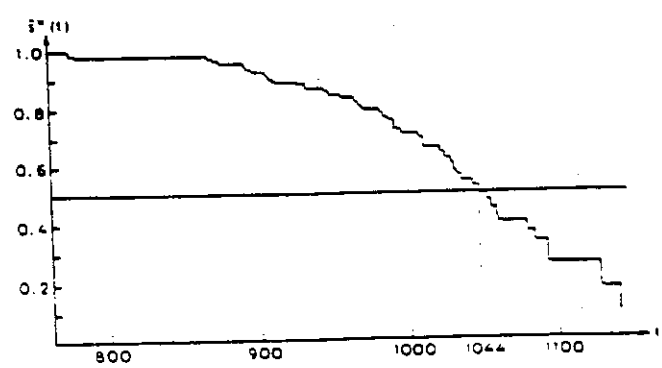

FIG. 9. *Kaplan–Meier estimated survival curve for the Channing House men: t = age in months. The median survival age is estimated to be 1044 months (87 years).*

bootstrap process is automatic: $\hat{S}^0$ and $\hat{R}$ replace S^0 and R in (5.12) and (5.13); n pairs (X_i^*, D_i^*) are independently generated according to rules (5.12)–(5.15), giving the bootstrap data set $\mathbf{y}^* = \{x_1^*, d_1^*, \cdots, (x_n^*, d_n^*)\}$; and finally the bootstrap Kaplan–Meier curve $\hat{S}^{0*}$ is constructed according to formula (5.16), and the bootstrap observed median $\hat{\theta}^*$ calculated. For the Channing House data, $B = 1600$ bootstrap replications of $\hat{\theta}^*$ gave estimated standard error $\hat{\sigma} = 14.0$ months for $\hat{\theta}$. An estimated bias of 4.1 months was calculated as at (4.4). Efron (1981b) gives a fuller description.

Once again there is a simpler way to apply to bootstrap. Consider each pair $y_i = (x_i, d_i)$ as an observed point obtained by simple random sampling from a bivariate distribution F, and apply the bootstrap as described in Section 2 to the data set $y_1, y_2, \cdots, y_n \sim_{iid} F$. This method makes no use of the special structure (5.12)–(5.15). Surprisingly, it gives *exactly the same answers* as the more complicated bootstrap method described earlier (Efron, 1981a). This leads to a surprising conclusion: bootstrap estimates of variability for the Kaplan–Meier curve give correct standard errors even when the usual assumptions about the censoring mechanism, (5.12)–(5.15), fail.

6. EXAMPLES WITH MORE COMPLICATED DATA STRUCTURES

Example 1: Autoregressive Time Series Model

This example illustrates an application of the bootstrap to a famous time series.

The data are the Wolfer annual sunspot numbers for the years 1770–1889 (taken from Anderson, 1975). Let the count for the ith year be z_i. After centering the data (replacing z_i by $z_i - \bar{z}_i$), we fit a first-order autoregressive model

$$z_i = \phi z_{i-1} + \varepsilon_i \tag{6.1}$$

where $\varepsilon_i \sim$ iid $N(0, \sigma^2)$. The estimate $\hat{\phi}$ turned out to be .815 with an estimated standard error, one over the square root of the Fisher information, of .053.

A bootstrap estimate of the standard error of $\hat{\phi}$ can be obtained as follows. Define the residuals $\hat{\varepsilon}_i = z_i - \hat{\phi} z_{i-1}$ for $i = 2, 3, \cdots, 120$. A bootstrap sample $z_1^*, z_2^*, \cdots, z_{120}^*$ is created by sampling $\hat{\varepsilon}_2^*, \hat{\varepsilon}_3^*, \cdots, \hat{\varepsilon}_{120}^*$ with replacement from the residuals, then letting $z_1^* = z_1$, and $z_i^* = \hat{\phi} z_{i-1}^* + \hat{\varepsilon}_i^*$, $i = 2, \cdots, 120$. Finally, after centering the time series $z_1^*, z_2^*, \cdots, z_{120}^*$, $\hat{\phi}^*$ is the estimate of the autoregressive parameter for this new time series. (We could, if we wished, sample the $\hat{\varepsilon}_i^*$ from a fitted normal distribution.)

A histogram of 1000 such bootstrap values $\phi_1^*, \phi_2^*, \cdots, \phi_{1000}^*$ is shown in Fig. 10.

The bootstrap estimate of standard error was .055, agreeing nicely with the usual formula. Note however

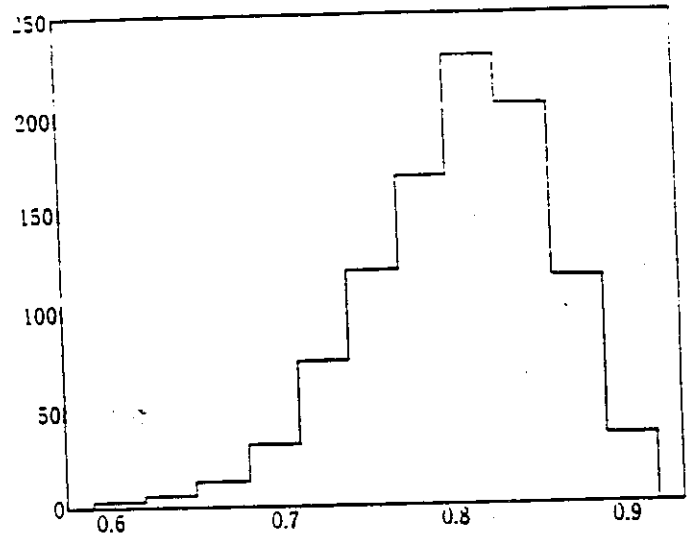

FIG. 10. *Bootstrap histogram of $\hat{\phi}_1^*, \cdots, \hat{\phi}_{1000}^*$ for the Wolfer sunspot data, model (6.1).*

that the distribution is skewed to the left, so a confidence interval for ϕ might be asymmetric about $\hat{\phi}$ as discussed in Sections 8 and 9.

In bootstrapping the residuals, we have assumed that the first-order autoregressive model is correct. (Recall the discussion of regression models in Section 5.) In fact, the first-order autoregressive model is far from adequate for this data. A fit of second-order autoregressive model

$$z_i = \alpha z_{i-1} + \theta z_{i-2} + \varepsilon_i \tag{6.2}$$

gave estimates $\hat{\alpha} = 1.37$, $\hat{\theta} = -.677$, both with an estimated standard error of .067, based on Fisher information calculations. We applied the bootstrap to this model, producing the histograms for $\alpha_1^*, \cdots, \alpha_{1000}^*$ and $\theta_1^*, \cdots, \theta_{1000}^*$ shown in Figs. 11 and 12, respectively.

The bootstrap standard errors were .070 and .068, respectively, both close to the usual value. Note that the additional term has reduced the skewness of the first coefficient.

Example 2: Estimating a Response Transformation in Regression

Box and Cox (1964) introduced a parametric family for estimating a transformation of the response in a regression. Given regression data $\{(x_1, y_1), \cdots, (x_n, y_n)\}$, their model takes the form

$$z_i(\lambda) = x_i \cdot \beta + \varepsilon_i \tag{6.3}$$

where $z_i(\lambda) = (y_i^\lambda - 1)/\lambda$ for $\lambda \neq 0$ and $\log y_i$ for $\lambda = 0$, and $\varepsilon_i \sim$ iid $N(0, \sigma^2)$. Estimates of λ and β are found by minimizing $\sum_1^n (z_i - x_i \cdot \beta)^2$.

Breiman and Friedman (1985) proposed a nonparametric solution for this problem. Their so called ACE

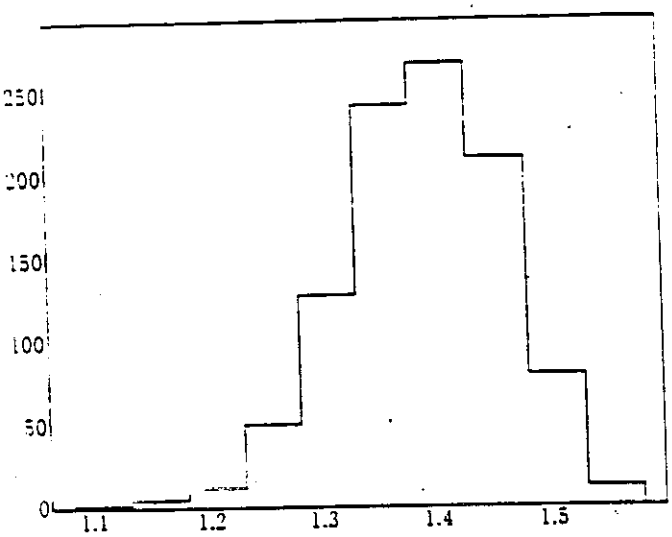

FIG. 11. *Bootstrap histogram of $\hat{a}^*, \cdots, \hat{a}^*_{1000}$ for the Wolfer sunspot data, model (6.2).*

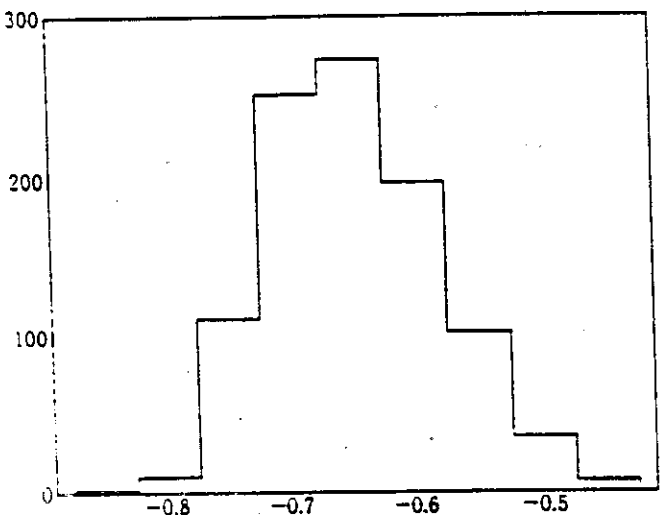

FIG. 12. *Bootstrap histogram of $\hat{\theta}^*, \cdots, \hat{\theta}^*_{1000}$ for the Wolfer sunspot data, model (6.2).*

(alternating conditional expectation) model generalizes (6.3) to

$$s(y_i) = x_i \cdot \beta + \epsilon_i, \tag{6.4}$$

where $s(\cdot)$ is an unspecified smooth function. (In its most general form, ACE allows for transformations of the covariates as well.) The function $s(\cdot)$ and parameter β are estimated in an alternating fashion, utilizing a nonparametric smoother to estimate $s(\cdot)$.

In the following example, taken from Friedman and Tibshirani (1984), we compare the Box and Cox procedure to ACE and use the bootstrap to assess the variability of ACE.

The data from Box and Cox (1964) consist of a 3 × 3 × 3 experiment on the strength of yarns, the response Y being number of cycles to failure, and the factors length of test specimen (X_1) (250, 300, and 350 mm), amplitude of loading cycle (X_2) (8, 9, or 10 mm), and load (X_3) (40, 45, or 50 g). As in Box and Cox, we treat the factors as quantitive and allow only a linear term for each. Box and Cox found that a logarithmic transformation was appropriate, with their procedure producing a value of −.06 for $\hat{\lambda}$ with an estimated 95% confidence interval of (−.18, .06).

Fig. 13 shows the transformation selected by the ACE algorithm. For comparison, the log function is plotted (normalized) on the same figure.

The similarity is truly remarkable! In order to assess the variability of the ACE curve, we can apply the bootstrap. Since the X matrix in this problem is fixed by design, we resampled from the residuals instead of from the (x_i, y_i) pairs. The bootstrap procedure was the following:

Calculate residuals $\hat{\epsilon}_i = \hat{s}(y_i) - x_i \cdot \hat{\beta}, \quad i = 1, 2, \cdots, n.$
Repeat B times
  Choose a sample $\hat{\epsilon}^*_1, \cdots, \hat{\epsilon}^*_n$
    with replacement from $\hat{\epsilon}_1, \cdots, \hat{\epsilon}_n$
  Calculate $y^*_i = \hat{s}^{-1}(x_i \cdot \hat{\beta} + \hat{\epsilon}^*_i), \quad i = 1, 2, \cdots, n$
  Compute $\hat{s}^*(\cdot)$ = result of ACE algorithm
    applied to $(x_1, y^*_1), \cdots, (x_n, y^*_n)$
End

The number of bootstrap replications B was 20. Note that the residuals are computed on the $s(\cdot)$ scale, not the y scale, because it is on the $s(\cdot)$ scale that the true residuals are assumed to be approximately iid. The 20 estimated transformations, $\hat{s}^*_1(\cdot), \cdots, \hat{s}^*_{20}(\cdot)$ are shown in Fig. 14.

The tight clustering of the smooths indicates that the original estimate $\hat{s}(\cdot)$ has low variability, especially for smaller values of Y. This agrees qualitatively with

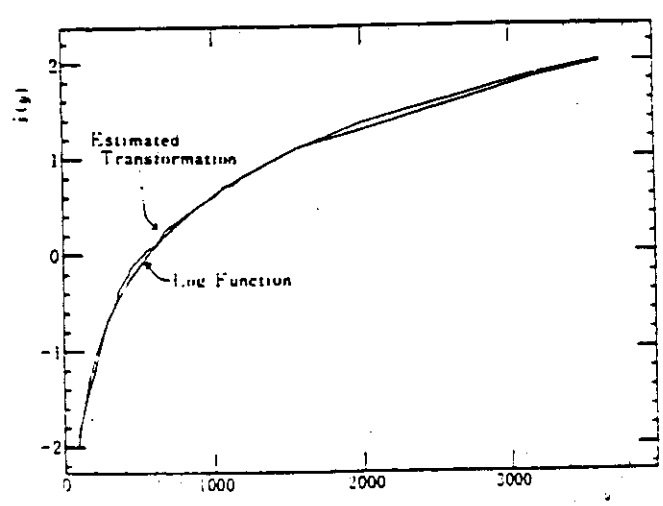

FIG. 13. *Estimated transformation from ACE and the log function for Box and Cox example.*

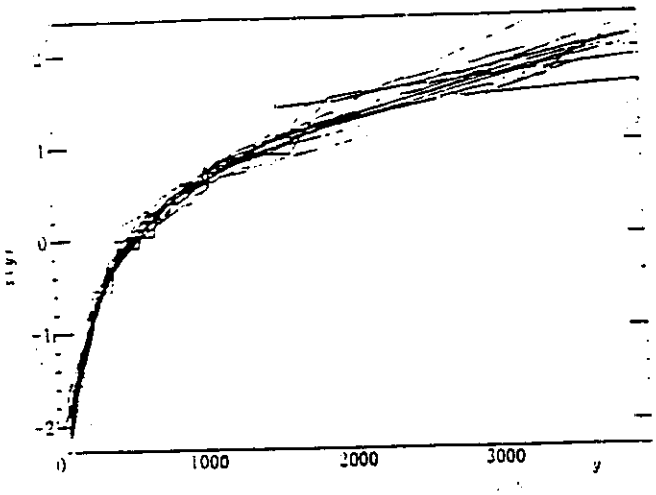

FIG. 14. *Bootstrap replications of ACE transformations for Box and Cox example.*

the short confidence interval for λ in the Box and Cox analysis.

7. BOOTSTRAP CONFIDENCE INTERVALS

This section presents three closely related methods of using the bootstrap to set confidence intervals. The discussion is in terms of simple parametric models, where the logical basis of the bootstrap methods is easiest to see. Section 8 extends the methods to multiparameter and nonparametric models.

We have discussed obtaining $\hat{\sigma}$, the estimated standard error of an estimator $\hat{\theta}$. In practice, $\hat{\theta}$ and $\hat{\sigma}$ are usually used together to form the approximate confidence interval $\theta \in \hat{\theta} \pm \hat{\sigma} z^{(\alpha)}$, (1.7), where $z^{(\alpha)}$ is the $100 \cdot \alpha$ percentile point of a standard normal distribution. The interval (1.7) is claimed to have approximate coverage probability $1 - 2\alpha$. For the law school example of Section 2, the values $\hat{\theta} = .776$, $\hat{\sigma} = .115$, $z^{(.05)} = -1.645$, give $\theta \in [.587, .965]$ as an approximate 90% central interval for the true correlation coefficient.

We will call (1.7) the *standard interval for* θ. When working within parametric families like the bivariate normal, $\hat{\sigma}$ in (1.7) is usually obtained by differentiating the log likelihood function, see Section 5a of Rao (1973), although in the context of this paper we might prefer to use the parametric bootstrap estimate of σ, e.g., $\hat{\sigma}_{\text{NORM}}$ in Section 2.

The standard intervals are an immensely useful statistical tool. They have the great virtue of being automatic: a computer program can be written which produces (1.7) directly from the data y and the form of the density function for y, with no further input required from the statistician. Nevertheless the standard intervals can be quite inaccurate as Table 5 shows. The standard interval (1.7), using $\hat{\sigma}_{\text{NORM}}$, (2.5), is

TABLE 5

Exact and approximate central 90% confidence intervals for θ, the true correlation coefficient, from the law school data of Fig. 1

1. Exact (normal theory)	[.496, .898]	R/L = .44
2. Standard (1.7)	[.587, .965]	R/L = 1.00
3. Transformed standard	[.508, .907]	R/L = .49
4. Parametric bootstrap (BC)	[.488, .900]	R/L = .43
5. Nonparametric bootstrap (BC_a)	[.43, .92]	R/L = .42

Note: R/L = ratio of right side of interval, measured from $\hat{\theta} = .776$, to left side. The exact interval is strikingly asymmetric about $\hat{\theta}$. Section 8 discusses the nonparametric method of line 5.

strikingly different from the exact normal theory interval based on the assumption of a bivariate normal sampling distribution F.

In this case, it is well known that it is better to make the transformation $\hat{\phi} = \tanh^{-1}(\hat{\theta})$, $\phi = \tanh^{-1}(\theta)$, apply (1.7) on the ϕ scale, and then transform back to the θ scale. The resulting interval, line 3 of Table 5, is moved closer to the exact interval. However, there is nothing automatic about the $\tanh^{-1}$ transformation. For a different statistic from the correlation coefficient or a different distributional family from the bivariate normal, we might very well need other tricks to make (1.7) perform satisfactorily.

The bootstrap can be used to produce approximate confidence intervals in an automatic way. The following discussion is abridged from Efron (1984 and 1985) and Efron (1982a, Chapter 10). Line 4 of Table 5 shows that the parametric bootstrap interval for the correlation coefficient θ is nearly identical with the exact interval. "Parametric" in this case means that the bootstrap algorithm begins from the bivariate normal MLE $\hat{F}_{\text{NORM}}$, as for the normal theory curve of Fig. 2. This good performance is no accident. The bootstrap method used in line 4 in effect transforms $\hat{\theta}$ to the best (most normal) scale, finds the appropriate interval, and transforms this interval back to the θ scale. All of this is done automatically by the bootstrap algorithm, without requiring special intervention from the statistician. The price paid is a large amount of computing, perhaps $B = 1000$ bootstrap replications, as discussed in Section 10.

Define $\hat{G}(s)$ to be the parametric bootstrap cdf of $\hat{\theta}^*$,

$$\hat{G}(s) = \text{Prob}_*\{\hat{\theta}^* < s\}, \tag{7.1}$$

where Prob_* indicates probability computed according to the bootstrap distribution of $\hat{\theta}^*$. In Fig. 2 $\hat{G}(s)$ is obtained by integrating the normal theory curve. We will present three different kinds of bootstrap confidence intervals in order of increasing generality. All three methods use percentiles of $\hat{G}$ to define the confidence interval. They differ in which percentiles are used.

The simplest method is to take $\theta \in [\hat{G}^{-1}(\alpha), \hat{G}^{-1}(1-\alpha)]$ as an approximate $1-2\alpha$ central interval for θ. This is called the *percentile method* in Section 10.4 of Efron (1982a). The percentile method interval is just the interval between the $100 \cdot \alpha$ and $100 \cdot (1-\alpha)$ percentiles of the bootstrap distribution of $\hat{\theta}^*$.

We will use the notation $\theta[\alpha]$ for the α level endpoint of an approximate confidence interval for θ, so $\theta \in [\theta[\alpha], \theta[1-\alpha]]$ is the central $1-2\alpha$ interval. Subscripts will be used to indicate the various different methods. The percentile interval has endpoints

$$\theta_P[\alpha] = \hat{G}^{-1}(\alpha). \tag{7.2}$$

This compares with the standard interval,

$$\theta_S[\alpha] = \hat{\theta} + \hat{\sigma} z^{(\alpha)}. \tag{7.3}$$

Lines 1 and 2 of Table 6 summarize these definitions.

Suppose the bootstrap cdf $\hat{G}$ is perfectly normal, say

$$\hat{G}(s) = \Phi((s-\hat{\theta})/\hat{\sigma}), \tag{7.4}$$

where $\Phi(s) = \int_{-\infty}^{s} (2\pi)^{-1/2} e^{-t^2/2}\, dt$, the standard normal cdf. In other words, suppose that $\hat{\theta}^*$ has bootstrap distribution $N(\hat{\theta}, \hat{\sigma}^2)$. In this case the standard method and the percentile method agree, $\theta_S[\alpha] = \theta_P[\alpha]$. In situations like that of Fig. 2, where $\hat{G}$ is markedly nonnormal, the standard interval is quite different from (7.2). Which is better?

To answer this question, consider the simplest possible situation, where for all θ

$$\hat{\theta} \sim N(\theta, \sigma^2). \tag{7.5}$$

That is, we have a single unknown parameter θ with no nuisance parameters, and a single summary statistic $\hat{\theta}$ normally distributed about θ with constant standard error σ. In this case the parametric bootstrap cdf is given by (7.4), so $\theta_S[\alpha] = \theta_P[\alpha]$. (The bootstrap estimate $\hat{\sigma}$ equals σ.)

Suppose though that instead of (7.5) we have, for all θ,

$$\hat{\phi} \sim N(\phi, \tau^2), \tag{7.6}$$

for some monotone transformation $\hat{\phi} = g(\hat{\theta})$, $\phi = g(\theta)$, where τ is a constant. In the correlation coefficient example the function g was $\tanh^{-1}$. The standard limits (7.2) can now be grossly inaccurate. However it is easy to verify that the percentile limits (7.2) are still correct. "Correct" here means that (7.2) is the mapping of the obvious interval for ϕ, $\hat{\phi} \pm \tau z^{(\alpha)}$, back to the θ scale, $\theta_P[\alpha] = g^{-1}(\hat{\phi} + \tau z^{(\alpha)})$. It is also correct in the sense of having exactly the claimed converge probability $1-2\alpha$.

Another way to state things is that the percentile intervals are transformation invariant,

$$\phi_P[\alpha] = g(\theta_P[\alpha]) \tag{7.7}$$

for any monotone transformation g. This implies that if the percentile intervals are correct on some transformed scale $\phi = g(\theta)$, then they must also be correct on the original scale θ. The statistician does not need to know the normalizing transformation g, only that it exists. Definition (7.2) automatically takes care of the bookkeeping involved in the use of normalizing transformations for confidence intervals.

Fisher's theory of maximum likelihood estimation says that we are always in situation (7.5) to a first order of asymptotic approximation. However, we are also in situation (7.6), for any choice of g, to the same order of approximation. Efron (1984 and 1985) uses higher order asymptotic theory to differentiate between the standard and bootstrap intervals. It is the higher order asymptotic terms which often make exact intervals strongly asymmetric about the MLE $\hat{\theta}$ as in Table 5. The bootstrap intervals are effective at capturing this asymmetry.

The percentile method automatically incorporates normalizing transformations, as in going from (7.5)–(7.6). It turns out that there are two other important ways that assumption (7.5) can be misleading, the first of which relates to possible bias in $\hat{\theta}$. For example consider $f_\theta(\hat{\theta})$, the family of densities for the observed correlation coefficient $\hat{\theta}$ when sampling $n = 15$ times from a bivariate normal distribution with true corre-

TABLE 6

Four methods of setting approximate confidence intervals for a real valued parameter θ

Method	Abbreviation	α level endpoint	Correct if	
1. Standard	$\theta_S[\alpha]$	$\hat{\theta} + \hat{\sigma} z^{(\alpha)}$	$\hat{\theta} \sim N(\theta, \sigma^2)$	σ constant
			There exists monotone transformation $\hat{\phi} = g(\hat{\theta})$, $\phi = g(\theta)$ such that:	
2. Percentile	$\theta_P[\alpha]$	$\hat{G}^{-1}(\alpha)$	$\hat{\phi} \sim N(\phi, \tau^2)$	τ constant
3. Bias-corrected	$\theta_{BC}[\alpha]$	$\hat{G}^{-1}(\Phi[2z_0 + z^{(\alpha)}])$	$\hat{\phi} \sim N(\phi - z_0\tau, \tau^2)$	z_0, τ constant
4. BC$_a$	$\theta_{BC_a}[\alpha]$	$\hat{G}^{-1}\left(\Phi\left\{z_0 + \frac{(z_0 + z^{(\alpha)})}{1 - a(z_0 + z^{(\alpha)})}\right\}\right)$	$\hat{\phi} \sim N(\phi - z_0\tau_\phi, \tau_\phi^2)$ where $\tau_\phi = 1 + a\phi$	z_0, a constant

Note: Each method is correct under more general assumptions than its predecessor. Methods 2, 3, and 4 are defined in terms of the percentiles of $\hat{G}$, the bootstrap distribution (7.1).

lation θ. In fact it is easy to see that no monotone mapping $\hat{\phi} = g(\hat{\theta})$, $\phi = g(\theta)$ transforms this family to $\hat{\phi} \sim N(\phi, \tau^2)$, as in (7.6). If there were such a g, then $\text{Prob}_*\{\hat{\theta} < \theta\} = \text{Prob}_*\{\hat{\phi} < \phi\} = .50$, but for $\theta = .776$ integrating the density function $f_{.776}(\hat{\theta})$ gives $\text{Prob}_{*=.776}\{\hat{\theta} < \theta\} = .431$.

The *bias-corrected percentile method* (BC method), line 3 of Table 6, makes an adjustment for this type of bias. Let

$$z_0 = \Phi^{-1}\{\hat{G}(\hat{\theta})\}, \tag{7.8}$$

where Φ^{-1} is the inverse function of the standard normal cdf. The BC method has α level endpoint

$$\theta_{BC}[\alpha] = \hat{G}^{-1}(\Phi\{2z_0 + z^{(\alpha)}\}). \tag{7.9}$$

Note: if $\hat{G}(\hat{\theta}) = .50$, that is if half of the bootstrap distribution of $\hat{\theta}^*$ is less than the observed value $\hat{\theta}$, then $z_0 = 0$ and $\theta_{BC}[\alpha] = \theta_P[\alpha]$. Otherwise definition (7.9) makes a bias correction.

Section 10.7 of Efron (1982a) shows that the BC interval for θ is exactly correct if

$$\hat{\phi} \sim N(\phi - z_0\tau, \tau^2) \tag{7.10}$$

for some monotone transformation $\hat{\phi} = g(\hat{\theta})$, $\phi = g(\theta)$ and some constant z_0. It does not look like (7.10) is much more general than (7.6), but in fact the bias correction is often important.

In the example of Table 5, the percentile method (7.2) gives central 90% interval [.536, .911] compared to the BC interval [.488, .900] and the exact interval [.496, .898]. By definition the endpoints of the exact interval satisfy

$$\begin{aligned} \text{Prob}_{*=.496}\{\hat{\theta} > .776\} &= .05 \\ &= \text{Prob}_{*=.898}\{\hat{\theta} < .776\}. \end{aligned} \tag{7.11}$$

The corresponding quantities for the BC endpoints are

$$\begin{aligned} \text{Prob}_{*=.488}\{\hat{\theta} > .776\} &= .0465, \\ \text{Prob}_{*=.900}\{\hat{\theta} < .776\} &= .0475, \end{aligned} \tag{7.12}$$

compared to

$$\begin{aligned} \text{Prob}_{*=.536}\{\hat{\theta} > .776\} &= .0725, \\ \text{Prob}_{*=.911}\{\hat{\theta} < .776\} &= .0293. \end{aligned} \tag{7.13}$$

for the percentile endpoints. The bias correction is quite important in equalizing the error probabilities at the two endpoints. If z_0 can be approximated accurately (as mentioned in Section 9), then it is preferable to use the BC intervals.

Table 7 shows a simple example where the BC method is less successful. The data consists of the single observation $\hat{\theta} \sim \theta(\chi^2_{19}/19)$, the notation indicating an unknown scale parameter θ times a random variable with distribution $\chi^2_{19}/19$. (This definition makes $\hat{\theta}$ unbiased for θ.) A confidence interval is desired for the scale parameter θ. In this case the BC interval based on $\hat{\theta}$ is a definite improvement over the standard interval (1.7), but goes only about half as far as it should toward achieving the asymmetry of the exact interval.

TABLE 7

Central 90% confidence intervals for θ having observed $\hat{\theta} = \theta(\chi^2_{19}/19)$

1. Exact	$[.631 \cdot \hat{\theta}, 1.88 \cdot \hat{\theta}]$	R/L = 2.98
2. Standard (1.7)	$[.466 \cdot \hat{\theta}, 1.53 \cdot \hat{\theta}]$	R/L = 1.00
3. BC (7.9)	$[.580 \cdot \hat{\theta}, 1.69 \cdot \hat{\theta}]$	R/L = 1.64
4. BC$_a$ (7.15)	$[.630 \cdot \hat{\theta}, 1.88 \cdot \hat{\theta}]$	R/L = 2.37
5. Nonparametric BC$_a$	$[.640 \cdot \hat{\theta}, 1.68 \cdot \hat{\theta}]$	R/L = 1.88

Note: The exact interval is sharply skewed to the right of $\hat{\theta}$. The BC method is only a partial improvement over the standard interval. The BC$_a$ interval, $a = .108$, agrees almost perfectly with the exact interval.

It turns out that the parametric family $\hat{\theta} \sim \theta(\chi^2_{19}/19)$ cannot be transformed into (7.10), not even approximately. The results of Efron (1982b) show that there does exist a monotone transformation g such that $\hat{\phi} = g(\hat{\theta})$, $\phi = g(\theta)$ satisfy to a high degree of approximation

$$\hat{\phi} \sim N(\phi - z_0\tau_*, \tau_*^2) \quad (\tau_* = 1 + a\phi). \tag{7.14}$$

The constants in (7.14) are $z_0 = .1082$, $a = .1077$.

The BC$_a$ method (Efron, 1984), line 4 of Table 6, is a method of assigning bootstrap confidence intervals which are exactly right for problems which can be mapped into form (7.14). This method has α level endpoint

$$\theta_{BC_a}[\alpha] = \hat{G}^{-1}\left(\Phi\left\{z_0 + \frac{z_0 + z^{(\alpha)}}{1 - a(z_0 + z^{(\alpha)})}\right\}\right). \tag{7.15}$$

If $a = 0$ then $\theta_{BC_a}[\alpha] = \theta_{BC}[\alpha]$, but otherwise the BC$_a$ intervals can be a substantial improvement over the BC method as shown in Table 7.

The constant z_0 in (7.15) is given by $z_0 = \Phi^{-1}\{\hat{G}(\hat{\theta})\}$, (7.8), and so can be computed directly from the bootstrap distribution. How do we know a? It turns out that in one-parameter families $f_\theta(\hat{\theta})$, a good approximation is

$$a \doteq \frac{\text{SKEW}_{\theta=\hat{\theta}}(\dot{L}_\theta(t))}{6}, \tag{7.16}$$

where $\text{SKEW}_{\theta=\hat{\theta}}(\dot{L}_\theta(t))$ is the skewness at parameter value $\theta = \hat{\theta}$ of the score statistic $\dot{L}(t) = (\partial/\partial\theta)\log f_\theta(t)$. For $\hat{\theta} \sim \theta(\chi^2_{19}/19)$ this gives $a \doteq .1081$, compared to the actual value $a = .1077$ derived in Efron (1984). For the normal theory correlation family of Table 5 $a \doteq 0$ which explains why the BC method, which takes $a = 0$, works so well there.

The advantage of formula (7.18) is that we need not know the transformation g leading to (7.14) in order to approximate a. In fact $\theta_{BC_a}[\alpha]$, like $\theta_{BC}[\alpha]$ and $\theta_P[\alpha]$, is transformation invariant, as in (7.7). Like the bootstrap methods, the BC_a intervals are computed directly from the form of the density function $f_\theta(\cdot)$, for θ near $\hat{\theta}$.

Formula (7.16) applies to the case where θ is the only parameter. Section 8 briefly discusses the more challenging problem of setting confidence intervals for a parameter θ in a multiparameter family, and also in nonparametric situations where the number of nuisance parameters is effectively infinite.

To summarize this section, the progression from the standard intervals to the BC_a method is based on a series of increasingly less restrictive assumptions, as shown in Table 6. Each successive method in Table 6 requires the statistician to do a greater amount of computation; first the bootstrap distribution $\hat{G}$, then the bias correction constant z_0, and finally the constant a. However, all of these computations are algorithmic in character, and can be carried out in an automatic fashion.

Chapter 10 of Efron (1982a) discusses several other ways of using the bootstrap to construct approximate confidence intervals, which will not be presented here. One of these methods, the "bootstrap t," was used in the blood serum example of Section 4.

8. NONPARAMETRIC AND MULTIPARAMETER CONFIDENCE INTERVALS

Section 7 focused on the simple case $\hat{\theta} \sim f_\theta$, where we have only a real valued parameter θ and a real valued summary statistic $\hat{\theta}$ from which we are trying to construct a confidence interval for θ. Various favorable properties of the bootstrap confidence intervals were demonstrated in the simple case, but of course the simple case is where we least need a general method like the bootstrap.

Now we will discuss the more common situation where there are nuisance parameters besides the parameter of interest θ; or even more generally the nonparametric case, where the number of nuisance parameters is effectively infinite. The discussion is limited to a few brief examples. Efron (1984 and 1985) develops the theoretical basis of bootstrap approximate confidence intervals for complicated situations, and gives many more examples. The word "approximate" is important here since exact nonparametric confidence intervals do not exist for most parameters (see Bahadur and Savage, 1956).

Example 1. Ratio Estimation

The data consists of $\mathbf{y} = (y_1, y_2)$, assumed to come from a bivariate normal distribution with unknown mean vector $\boldsymbol{\eta}$ and covariance matrix the identity,

$$\mathbf{y} \sim N_2(\boldsymbol{\eta}, \mathbf{I}). \tag{8.1}$$

The parameter of interest, for which we desire a confidence interval, is the ratio

$$\theta = \eta_2/\eta_1. \tag{8.2}$$

Fieller (1954) provided well known exact intervals for θ in this case. The Fieller intervals are based on a clever trick, which seems very special to situation (8.1), (8.2).

TABLE 8

Central 90% confidence intervals for $\theta = \eta_2/\eta_1$ and for $\phi = 1/\theta$ having observed $(y_1, y_2) = (8, 4)$ from a bivariate normal distribution $\mathbf{y} \sim N_2(\boldsymbol{\eta}, \mathbf{I})$

	For θ	For ϕ
1. Exact (Fieller)	[.29, .76]	[1.32, 3.50]
2. Parametric boot (BC)	[.29, .76]	[1.32, 3.50]
3. Standard (1.7)	[.27, .73]	[1.08, 2.92]
MLE	$\hat{\theta} = .5$	$\hat{\phi} = 2$

Note: The BC intervals, line 2, are based on the parametric bootstrap distribution of $\hat{\theta} = y_2/y_1$.

Table 8 shows Fieller's central 90% interval for θ having observed $\mathbf{y} = (8, 4)$. Also shown is the Fieller interval for $\phi = 1/\theta = \eta_1/\eta_2$, which equals $[.76^{-1}, .29^{-1}]$, the obvious transformation of the interval for θ. The standard interval (1.7) is satisfactory for θ, but not for ϕ. Notice that the standard interval does not transform correctly from θ to ϕ.

Line 2 shows the BC intervals based on applying definitions (7.8) and (7.9) to the parametric bootstrap distribution of $\hat{\theta} = y_2/y_1$ (or $\hat{\phi} = y_1/y_2$). This is the distribution of $\hat{\theta}^* = y_2^*/y_1^*$ when sampling $\mathbf{y}^* = (y_1^*, y_2^*)$ from $\hat{F}_{NORM} \sim N_2((y_1, y_2), \mathbf{I})$. The bootstrap intervals transform correctly, and in this case they agree with the exact interval to three decimal places.

Example 2. Product of Normal Means

For most multiparameter situations, there do not exist exact confidence intervals for a single parameter of interest. Suppose for instance that (8.2) is changed to

$$\theta = \eta_1\eta_2, \tag{8.3}$$

still assuming (8.1). Table 9 shows approximate intervals for θ, and also for $\phi = \theta^2$, having observed $\mathbf{y} = (2, 4)$. The "almost exact" intervals are based on an analog of Fieller's argument (Efron, 1985), which with suitable care can be carried through to a high degree of accuracy. Once again, the parametric BC intervals are a close match to line 1. The fact that the standard intervals do not transform correctly is particularly obvious here.

TABLE 9
Central 90% confidence intervals for $\theta = \eta_1\eta_2$ and $\phi = \theta^2$ having observed $y = (2, 4)$, where $y \sim N_2(\eta, I)$

	For θ	For ϕ
1. Almost exact	[1.77, 17.03]	[3.1, 290.0]
2. Parametric boot (BC)	[1.77, 17.12]	[3.1, 239.1]
3. Standard (1.7)	[0.64, 15.36]	[−53.7, 181.7]
MLE	$\hat\theta = 8$	$\hat\phi = 64$

Note: The almost exact intervals are based on the high order approximation theory of Efron (1985). The BC intervals of line 2 are based on the parametric bootstrap distribution of $\hat\theta = y_1y_2$.

The good performance of the parametric BC intervals is not accidental. The theory developed in Efron (1985) shows that the BC intervals, based on bootstrapping the MLE $\hat\theta$, agree to high order with the almost exact intervals in the following class of problems: the data y comes from a multiparameter family of densities $f_\eta(y)$, both y and η k-dimensional vectors; the real valued parameter of interest θ is a smooth function of η, $\theta = t(\eta)$; and the family $f_\eta(y)$ can be transformed to multivariate normality, say

$$g(y) \sim N_k(h(\eta), I), \tag{8.4}$$

by some one-to-one transformations g and h.

Just as in Section 7, it is not necessary for the statistician to know the normalizing transformations g and h, only that they exist. The BC intervals are obtained directly from the original densities f_η: we find $\hat\eta = \hat\eta(y)$, the MLE of η; sample $y^* \sim f_{\hat\eta}$; compute $\hat\theta^*$, the bootstrap MLE of θ; calculate $\hat G$, the bootstrap cdf of $\hat\theta^*$, usually by Monte Carlo sampling, and finally apply definitions (7.8) and (7.9). This process gives the same interval for θ whether or not the transformation to form (8.4) has been made.

Not all problems can be transformed as in (8.4) to a normal distribution with constant covariance. The case considered in Table 7 is a one-dimensional counter example. As a result the BC intervals do not always work as well as in Tables 8 and 9, although they usually improve on the standard method. However, in order to take advantage of the BC_a method, which is based on more general assumptions, we need to be able to calculate the constant a.

Efron (1984) gives expressions for "a" generalizing (7.16) to multiparameter families, and also to nonparametric situations. If (8.4) holds, then "a" will have value zero, and the BC_a method reduces to the BC case. Otherwise the two intervals differ.

Here we will discuss only the nonparametric situation: the observed data $y = (x_1, x_2, \cdots, x_n)$ consists of iid observations $X_1, X_2, \cdots, X_n \sim F$, where F can be *any* distribution on the sample space $\mathscr{X}$; we want a confidence interval for $\theta = t(F)$, some real valued functional of F; and the bootstrap interval are based on bootstrapping $\hat\theta = t(\hat F)$, which is the nonparametric MLE of θ. In this case a good approximation to the constant a is given in terms of the empirical influence function U_i^0, defined in Section 10 at (10.11),

$$a \doteq \frac{1}{6}\,\frac{\sum_{i=1}^n (U_i^0)^3}{[\sum_{i=1}^n (U_i^0)^2]^{3/2}}. \tag{8.5}$$

This is a convenient formula, since it is easy to numerically evaluate the U_i^0 by simply substituting a small value of θ into (10.11).

Example 3. The Law School Data

For $\hat\theta$ the correlation coefficient, the values of U_i^0 corresponding to the 15 data points shown in Fig. 1 are −1.507, .168, .273, .004, .525, −.049, −.100, .477, .310, .004, −.526, −.091, .434, .125, −.048. (Notice how influential law school 1 is.) Formula (8.5) gives $a \doteq -.0817$. $B = 100{,}000$ bootstrap replications, about 100 times more than was actually necessary (see Section 10), gave $z_0 = -.0927$, and the central 90% interval $\theta \in [.43, .92]$ shown in Table 5. The nonparametric BC_a interval is quite reasonable in this example, particularly considering that there is no guarantee that the true law school distribution F is anywhere near bivariate normal.

Example 4. Mouse Leukemia Data (the First Example in Section 3)

The standard central 90% interval for β in formula (3.1) is [.835, 2.18]. The bias correction constant $z_0 \doteq .0275$, giving BC interval [1.00, 2.39]. This is shifted far right of the standard interval, reflecting the long right tail of the bootstrap histogram seen in Fig. 3. We can calculate "a" from (8.5), considering each of the $n = 42$ data points to be a triple (y_i, x_i, δ_i): $a \doteq -.152$. Because a is negative, the BC_a interval is shifted back to the left, equaling [.788, 2.10]. This contrasts with the law school example, where a, z_0, and the skewness of the bootstrap distribution added to each other rather than cancelling out, resulting in a BC_a interval much different from the standard interval.

Efron (1984) provides some theoretical support for the nonparametric BC_a method. However the problem of setting approximate nonparametric confidence intervals is still far from well understood, and all methods should be interpreted with some caution. We end this section with a cautionary example.

Example 5. The Variance

Suppose X is the real line, and $\theta = \mathrm{Var}_F X$, the variance. Line 5 of Table 2 shows the result of applying the nonparametric BC_a method to data sets $x_1, x_2, \cdots, x_{20}$ which were actually iid samples from a $N(0, 1)$ distribution. The number .640 for example is the

average of $\theta_{BC_a}(.05)/\hat{\theta}$ over 40 such data sets, $B = 4000$ bootstrap replications per data set. The upper limit $1.68 \cdot \hat{\theta}$ is noticeably small, as pointed out by Schenker (1985). The reason is simple: the nonparametric bootstrap distribution of $\hat{\theta}^*$ has a short upper tail; compared to the parametric bootstrap distribution which is a scaled χ^2_9 random variable. The results of Beran (1984), Bickel and Freedman (1981), and Singh (1981) show that the nonparametric bootstrap distribution is highly accurate asymptotically, but of course that is not a guarantee of good small sample behavior. Bootstrapping from a smoothed version of $\hat{F}$, as in lines 3, 4, and 5 of Table 2 alleviates the problem in this particular example.

9. BOOTSTRAP SAMPLE SIZES

How many bootstrap replications must we take? Consider the standard error estimate $\hat{\sigma}_B$ based on B bootstrap replications, (2.4). As $B \to \infty$, $\hat{\sigma}_B$ approaches $\hat{\sigma}$, the bootstrap estimate of standard error as originally defined in (2.3). Because $\hat{F}$ does not estimate F perfectly, $\hat{\sigma} = \sigma(\hat{F})$ will have a non-zero coefficient of variation for estimating the true standard error $\sigma = \sigma(F)$; $\hat{\sigma}_B$ will have a larger CV because of the randomness added by the Monte Carlo bootstrap sampling.

It is easy to derive the following approximation,

$$\text{(9.1)} \qquad \mathrm{CV}(\hat{\sigma}_B) \doteq \left\{\mathrm{CV}(\hat{\sigma})^2 + \frac{E\{\hat{\delta}\} + 2}{4B}\right\}^{1/2},$$

where $\hat{\delta}$ is the kurtosis of the bootstrap distribution of $\hat{\theta}^*$, given the data $\mathbf{y}$, and $E\{\hat{\delta}\}$ its expected value averaged over $\mathbf{y}$. For typical situations, $\mathrm{CV}(\hat{\sigma})$ lies between .10 and .30. For example, if $\hat{\theta} = \bar{x}$, $n = 20$, $x_i \sim_{\text{iid}} N(0, 1)$, then $\mathrm{CV}(\hat{\sigma}) \doteq .16$.

Table 10 shows $\mathrm{CV}(\hat{\sigma}_B)$ for various values of B and $\mathrm{CV}(\hat{\sigma})$, assuming $E\{\hat{\delta}\} = 0$ in (9.1). For values of $\mathrm{CV}(\hat{\sigma}) > .10$, *there is little improvement past* $B = 100$. In fact B as small as 25 gives reasonable results. Even smaller values of B can be quite informative, as we saw in the Stanford Heart Transplant Data (Fig. 7 of Section 3).

TABLE 10

Coefficient of variation of $\hat{\sigma}_B$, the bootstrap estimate of standard error based on B Monte Carlo replications, as a function of B and $\mathrm{CV}(\hat{\sigma})$, the limiting CV as $B \to \infty$

		$B \to$				
		25	50	100	200	∞
$\mathrm{CV}(\hat{\sigma})$	.25	.29	.27	.26	.25	.25
↓	.20	.24	.22	.21	.21	.20
	.15	.21	.18	.17	.16	.15
	.10	.17	.14	.12	.11	.10
	.05	.15	.11	.09	.07	.05
	0	.14	.10	.07	.05	0

Note: Based on (9.1), assuming $E\{\hat{\delta}\} = 0$.

The situation is quite different for setting bootstrap confidence intervals. The calculations of Efron (1984), Section 8, show that $B = 1000$ is a rough minimum for the number of Monte Carlo bootstraps necessary to compute the BC or BC_a intervals. Somewhat smaller values, say $B = 250$, can give a useful percentile interval, the difference being that then the constant z_0 need not be computed. Confidence intervals are a fundamentally more ambitious measure of statistical accuracy than standard errors, so it is not surprising that they require more computational effort.

10. THE JACKKNIFE AND THE DELTA METHOD

This section returns to the simple case of assigning a standard error to $\hat{\theta}(\mathbf{y})$, where $\mathbf{y} = (x_1, \cdots, x_n)$ is obtained by random sampling from a single unknown distribution, $X_1, \cdots, X_n \sim_{\text{iid}} F$. We will give another description of the bootstrap estimate $\hat{\sigma}$, which illustrates the bootstrap's relationship to older techniques of assigning standard errors, like the jackknife and the delta method.

For a given bootstrap sample $\mathbf{y}^* = (x_1^*, \cdots, x_n^*)$, as described in step (i) of the algorithm in Section 2, let p_i^* indicate the proportion of the bootstrap sample equal to x_i,

$$\text{(10.1)} \qquad p_i^* = \frac{\#\{x_j^* = x_i\}}{n} \quad i = 1, 2, \cdots, n,$$

$\mathbf{p}^* = (p_1^*, p_2^*, \cdots, p_n^*)$. The vector $\mathbf{p}^*$ has a rescaled multinomial distribution

$$\text{(10.2)} \qquad \mathbf{p}^* \sim \mathrm{Mult}_n(n, \mathbf{p}^0)/n \qquad (\mathbf{p}^0 = (1/n, 1/n, \cdots, 1/n)),$$

where the notation indicates the proportions observed from n random draws on n categories, each with probability $1/n$.

For $n = 3$ there are 10 possible bootstrap vectors $\mathbf{p}^*$. These are indicated in Fig. 15 along with their multinomial probabilities from (10.2). For example, $\mathbf{p}^* = (1/3, 0, 2/3)$, corresponding to $\mathbf{x}^* = (x_1, x_3, x_3)$ or any permutation of these values has bootstrap probability $1/9$.

To make our discussion easier suppose that the statistic of interest $\hat{\theta}$ is of functional form: $\hat{\theta} = \theta(\hat{F})$, where $\theta(F)$ is a functional assigning a real number to any distribution F on the sample space X. The mean, the correlation coefficient, and the trimmed mean are all of functional form. Statistics of functional form have the same value as a function of $\hat{F}$, no matter what the sample size n may be, which is convenient for discussing the jackknife and delta method.

For any vector $\mathbf{p} = (p_1, p_2, \cdots, p_n)$ having nonnegative weights summing to 1, define the weighted

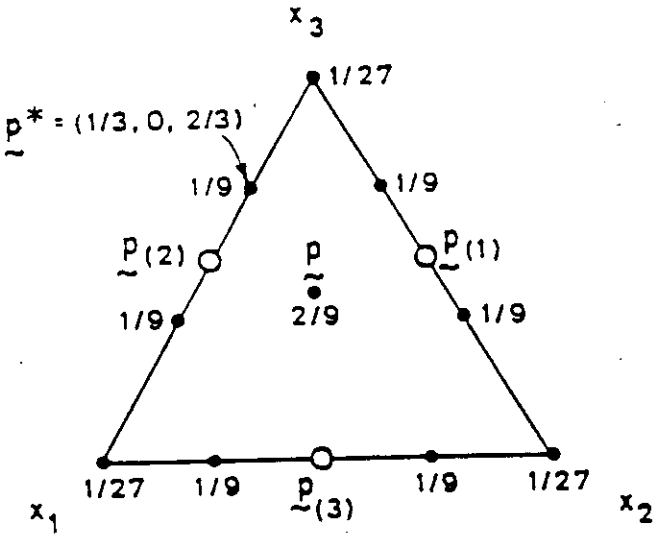

FIG. 15. *The bootstrap and jackknife sampling points in the case $n = 3$. The bootstrap points (·) are shown with their probabilities.*

empirical distribution

(10.3) $\hat{F}(\mathbf{p})$: probability p_i on x_i $\quad i = 1, \cdots, n$.

For $\mathbf{p} = \mathbf{p}^0 = 1/n$, the weighted empirical distribution equals $\hat{F}$, (1.4).

Corresponding to $\mathbf{p}$ is a resampled value of $\hat{\theta}$,

$$\hat{\theta}(\mathbf{p}) = \theta(\hat{F}(\mathbf{p})). \tag{10.4}$$

The shortened notation $\hat{\theta}(\mathbf{p})$ assumes that the data $(x_1, x_2, \cdots, x_n)$ is considered fixed. Notice that $\hat{\theta}(\mathbf{p}^0) = \theta(\hat{F})$ is the observed value of the statistic of interest. The bootstrap estimate $\hat{\sigma}$, (2.3), can then be written

$$\hat{\sigma} = [\mathrm{var}_*\hat{\theta}(\mathbf{p}^*)]^{1/2}, \tag{10.5}$$

where var_* indicates variance with respect to distribution (10.2). In terms of Fig. 15, $\hat{\sigma}$ is the standard deviation of the ten possible bootstrap values $\hat{\theta}(\mathbf{p}^*)$ weighted as shown.

It looks like we could always calculate $\hat{\sigma}$ simply by doing a finite sum. Unfortunately, the number of bootstrap points is $\binom{2n-1}{n}$, 77,558,710 for $n = 15$ so straightforward calculation of $\hat{\sigma}$ is usually impractical. That is why we have emphasized Monte Carlo approximations to $\hat{\sigma}$. Therneau (1983) considers the question of methods more efficient than pure Monte Carlo, but at present there is no generally better method available.

However, there is another approach to approximating (10.5). We can replace the usually complicated function $\hat{\theta}(\mathbf{p})$ by an approximation linear in $\mathbf{p}$, and then use the well known formula for the multinomial variance of a linear function. The *jackknife approximation* $\hat{\theta}_J(\mathbf{p})$ is the linear function of $\mathbf{p}$ which matches $\hat{\theta}(\mathbf{p})$, (10.4), at the n points corresponding to the deletion of a single $\mathbf{x}_i$ from the observed data set $x_1, x_2, \cdots, x_n$,

$$\mathbf{p}_{(i)} = \frac{1}{n-1}(1, 1, \cdots, 1, 0, 1, \cdots, 1) \tag{10.6}$$

$i = 1, 2, \cdots, n$. Fig. 15 indicates the jackknife points for $n = 3$; because $\hat{\theta}$ is the functional form, (10.4), it does not matter that the jackknife points correspond to sample size $n - 1$ rather than n.

The linear function $\hat{\theta}_J(\mathbf{p})$ is calculated to be

$$\hat{\theta}_J(\mathbf{p}) = \hat{\theta}_{(i)} + (\mathbf{p} - \mathbf{p}^0) \cdot \mathbf{U} \tag{10.7}$$

where, in terms of $\hat{\theta}_{(i)} = \hat{\theta}(\mathbf{p}_{(i)})$, $\hat{\theta}_{(\cdot)} = \sum_{i=1}^n \hat{\theta}_{(i)}/n$, and $\mathbf{U}$ is the vector with ith coordinate

$$U_i = (n-1)(\hat{\theta}_{(\cdot)} - \hat{\theta}_{(i)}). \tag{10.8}$$

The jackknife estimate of standard error (Tukey, 1958; Miller, 1974) is

$$\hat{\sigma}_J = \left[\frac{n-1}{n}\sum_{i=1}^n \{\hat{\theta}_{(i)} - \hat{\theta}_{(\cdot)}\}^2\right]^{1/2} = \left[\frac{\sum_1^n U_i^2}{n(n-1)}\right]^{1/2}. \tag{10.9}$$

A standard multinomial calculation gives the following theorem (Efron, 1982a),

THEOREM. *The jackknife estimate of standard error equals $[n/(n-1)]^{1/2}$ times the bootstrap estimate of standard error for $\hat{\theta}_J$,*

$$\hat{\sigma}_J = \left[\frac{n}{n-1}\,\mathrm{var}_*\hat{\theta}_J(\mathbf{p}^*)\right]^{1/2}. \tag{10.10}$$

In other words, the jackknife estimate is itself almost a bootstrap estimate applied to a linear approximation of $\hat{\theta}$. The factor $[n/(n-1)]^{1/2}$ in (10.10) makes $\hat{\sigma}_J^2$ unbiased for σ^2 in the case where $\hat{\theta} = \bar{x}$, the sample mean. We could multiply the bootstrap estimate $\hat{\sigma}$ by this same factor, and achieve the same unbiasedness, but there does not seem to be any consistent advantage to doing so. The jackknife requires n, rather than $B = 50$ to 200 resamples, at the expense of adding a linear approximation to the standard error estimate. Tables 1 and 2 indicate that there is some estimating efficiency lost in making this approximation. For statistics like the sample median which are difficult to approximate linearly, the jackknife is useless (see Section 3.4 of Efron, 1982a).

There is a more obvious linear approximation to $\hat{\theta}(\mathbf{p})$ than $\hat{\theta}_J(\mathbf{p})$. Why not use the first-order Taylor series expansion for $\hat{\theta}(\mathbf{p})$ about the point $\mathbf{p} = \mathbf{p}^0$? This is the idea of Jaeckel's *infinitesimal jackknife* (1972). The Taylor series approximation turns out to be

$$\hat{\theta}_T(\mathbf{p}) = \hat{\theta}(\mathbf{p}^0) + (\mathbf{p} - \mathbf{p}^0)'\mathbf{U}^0$$

where

$$U_i^0 = \lim_{\varepsilon \to 0} \frac{\hat{\theta}((1-\varepsilon)\mathbf{p}^0 + \varepsilon\delta_i) - \hat{\theta}(\mathbf{p}^0)}{\varepsilon}, \tag{10.11}$$

δ_i being the ith coordinate vector. This suggests the

infinitesimal jackknife estimate of standard error

$$(10.12) \quad \hat{\sigma}_{IJ} \equiv [\mathrm{var}_* \hat{\theta}_T(\mathbf{p}^*)]^{1/2} = [\Sigma U_i^{02}/n^2]^{1/2}$$

with var_* still indicating variance under (10.2). The ordinary jackknife can be thought of as taking $\epsilon = -1/(n-1)$ in the definition of U_i^0, while the infinitesimal jackknife lets $\epsilon \to 0$, thereby earning the name.

The U_i^0 are values of what Mallows (1974) calls the empirical influence function. Their definition is a nonparametric estimate of the true influence function

$$IF(x) = \lim_{\epsilon \to 0} \frac{\theta((1-\epsilon)F + \epsilon\delta_x) - \theta(F)}{\epsilon},$$

[illegible] the degenerate distribution putting mass 1 on x. The right side of (10.12) is then the obvious estimate of the influence function approximation to the standard error of $\hat{\theta}$ (Hampel, 1974), $\sigma(F) \doteq [\int IF^2(x)\, dF(x)/n]^{1/2}$. The empirical influence function method and the infinitesimal jackknife give identical estimates of standard error.

How have statisticians gotten along for so many years without methods like the jackknife and the bootstrap? The answer is the delta method, which is still the most commonly used device for approximating standard errors. The method applies to statistics of the form $t(\bar{Q}_1, \bar{Q}_2, \cdots, \bar{Q}_A)$, where $t(\cdot, \cdot, \cdots, \cdot)$ is a known function and each $\bar{Q}_a$ is an observed average, $\bar{Q}_a = \sum_{i=1}^n Q_a(X_i)/n$. For example, the correlation $\hat{\theta}$ is a function of $A = 5$ such averages; the average of the first coordinate values, the second coordinates, the first coordinates squared, the second coordinates squared, and the cross-products.

In its nonparametric formulation, the delta method works by (a) expanding t in a linear Taylor series about the expectations of the $\bar{Q}_a$; (b) evaluating the standard error of the Taylor series using the usual expressions for variances and covariances of averages; and (c) substituting $\gamma(\hat{F})$ for any unknown quantity $\gamma(F)$ occurring in (b). For example, the nonparametric delta method estimates the standard error of the correlation $\hat{\theta}$ by

$$\left\{\frac{\hat{\theta}^2}{4n}\left[\frac{\hat{\mu}_{40}}{\hat{\mu}_{20}^2} + \frac{\hat{\mu}_{04}}{\hat{\mu}_{02}^2} + \frac{2\hat{\mu}_{22}}{\hat{\mu}_{20}\hat{\mu}_{02}} + \frac{4\hat{\mu}_{22}}{\hat{\mu}_{11}^2} - \frac{4\hat{\mu}_{31}}{\hat{\mu}_{11}\hat{\mu}_{02}} + \frac{4\hat{\mu}_{13}}{\hat{\mu}_{11}\hat{\mu}_{02}}\right]\right\}^{1/2}$$

where, in terms of $x_i = (y_i, z_i)$,

$$\hat{\mu}_{sh} \equiv \Sigma(y_i - \bar{y})^s(z_i - \bar{z})^h/n$$

(Cramér (1946), p. 359).

THEOREM. *For statistics of the form $\hat{\theta} = t(\bar{Q}_1, \cdots, \bar{Q}_A)$, the nonparametric delta method and the infinitesimal jackknife give the same estimate of standard error* (Efron, 1982c).

The infinitesimal jackknife, the delta method, and the empirical influence function approach are three names for the same method. Notice that the results reported in line 7 of Table 2 show a severe downward bias. Efron and Stein (1981) show that the ordinary jackknife is always biased upward, in a sense made precise in that paper. In the authors' opinion the ordinary jackknife is the method of choice if one does not want to do the bootstrap computations.

ACKNOWLEDGMENT

This paper is based on a previous review article appearing in *Behaviormetrika*. The authors and Editor are grateful to that journal for graciously allowing this revision to appear here.

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Comment

J. A. Hartigan

Efron and Tibshirani are to be congratulated on a wide-ranging persuasive survey of the many uses of the boostrap technology. They are a bit cagey on what is or is not a bootstrap, but the description at the end of Section 4 seems to cover all the cases; some data y comes from an unknown probability distribution F; it is desired to estimate the distribution of some function $R(y, F)$ given F; and this is done by estimating the distribution of $R(y^*, \hat{F})$ given $\hat{F}$ where $\hat{F}$ is an estimate of F based on y, and y^* is sampled from the known $\hat{F}$.

There will be three problems in any application of the bootstrap: (1) how to choose the estimate $\hat{F}$? (2) how much sampling of y^* from $\hat{F}$? and (3) how close is the distribution of $R(y^*, \hat{F})$ given $\hat{F}$ to $R(y, F)$ given F?

Efron and Tibshirani suggest a variety of estimates $\hat{F}$ for simple random sampling, regression, and autoregression: their remarks about (3) are confined mainly to empirical demonstrations of the bootstrap in specific situations.

I have some general reservations about the bootstrap based on my experiences with subsampling techniques (Hartigan, 1969, 1975). Let $X_1, \ldots, X_n$ be a random sample from a distribution F, let F_n be the empirical distribution, and suppose that $t(F_n)$ is an estimate of some population parameter $t(F)$. The statistic $t(\hat{F}_n)$ is computed for several random subsamples (each observation appearing in the subsample with probability ½), and the set of $t(\hat{F}_n)$ values obtained is regarded as a sample from the posterior distribution of $t(F)$. For example, the standard deviation of the $t(\hat{F}_n)$ is an estimate of the standard error of $t(F_n)$ from $t(F)$; however, the procedure is not restricted to real valued t.

The procedure seems to work not too badly in getting at the first- and second-order behaviors of $t(F_n)$ when $t(F_n)$ is near normal, but it not effective in handling third-order behavior, bias, and skewness. Thus there is not much point in taking huge samples $t(\hat{F}_n)$ since the third-order behavior is not relevant; and if the procedure works only for $t(F_n)$ near normal, there are less fancy procedures for estimating standard error such as dividing the sample up into 10 subsamples of equal size and computing their standard deviation. (True, this introduces more bias than having random subsamples each containing about half the observations.) Indeed, even if $t(F_n)$ is not normal, we can obtain exact confidence intervals for the median of $t(F_{n/10})$ using the 10 subsamples. Even five subsamples will give a respectable idea of the standard error.

Transferring back to the bootstrap: (A) is the boot-

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strap effective for non-normal situations? (B) in the normal case, does the bootstrap give accurate assessment of third-order terms? If not, it is scarcely justified to do many bootstrap simulations, since you will only use them to estimate a variance. The asymptotic justifications of the bootstrap such as in Bickel and Freeman (1981) or Singh (1981) do consider behavior near the normal.

To be specific, consider the case where a statistic $t(F_n)$ estimates a parameter $t(F)$. The first kind of bootstrapping might be on the quantity $t(F_n) - t(F)$; to estimate its variance $\sigma^2(F)/n$ we compute repeatedly $t(\hat{F}_n) - t(F_n)$ where $\hat{F}_n$ is the empirical distribution of a sample of size n from F_n. Thus $\sigma^2(F_n)$ will be used to estimate $\sigma^2(F)$. We might hope that

$$t(F_n) = t(F) + \xi \frac{\sigma(F)}{\sqrt{n}} + O\left(\frac{1}{n}\right)$$

where $\xi \sim N(0, 1)$. This is the case referred to above where $t(F_n)$ is normal and numerous resampling estimates are available to estimate $\sigma^2(F)$. To do better, consider the higher order terms:

$$t(F_n) = t(F) + \xi \frac{\sigma(F)}{\sqrt{n}} + \frac{s_3(F)}{n}(\xi^2 - 1) + \frac{b(F)}{n} + O(n^{-3/2}).$$

Then

$$t(\hat{F}_n) = t(F_n) + \xi \frac{\sigma(F_n)}{\sqrt{n}} + \frac{s_3(F_n)}{n}(\xi^2 - 1) + \frac{b(F_n)}{n} + O(n^{-3/2}).$$

We might expect that the sample quantities $\sigma(F_n)$, $s_3(F_n)$; $b(F_n)$ are within $O(n^{-1/2})$ of the population quantities; but since $\sigma(F_n) - \sigma(F) = O(n^{-1/2})$, the error in approximating the distribution of $t(F_n) - t(F)$ by that of $t(\hat{F}_n) - t(F_n)$ is $O(n^{-1/2})$, so that the additional skewness and bias terms are of no interest:

$$P\left[(t(F_n) - t(F) \le \frac{a}{\sqrt{n}}\right] - P\left[t(\hat{F}_n) - t(F_n) \le \frac{a}{\sqrt{n}}\right] = O(n^{-1/2}).$$

The bootstrap distribution is no better than any normal approximation using an estimate of variance accurate to $O(n^{-1/2})$!

On the other hand, if

$$R(y, F) = [t(F_n) - t(F)]/\sigma(F),$$

$$[t(F_n) - t(F)]/\sigma(F) = \frac{\xi}{\sqrt{n}} + \frac{s_3'(F)}{n}(\xi^2 - 1) + \frac{b'(F)}{n} + O(n^{-3/2})$$

$$[t(\hat{F}_n) - t(F_n)]/\sigma(F_n) = \frac{\xi}{\sqrt{n}} + \frac{s_3'(F_n)}{n}(\xi^2 - 1) + \frac{b'(F_n)}{n} + O(n^{-3/2}).$$

Now $s_3'(F_n)$ estimates $s_3'(F)$ and $b'(F_n)$ estimates $b'(F)$ to within $O(n^{-1/2})$, and the Cornish-Fisher expansion is accurate to skewness and bias terms:

$$P\left(\frac{t(F_n) - t(F)}{\sigma(F)} \le \frac{a}{\sqrt{n}}\right) - P\left(\frac{t(\hat{F}_n) - t(F_n)}{\sigma(F_n)} \le \frac{a}{\sqrt{n}}\right) = O(n^{-1}).$$

These results are given for $t(F_n) = \bar{X}$ in Singh (1981).

The conclusion is that for $t(F_n)$ near normal there is no advantage for the bootstrap over other resampling methods, unless the pivotal $[t(F_n) - t(F)]/\sigma(F)$ is used. Usually $\sigma(F)$ is not known; that's why we are resampling in the first place. We would need to estimate it by bootstrapping and use the pivotal $(t(F_n) - t(F))/\sigma(F_n)$. And the distribution of this pivotal would be determined by bootstrapping to obtain $[t(\hat{F}_n) - t(F_n)]/\sigma(\hat{F}_n)$. Note that $\sigma(\hat{F}_n)$ requires two levels of bootstrapping; this might get close to Professor Efron's objective of soaking up all the spare cycles on the West Coast!

Let us consider the modest objective of estimating the variance of $t(F_n)$. The various resampling techniques compute the variance of $t(W^1)$, $t(W^2)$, ..., $t(W^k)$ where $t(W^i)$ denotes the statistic computed on X_i repeated W_i^i times, $1 \le i \le n$. What is a good choice of $W^1, W^2, \ldots, W^k$? If in fact $X_1, \ldots, X_n$ are sampled from $N(\mu, \sigma^2)$ and $t = \bar{X}$, a minimum variance unbiased estimate of σ^2 is obtained by setting $W_i^i = 1 + \sqrt{n}\xi_i^i$ where $\xi^1, \sigma^2, \ldots, \xi^k$ are any k orthonormal vectors orthogonal to 1. The quantities $\sqrt{n}\xi_i^i$ can be obtained roughly by sampling each of them independently from $N(0, 1)$. Bootstrap resampling, for large n, has W_i^i approximately independently Poisson with expectation 1. Random subsampling, for large n has W_i^i approximately independent and approximately taking values 0 and 2 with probability ½. The Dirichlet distribution for F given F_n produces weights W_i^i that are approximately exponential with expectation 1. Any resampling scheme in which the weights are approximately independent with mean and variance 1 will give the right expected variance, but the efficiency

of the estimate (at normal means) is optimal for $W_i^1 = 1 + \sqrt{n}\xi_i^1$.

For $n = 8$, obtain an efficient estimate from subsamples (1234), (1256), (1278), (1357), (1368), (1458), (1467); use as many as you need, and if $n > 8$ divide the sample into 8 groups as evenly as possible. I think it must be rare that the various approximations needed to connect the resampled computation to the computation of interest will be satisfied well enough to justify more than a few resamples. Perhaps this method might be called the *shoestring*.

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Rejoinder

B. Efron and R. Tibshirani

Professor Hartigan, who is one of the pioneers of resampling theory, raises the question of higher order accuracy. This question has bothered resamplers since the early days of the jackknife. Sections 7 and 8 of our paper show that the bootstrap can indeed achieve higher levels of accuracy, going the next step beyond simple estimates of standard error. The bootstrap confidence intervals we discuss are *not* of the crude (although useful) first-order form $\hat{\theta} \pm \hat{\sigma}z^{(\alpha)}$. They explicitly incorporate the higher order corrections about which Hartigan is legitimately concerned.

In particular the "z_0" term (7.8) is a correction for bias, and the acceleration constant "a," (7.16), is a correction for skewness. These correspond to Hartigan's $b(F)$ and $s_3(F)$, respectively. The reader who follows through Tables 5 and 7 will see these corrections in action. The fact that they produce highly accurate confidence intervals is no accident. The theory in Efron (1984a, 1984b) demonstrates higher order accuracy of the BC_a intervals in a wide class of situations. This demonstration does not yet apply to fully general problems, but current research indicates that it soon will. (The impressive higher order asymptotic results of Beran, Singh, Bickel, and Freedman, referred to in the paper, underpin these conclusions.)

It is worth mentioning that the bias and skewness corrections of the bootstrap confidence intervals are not of the simple "plug into an approximate pivotal" form suggested in Hartigan's remarks. The theory is phrased in a way which automatically corrects for arbitrary nonlinear transformations, even of the violent sort encountered in the correlation example of Table 5. In this sense the bootstrap theory does handle "non-normal situations."

Since this paper was written, research by several workers, including T. Hesterberg, R. Tibshirani, and T. DiCiccio, has substantially improved the computational outlook for bootstrap confidence intervals. It now appears possible that bootstrap sample sizes closer to $B = 100$ than $B = 1000$ may be sufficient for the task. However, these improvements are still in the process of development.

Professor Hartigan's last remarks, on the comparative efficiency of different resampling methods, need careful interpretation. There are two concepts of efficiency involved: the efficiency of the numerical algorithm in producing an estimate of variance, and the statistical efficiency of the estimate produced. There is no question that other resampling techniques, for example, the jackknife, can produce variance estimates more economically than does the bootstrap. We have argued, both by example and theory, that the bootstrap variance is generally more efficient as a statistical estimator of the unknown true variance.

This is not surprising given that methods like the jackknife are Taylor series approximations to the bootstrap (see Section 10). The simple idea in (2.3), substituting $\hat{F}$ for F, lies at the heart of all nonparametric estimates of accuracy. The bootstrap is the crudest of these methods in that it computes $\sigma(\hat{F})$ directly by Monte Carlo. For this reason it is also the method that involves the least amount of analytic approximation. It is perhaps surprising, and certainly gratifying, that a method based on such a simple form of inference is capable of producing quite accurate confidence intervals.

To say that the bootstrap is good, as we have been blatantly doing, doesn't imply that other methods are bad. Professor Hartigan's own work shows that for some problems, for example, forming a confidence interval for the center of a symmetric distribution, other methods are better. We hope that resampling methods in general will continue to be a lively research topic.

APPENDIX E

EXPOSURE TO ACETALDEHYDE FROM INDOOR AIR

EXPOSURE TO ACETALDEHYDE FROM INDOOR AIR

I. BACKGROUND

California Health and Safety Code Section 39660.5 directs the Board to assess exposures to toxic air contaminants in indoor as well as outdoor environments, and to identify the contribution of indoor concentrations to total air exposure. Indoor exposure assessment has become increasingly important as an integral part of assessing exposure to toxic air contaminants because:

1. Californians spend most of their time (about 87 percent on average) indoors (Wiley et al., 1989); and

2. personal and indoor air monitoring data indicate that some pollutant concentrations are regularly higher indoors than outdoors.

Thus, consideration of indoor air exposure data is critical in developing a realistic estimate of personal exposures through the air environment.

While the main objective of this report is to estimate the exposure to acetaldehyde in the indoor air environment, limited data are also presented on exposure through other media, such as food and water. This is not by any means an exhaustive review of all available data, but is included to provide a broader perspective of environmental exposure to acetaldehyde.

II. INDOOR AIR CONCENTRATIONS OF ACETALDEHYDE

Only a small number of limited surveys that measured acetaldehyde concentrations in indoor air have been published. Those surveys monitored a small number of homes, and the homes that were monitored were not selected randomly. With such limitations, it is not possible to extrapolate the monitoring results to apply to the general population of homes in the individual surveyed. However, when viewed together, the results of individual surveys can at least provide a general idea of the magnitude of indoor acetaldehyde concentrations. It is in that context that those surveys are presented below.

A. Residences

In one of the larger published surveys, Zweidinger et al. (1988) measured acetaldehyde concentrations inside 20 homes of non-smokers in Boise, Idaho from November, 1986, to February 1987. From Saturday through Tuesday during each week of the survey the investigators measured acetaldehyde concentrations inside a pair of homes; each pair consisted of one home with a woodstove and one without. Consecutive 12-hour air samples were obtained from each home

using 2,4-dinitrophenylhydrazine (2,4-DNPH) coated silica gel cartridges. Sample analysis was performed by high performance liquid chromatography (HPLC). Average acetaldehyde concentrations (as calculated from data presented) inside the homes ranged from 9.3 to 11.8 ppbv (16.7 to 21.2 $\mu g/m^3$). The presence of a woodstove did not appear to affect indoor acetaldehyde concentrations. Concurrently-sampled average outdoor acetaldehyde concentrations (sampled only outside the homes without woodstoves) ranged from 2.1 to 2.6 ppbv (3.8 to 4.7 $\mu g/m^3$) (as calculated from data presented).

A similar survey was recently conducted in Roanoke, Virginia, the results of which have not yet been published (R. Zweidinger, personal communication). Twenty homes of non-smokers were monitored in pairs that consisted of one home that used oil as a heating fuel and one home that did not. The monitoring methods and sample collection times were the same as those used in the Boise survey. Preliminary data indicate that the average acetaldehyde concentrations in those homes was 8.3 ppbv (14.9 $\mu g/m^3$). Indoor concentrations ranged 3 to 26 ppbv (5.4 to 46.8 $\mu g/m^3$), but contamination of some of the sample blanks casts doubt on the validity of some of the high values. At this preliminary stage of the data analysis, conclusions have not been drawn concerning the effect of oil heating on indoor acetaldehyde concentrations.

In an earlier pilot study conducted in February, 1985 (Zweidinger et al., 1987; Highsmith et al., 1988) the investigators used similar methods to measure acetaldehyde concentrations inside and outside three homes in Raleigh, North Carolina. All three homes were occupied by non-smokers and were monitored during two nights for 12 hours per night (one house was monitored only once) while their woodstoves were in operation. The investigators reported that the average indoor acetaldehyde concentrations reported ranged from 4.0 to 8.5 ppbv (7.2 to 15.3 $\mu g/m^3$). Average concurrently-measured outdoor concentrations ranged from 1.3 to 4.4 ppbv (2.3 to 7.9 $\mu g/m^3$); the highest outdoor value was observed outside a home where the chimney plume down washed directly on top of the outdoor samplers.

Limited measurements of acetaldehyde inside two California homes were performed in 1983 by Rogozen et al. (1984). Those two homes were selected from 64 homes, located throughout the State, which had been randomly selected for a formaldehyde survey. Air inside the two homes was sampled for one hour using impingers containing a 2,4-DNPH solution and analysis was performed by HPLC. The reported acetaldehyde concentrations inside the two homes were 7.1 and 2.6 ppbv (12.8 and 4.7 $\mu g/m^3$).

Acetaldehyde levels were measured in a subsample of 8 homes in Baltimore, Maryland, in 1987 as part of a larger survey of 155 homes (W. Nelson, personal communication; Nelson et al., 1988). In the larger survey, the 155 homes (which included homes of smokers) were selected at random; the 8-home subsample was comprised of homes that were monitored during

one week of the larger survey, and were thus not selected strictly at random. Two consecutive 12-hour samples were collected inside and outside each of the 8 homes using 2,4-DNPH-coated silica gel cartridges followed by HPLC analysis. The mean indoor acetaldehyde concentration was 14.8 ppbv (26.6 $\mu g/m^3$) and the values ranged from 6.2 to 37.4 ppbv (11.2 to 67.3 $\mu g/m^3$). Concurrent outdoor acetaldehyde concentrations averaged 1.7 ppbv (3.1 $\mu g/m^3$) and ranged from 0.3 to 4.1 ppbv (0.5 to 7.4 $\mu g/m^3$).

In an unpublished pilot study conducted in the Raleigh/Durham area of North Carolina in 1983, investigators measured acetaldehyde concentrations inside 15 residences (12 conventional homes and 3 mobile homes; S. Tejada, personal communication). Air samples were collected for one to two hours using impingers containing 2,4-DNPH. The mean concentration measured in all 15 homes was 20.4 ppbv (36.7 $\mu g/m^3$); one high value measured in a mobile home drove this mean value up somewhat. The mean acetaldehyde concentration for just the 12 conventional homes was 15.2 ppbv (27.4 $\mu g/m^3$).

Another unpublished pilot study was conducted in the same area in 1984 (J. Bufalini, personal communication). In that study, investigators measured acetaldehyde concentrations inside two homes during times when their fireplaces were in use and not in use. Several 30-minute samples were collected inside each home using impingers containing 2,4-DNPH. The acetaldehyde concentrations ranged from 3.6 to 15.0 ppbv (6.5 to 27.0 $\mu g/m^3$). Fireplace usage did not appear to alter indoor acetaldehyde concentrations significantly.

B. Public Buildings

Bufalini and his co-investigators also used similar methods to measure acetaldehyde concentrations inside two offices located in Research Triangle Park, North Carolina (J. Bufalini, personal communication). The acetaldehyde concentration inside a non-smoking office was 1.2 ppbv (2.2 $\mu g/m^3$), while that inside an office where smoking occurred was 12.8 ppbv (23.0 $\mu g/m^3$). The offices were located down the hall from each other and had similar air exchange rates (approximately 4 to 5 air changes per hour).

As part of a study on environmental tobacco smoke, Lofroth <u>et al</u>. (1989) measured acetaldehyde concentrations inside a North Carolina tavern which was about 180 m^3 in volume and was variously occupied by 5 to 25 people, many of whom were smoking. Samples were collected on two separate days for three and four hours, respectively, using 2,4-DNPH-coated silica gel cartridges followed by HPLC analysis. The reported acetaldehyde concentrations measured for those two days was 102 ppbv; using a conversion factor of 1 ppbv = 1.8 $\mu g/m^3$ (183 $\mu g/m^3$) and 113 ppbv (204 $\mu g/m^3$).

Druzik et al., (1990) measured indoor concentrations of acetaldehyde in five museums and one library located in Los Angeles. Samples were collected with DNPH-coated cartridges. Indoor concentrations ranged from 4.2 to 35 ppbv (7.6 to 63.0 $\mu g/m^3$). Outdoor concentrations measured in Los Angeles using the same method were lower; they ranged from 1.7 to 9.9 ppbv (3.1 to 17.8 $\mu g/m^3$).

C. In-vehicle Concentrations

The air in the enclosed space encountered in vehicles is not strictly "indoor air", but measurements of acetaldehyde concentrations in such enclosed spaces are included here to facilitate consideration of people's total exposures to acetaldehyde. A study which measured acetaldehyde levels in the cars of volunteers during their daily commute to and from an office complex in El Monte, California was conducted from May to October, 1987 and from November to March, 1988. Measurements were made using a cartridge impregnated with 2,4-DNPH with HPLC analysis. The daily one-way commute of the volunteers averaged 33 minutes; the mean acetaldehyde concentrations of 194 total samples was 7.6 ppbv (13.7 $\mu g/m^3$). The maximum concentration was 37.0 ppbv (66.6 $\mu g/m^3$) (Shikiya et al., 1989).

D. Summary of Indoor Concentrations

There is only limited information available concerning indoor concentrations of acetaldehyde. Based on the results of a number of small-scale surveys (summarized in Table 1), a very crude estimate of an average acetaldehyde concentration that would be expected to occur inside residences is about 3 to 15 ppbv (5.4 to 27.0 $\mu g/m^3$). The highest acetaldehyde concentration reported inside a residence was 37.4 ppbv (67.3 $\mu g/m^3$). The results of one study suggest that higher levels may occur in some indoor environments, in this case a tavern occupied by a number of people who were smoking, where levels of over 100 ppbv (180 $\mu g/m^3$) were reported. Average and maximum in-vehicle acetaldehyde concentrations [7.6 and 37.0 ppbv (13.7 and 66.6 $\mu g/m^3$), respectively] appear to be similar in magnitude to those inside residences.

III. POTENTIAL SOURCES OF ACETALDEHYDE IN INDOOR AIR

Acetaldehyde is formed as a combustion by-product and can be emitted from a number of indoor sources including cigarettes, fireplaces and woodstoves, and cooking. Acetaldehyde occurs in traces in all ripe fruit and may form in alcoholic beverages after exposures to the air (Fishbein, 1979), although it is not known if volatilization from those sources could affect indoor acetaldehyde concentrations to any significant degree. Vehicle exhaust may also contribute to indoor acetaldehyde levels. Limited information indicates that acetaldehyde is emitted from some building materials and consumer products.

A. Cigarette Smoke

Acetaldehyde has been reported in fresh leaf tobacco as well as in tobacco smoke (Fishbein, 1979). Mainstream cigarette smoke (the smoke that

TABLE 1

Indoor Air Concentrations of Acetaldehyde*
(parts per billion)

LOCATION	AVERAGE CONCENTRATION	RANGE	N	COMMENTS	REFERENCES
RESIDENCES					
Boise, ID	9.3-11.8		20	non-smokers	Zweidinger et al., 1988
California		2.6 & 7.1	2		Rogozen et al., 1984
Raleigh, NC	4.0-8.5		3	non-smokers	Zweidinger, et al., 1987 Highsmith, et al., 1988
Roanoke, VA	8.3	3-26**	20	non-smokers	Zweidinger, personal communication
Baltimore, MD	14.8	6.2-37.4	8	smokers may be included	Nelson, personal communication
Raleigh/ Durham, NC	20.4 15.2		15 12	+3 mobile -3 mobile	Tejada, personal communication
Raleigh/ Durham, NC		3.6-15	2		Bufalini, personal communication
PUBLIC BLDGS.					
Los Angeles, CA 5 museums, 1 library		4.2-35	6		Druzik et al., 1990
North Carolina office bldg.		1.2 12.8	1 non-smoking 1 smoking		Bufalini, personal communication
North Carolina tavern		102 & 113	1 heavy smoking		Lofroth et al., 1989

(continued on next page)

INDOOR AIR CONCENTRATIONS OF ACETALDEHYDE continued

LOCATION	AVERAGE CONCENTRATION	RANGE	N	COMMENTS	REFERENCES
INSIDE VEHICLES					
Southern California	7.6	max. 37.0	194	commute driving	Shikiya et al., 1989
SMOKING CHAMBER					
		48 & 52		1 cig./30 min.	Lofroth et al., 1989
		114 & 129		1 cig./15 min.	

* Data on indoor air concentrations are limited; data cannot be extrapolated to apply to general population of homes in the respective areas surveyed. The data presented here are intended to provide a general idea of the magnitude of indoor acetaldehyde concentrations.

** Contamination of some field blanks casts doubt on the validity of some of the high values.

is generated during a puff and is inhaled by the smoker) contains from 400 to 1,400 μg of acetaldehyde per unfiltered cigarette (U. S. Department of Health and Human Services, 1989). Lofroth et al. (1989) recently measured acetaldehyde concentrations in sidestream cigarette smoke (smoke which arises mainly from the passive burning of the cigarette and is released into the environment) and determined the airborne yield per cigarette to be 2,400 μg. It should be noted that the above values were determined using machine-smoked cigarettes under standard laboratory conditions, which do not reflect present-day smoking behavior (U.S. Department of Health and Human Services, 1989).

B. Woodsmoke and Cooking

Acetaldehyde is formed as a product of incomplete wood combustion in residential fireplaces and woodstoves. It is among the major aldehydes emitted from wood-burning fireplaces (Lipari et al., 1984). Although the results of limited residential surveys suggest that properly-operating fireplaces and woodstoves do not affect indoor acetaldehyde concentrations to any significant degree (see section II.), wood smoke can enter the living space when wind causes variations in room pressure or when flues or chimneys are blocked. Smoke which exits the residence or smoke from nearby neighbors might also be drawn indoors under certain meteorological conditions (Quraishi and Todd, 1987).

Sexton et al. (1986) noted that acetaldehyde was a major constituent of emissions from frying hamburger (levels not specified).

C. Other Indoor Sources

Vehicle exhausts. Vehicle exhaust contains acetaldehyde (Rogozen et al., 1987) and could contribute to indoor concentrations. For example, vehicle exhaust from attached garages or a nearby busy roadway may enter residences.

Building materials. Acetaldehyde emissions were detected from four sprayed-in-place rigid polyurethane foams (Krzymien, 1989). Such foams are used as insulation in aircraft, recreational vehicles, commercial buildings, and, to a limited extent, in residences.

Consumer products. Small amounts of acetaldehyde may be present as a contaminant in acetone, which is widely used in nail polish remover and other consumer products (Rogozen et al., 1987). Sexton et al. (1986) noted that acetaldehyde was a major constituent in the emissions from a deodorant spray (levels not specified). Acetaldehyde may be emitted from diverse products such as lubricants, inks, adhesives and coatings (Hodgson and Wooley, 1991).

IV. OTHER ROUTES OF EXPOSURE TO ACETALDEHYDE

Limited information is presented on exposure through routes other than inhalation. This is not an exhaustive review of all available data, but rather has been included to provide a broader perspective of environmental exposure to acetaldehyde.

A. Ingestion

Food. Acetaldehyde is a normal intermediate product in the respiration of higher plants (Fishbein, 1979) and is thus found naturally in many fruits. Acetaldehyde has been detected in apples, broccoli, coffee, grapefruit, strawberries, and blueberries (WHO, 1985). Levels measured in orange and grapefruit juices and other citrus products ranged from 50 to 190 ppm (w/v) (Lund et al., 1981). Acetaldehyde is found in the essential oils of various natural flavorings and scents. It has been detected in cheese, heated skim milk, cooked beef, cooked chicken, and rum. It has also been detected at trace levels in two kinds of mushrooms (WHO, 1985).

Acetaldehyde is also added to foods as a flavoring agent and a preservative. It is "generally recognized as safe" by the U.S. Food and Drug Administration for use as a synthetic flavoring substance and adjuvant (WHO, 1985). The FAO/WHO (Food and Agriculture Organization/World Health Organization) has listed the acceptable daily intake of synthetic flavorings (which specifically includes acetaldehyde) at 0 to 2.5 mg/kg body weight, with a typical level of use listed at 1-300 ppm (Doull et al., 1980). Acetaldehyde is an important component of many flavors added to foods, such as milk products, baked goods, fruit juices, candies, desserts, and soft drinks, at usual levels of up to 0.047 percent. It is present in flavoring used to impart a butter-like flavor to processed foods, especially margarine. Acetaldehyde is also used as a preservative for fruit and fish and is used as a storage fumigant for foods such as apples and strawberries (WHO, 1985).

Acetaldehyde is a product of alcohol fermentation and has been measured in 18 European beers at concentrations ranging from 2.6 to 13.5 mg/l (WHO, 1985). Additionally, acetaldehyde may form in alcoholic beverages after exposure to the air (Fishbein, 1979). Alcohol is a major source of acetaldehyde in the body; acetaldehyde is a metabolic intermediate in the oxidation of ethanol by liver enzymes (NRC, 1981). It should be noted that acetaldehyde is an intermediate product in the metabolism of sugars in the body and normally occurs at trace levels in the blood (Fishbein, 1979).

Water. Acetaldehyde levels were recently measured in ten California water treatment facilities located throughout the State. The facilities selected use source waters that are representative of supplies used by the majority of consumers in California. The results show that the median acetaldehyde concentration in drinking water samples was 2.1 μg/l and the 75th percentile concentration was approximately four μg/l (Metropolitan Water District of Southern California and JMM, Inc., 1989). Thus, a person drinking two liters of water per day may receive up to about 8 μg of acetaldehyde per day through this route.

B. Skin Absorption

No data on dermal absorption of acetaldehyde are readily available. However, based on its chemical similarity to formaldehyde, which is not absorbed systemically through the dermal route to any appreciable degree (World Health Organization, 1987, 29 CFR Parts 1910 and 1926), dermal absorption of acetaldehyde is likely to be negligible.

C. Summary of Other Routes of Exposure

Acetaldehyde is found commonly in a number of foods as a natural constituent and as an intentional food additive. The daily amount ingested through food cannot be estimated using readily available information. Levels in water are relatively low; a high estimate of the amount a Californian may ingest through water is 8 μg/day. Dermal absorption is surmised to be negligible. It should be noted that, with respect to the potential carcinogenicity of acetaldehyde, the ingestion route may not be of major significance; it is surmised that only in specialized organs such as the nasal cavity that inhalation of appreciable amounts may overcome local defense mechanisms (Casarett et al., 1986).

V. ESTIMATES OF THE PRESENTED DOSE OF ACETALDEHYDE FROM RESIDENTIAL INDOOR AIR AND ENVIRONMENTAL TOBACCO SMOKE

The inhalation route is of major importance to the toxic (eg. carcinogenic) effects of acetaldehyde. Estimates of the daily amounts of acetaldehyde inhaled through residential indoor air and from environmental tobacco smoke are shown in Table 2. These estimates are based on very limited data and are thus very crude. The term "presented dose" is used because the presented dose may not necessarily represent a true dose, since it does not take into account the fraction of the inhaled amount that is absorbed so that the already high level of uncertainty in the values reported is not increased further.

The estimates of presented doses from residential exposures were calculated using the indoor concentration estimates derived in section II and an average value for breathing volume. Those estimates assume that an average person inhales about the same indoor concentration of acetaldehyde (i.e the residential concentration) all day. This assumption was made because: 1) Californians spend most of their time indoors in the home (Wiley et al., 1989); and 2) limited evidence suggests that acetaldehyde

TABLE 2

Estimates of the Presented Dose of Acetaldehyde From Residential Indoor Air and Environmental Tobacco Smoke

	Acetaldehyde inhaled (micrograms per day)
Residential indoor air*	
a. average amount inhaled	108 - 540
b. high range of estimate	1,440
Environmental tobacco smoke**	1,740 - 4,660

* Based on very limited data; office building exposures and in-vehicle exposures are estimated to be very similar to residential exposures.

** Based on chamber and tavern concentrations measured by Lofroth et al. (1989) under specific conditions; does not necessarily represent range of all possible levels.

Assumptions:

1. The average person inhales about 20 cubic meters of air per day.
2. Ingestion and skin absorption are not significant routes of exposure.
3. A person inhales about the same acetaldehyde concentration all day.

concentrations inside vehicles and offices may be similar in magnitude to residential levels. Because the indoor concentration data are so limited, there would be little benefit in attempting to refine the estimates further (eg. by taking into account the average amount of time per day Californians spend in the home), so no such refinements were attempted.

Based on limited residential surveys, the average residential indoor acetaldehyde concentration is 3 to 15 ppbv (5.4 to 27.0 $\mu g/m^3$) and may range up to approximately 40 ppbv (72 $\mu g/m^3$). The average adult inhales approximately 20 m^3 of air per day (International Commission on Radiological Protection, 1975). Thus, a person may inhale approximately 108 to 540 μg of acetaldehyde per day on average. The amount inhaled could potentially range up to 1,440 μg/day.

A crude estimate of the amount of acetaldehyde that could potentially be inhaled from environmental tobacco smoke was calculated based on acetaldehyde concentrations measured in a smoking chamber and in a tavern with smokers present (see sections II and III). For simplicity, and because the data upon which the estimate is based are limited, the estimate assumes that the acetaldehyde concentration inhaled is about the same throughout the day. Acetaldehyde concentrations produced by sidestream smoke in a smoking chamber ranged from 87 $\mu g/m^3$ (one cigarette smoked every 30 minutes) to 233 $\mu g/m^3$ (one cigarette smoked every 15 minutes). A person breathing 20 m^3 of air would thus inhale between 1,740 and 4,660 μg of acetaldehyde concentration of III.) would inhale 4,080 μg of acetaldehyde per day. This value is within the range estimated using the chamber data.

<u>Summary</u>. Individuals are estimated to inhale about 108-540 μg of acetaldehyde per day in indoor residential environments and other indoor environments, on the average. Daily inhaled doses from indoor air may range up to 1,440 μg. If an individual were to spend the entire day in a smoke-filled environment such as a tavern, the daily inhaled dose could total from 1,740 to 4,660 μg. These estimates were based on very limited data and may not be representative of the California population.

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APPENDIX F

INFORMATION REQUEST LETTER WITH ATTACHMENTS AND RESPONSES

STATE OF CALIFORNIA

George Deukmejian, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

March 24, 1989

Dear Sir or Madam:

Request for Information Regarding Acetaldehyde

I am writing to request information on the atmospheric chemistry, sources, total exposure to, and health effects of acetaldehyde. The California Air Resources Board (ARB) is requesting this information as part of our toxic air contaminant program. This program is mandated by California Health and Safety Code Section 39650 eq seq. A summary of this program is contained in Attachment 1, which also describes the statutory basis for the program.

The information that you provide will be considered in an evaluation of acetaldehyde as a candidate toxic air contaminant; the evaluation will be conducted jointly by the ARB and the state's Department of Health Services (DHS). As part of the evaluation, we will consider all available health and exposure information regarding acetaldehyde.

In February 1989, we conducted a reference search on acetaldehyde exposure and health effects using several data bases from the Dialogue data retrieval system. These references include material published from 1972 to late 1988. The attached bibliography (Attachment 2) lists the most recent and relevant references from this information search. We are requesting additional, pertinent information on acetaldehyde health effects and exposure, including any material that may not be available to the public or that is not included in the attached bibliography.

We are also requesting information relevant to human exposure to acetaldehyde in California through media other than outdoor ambient air. Specifically, we are requesting information concerning total exposure to acetaldehyde through inhalation, ingestion, and skin absorption, with special emphasis on inhalation exposure in the indoor air environment. This includes acetaldehyde concentrations in various media, consumption information, bioabsorption rates, body burden studies, etc. We are also requesting data on emission sources responsible for acetaldehyde exposures in media other than outside air.

The information that you provide with the exception of trade secrets may be released to the public. The Air Resources Board's procedure for handling information claimed to be trade secrets is explained in Attachment 3.

If you believe that any of the information you are providing is a trade secret or otherwise exempt from disclosure under any other provision of law, you should identify it as such at the time of submission (Health and Safety Code Section 39660(e)). The ARB may ask you to provide documentation of your claim of trade secret or exemption at a later date.

I would appreciate receiving by April 28, 1989 any relevant information you wish to submit. Your help in expediting our review will be greatly appreciated. Please send the information to the attention of:

Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Re: Acetaldehyde
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have further questions regarding indoor acetaldehyde exposure, please contact John Batchelder at (916) 323-1505. For other questions, please contact Robert Rood at (916) 445-6138.

If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate substances, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

Peter D. Venturini, Chief
Stationary Source Division

Attachments

cc: Michael Lipsett, Department of Health Services
Rex Magee, Department of Food and Agriculture
Roxanne Jacques, President, California Air Pollution Control Officers Association
Stew Wilson, Executive Secretary, California Air Pollution Control Officers Association
David Howekamp, EPA, Region 9
Mike Stenburg, EPA, Region 9
Kathy Diehl, EPA, Region 9
Assemblywoman Sally Tanner, Chairwoman Committee on Toxic Materials
Senator Ralph Dills, Chairman Committee on Governmental Organization
Senator Art Torres, Chairman, Committee on Toxics and Public Safety Management
Robert D. Barham, Air Resources Board
John Batchelder, Air Resources Board
Robert Rood, Air Resources Board
Scientific Review Panel Members
Air Pollution Control Officers

Attachment 1
February 1989

State of California
AIR RESOURCES BOARD

Toxic Air Contaminant: Program Statutory Basis and Process

California's toxic air contaminant program is established by Health and Safety Code sections 39650-39674. This law sets forth the process for:

1. assessing the risk posed by substances;
2. identifying by regulation substances determined to be toxic air contaminants; and
3. managing the risk by adopting control measures for the identified toxic air contaminant

The law defines a toxic air contaminant as an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Two reports are prepared during this risk assessment and risk management process. The first report, which is prepared by the Air Resources Board (ARB) staff and the Department of Health Services (DHS), contains information on the health effects of the substance. This report is used to determine whether a substance should be identified as a toxic air contaminant. We refer to this report as the "ID" report. The second report, which is prepared by the ARB staff after a substance is identified as a toxic air contaminant, is on the need for and appropriate degree of regulation of that substance . We refer to this report as the "regulatory needs" report. Both reports are made available to the public for review and comment.

Before the ARB can formally identify a substance as a toxic air contaminant, several steps must be taken. First, the ARB must request the DHS to evaluate the health effects of the candidate substance. Second, the ARB staff must prepare the "ID" report that includes the estimate of exposure levels and also the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted by interested parties will be considered in the report to the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Last, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the ARB and will be the basis for any regulatory action to identify a substance as a toxic air contaminant.

The attached information request is the first step in preparing the "ID" report on whether a substance should be identified as a toxic air contaminant. Before either the ARB or the DHS begin their analysis of a substance, the ARB provides an opportunity for interested parties to submit information on the atmospheric chemistry, sources, exposure to and health effects of that substance. You are encouraged to submit any information that you believe would be important in DHS' and ARB's evaluation.

Attachment 2
February 1989

State of California
AIR RESOURCES BOARD

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Journal Code: ETR

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National Inst. for Occupational Safety and Health, Cincinnati, OH.
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Health Effects Research Lab., Research Triangle Park, NC.
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c1986 10p
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Location: Alcohol Res. Cent., Univ. Connecticut, Farmington, CT, USA
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Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland.
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Location: Dep. Alcohol Drug Addict. Res., Karolinska Inst., 104 01, Stockholm, Swed.
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Corp. Source Codes: 064598002; 9202165
Report No.: VW-FMT-8608-V/5
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Journal; J. Toxicol., Clin. Toxicol. Date: 1987 Volume: 25 Number 3 Pages: 185-98

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Location: Sch. Med., Univ. Sao Paulo, Sao Paulo, Brazil
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Joint Publications Research Service, Arlington, VA.
Corp. Source Codes: 056306000; J1957394
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Northrop Services Inc, Research Triangle Park, NC, USA
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Location: Natl. Inst. Forensic Toxicol., Oslo, Norway
Journal: Alcohol.: Clin. Exp. Res. Date: 1984 Volume: 8 Number: 5
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Southeastern Louisiana Univ., Hammond. Dept. of Biological Sciences.
Corp. Source Codes: 056586002; U5944451
Sponsor: National Aeronautics and Space Administration, Washington, DC.
Jun 87 14p
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Summer Faculty Fellowship Program, v2 14p 1986.
Journal Announcement: GRAI8721; STAR2519

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Health Assessment Document for Acetaldehyde. External Review Draft.
Location: Environ. Criter. Assess. Off., Research Triangle Park, NC, USA
Journal: Report Date: 1987 Number: EPA/600/8-86/015A; Order No. PB87-202446 Pages: 216 pp.

Yan, R. T.; Zhu, C. X.; Chen, J. S.
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Department of Anaerobic Microbiology, Virginia Polytechnic Institute, Blacksburg 24061.
Anal Biochem (United States) Aug 1 1987, 164 (2) p362-6,
ISSN 0003-2697 Journal Code: 4NK

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Metabolism of [14C]Paraldehyde in Mice in Vivo, Generation and Trapping of Acetaldehyde.
J Pharmacol Exp Ther Mar 1983, 224 (3) p614-9, ISSN 0022-3565
Journal Code: JP3

Attachment 3
February 1989

State of California
AIR RESOURCES BOARD

Procedure for Handling Trade Secret Information

The information that you provide to the Air Resources Board may be released (1) to the public upon request, except trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law, and (2) to the federal Environmental Protection Agency, which protects trade secrets as provided in Section 114(c) of the Clean Air Act and amendments thereto (42 USC 7401 et seq.) and in federal regulations and (3) to other public agencies provided that those agencies preserve the protections afforded information which is identified as a trade secret, or which is otherwise exempt from disclosure by law (Section 91000 Title 17, California Administrative Code and California Health and Safety Code Section 39660).

Trade secrets, which are defined in California Government Code Section 6254.7, are not considered public records and therefore will not be released to the general public. However, the Public Records Act (Government Code Section 6250 et seq.) provides that air pollution emission data are always public records, even if the data come within the definition of trade secrets. On the other hand, the information used to calculate air pollution emissions data may be withheld from the public if the information is a trade secret.

If you believe that any of the information you are providing is a trade secret or otherwise exempt from disclosure under any other provision of the law, you should identify it as such at the time of submission (Health and Safety Code Section 39660 (e)). The Air Resources Board may ask you to provide documentation of your claim of trade secret of exemption at a later date.

Chevron

Chevron Environmental Health Center, Inc.
A Subsidiary of Chevron Corporation
15299 San Pablo Avenue, Richmond, California
Mail Address: P.O. Box 4054, Richmond, CA 94804-0054

April 11, 1989

Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Re: Acetaldehyde
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Mr. Barham:

Thank you for the opportunity to provide input into your review of acetaldehyde. We do not have any in-house data on the possible health effects of acetaldehyde, but we suggest that the following useful citation be included in your list of references.

Egle, John L., Jr.
Retention of Inhaled Acetaldehyde in Man
Journal of Pharmacol. Expt'l. Therapeutics 174 (1):14-19, 1970.

If you have any questions, please don't hesitate to contact me at (415) 231-6088.

Sincerely,

Thomas F. Booze, Ph.D.
Toxicologist

TFB:temp2-c/0489-025

Pacific Gas and Electric Company

P.O. Box 7640
San Francisco, CA 94120
415/972-6901
Telecopy 415/972-9201

John F. McKenzie
Director
Environmental Planning

April 28, 1989

Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Re: Acetaldehyde
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

Request for Information on
Public Health Effects of Acetaldehyde

Pacific Gas and Electric Company (PG&E) has reviewed your March 24, 1989 bibliography on the health effects of acetaldehyde. We have no additional information relevant to human exposure at this time.

PG&E appreciates this opportunity to be invited to provide information regarding acetaldehyde. To assist ARB in implementing the toxic air contaminant program, PG&E would appreciate being requested to provide information for other candidate substances in the future. If you have any other questions, please call me or Kee Tsang at (415) 972-6911.

Sincerely,

NATIONAL STEEL AND SHIPBUILDING COMPANY
A MORRISON-KNUDSEN COMPANY

March 30, 1989

Robert Barham, Chief
Toxic Air Contaminent Identification Branch
Re: Acetaldehyde
California Air Resources Board
P. O. Box 2815
Sacramento, Ca. 95812

Dear Robert,

I am responding to your letter dated March 24, 1989, requesting information regarding acetaldehyde. I have reviewed our chemical inventory lists and discussed the request with our Industrial Hygienist and at this time we do not use acetaldehyde in any of our operations within the shipyard.

Sincerely,

Michael Chee
Sr. Facilities Engineer
NASSCO STEEL & SHIPBUILDING
P. O. Box 85278
San Diego, Ca. 92138

HARBOR DR. AND 28TH STREET. P O. BOX 85278. SAN DIEGO. CA 92138

UNITED NATIONS ENVIRONMENT PROGRAMME
PROGRAMME DES NATIONS UNIES POUR L'ENVIRONNEMENT

International Register of Potentially Toxic Chemicals

Le Registre international des substances chimiques potentiellement toxiques

QR 2124

18 April 1989

IRPTC/RISCPT

Avec les compliments
du

With the compliments
of

Meera Laurijssen (Mrs)
Asst. Scientific Affairs Officer
IRPTC/UNEP

Further to your letter of 24 March 1989 please find enclosed the IRPTC data profile on Acetaldehyde.

Mr Peter D. Venturini
Chief, Stationary Source Div.
Air Resources Board
1102 Q Street
Sacramento, CA. 95812
USA

Bureaux/Office location: 16, avenue Jean-Trembley, Petit-Saconnex, 1209 Genève
Telephone: 94 84 00 - 98 58 50 - Telex 28 877 UNEP-CH - Cables: UNITERRA, GENEVA

UNITED NATIONS ENVIRONMENT PROGRAMME

IRPTC

International Register of Potentially Toxic Chemicals
United Nations Environment Programme
IRPTC/UNEP, Palais des Nations, 1211 Genève 10, Suisse

QR 2124

APRIL 1989

IRPTC DATA PROFILE ON : ACETALDEHYDE

Appendix F-33

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AB1925000 ACETALDEHYDE
75-07-0

EVALUATION-APPRAISAL:
THERE IS SUFICIENT EVIDENCE FOR THE CARCINOGENICITY OF ACETALDEHYDE TO EXPERIMENTAL ANIMALS.
THERE IS INADEQUATE EVIDENCE FOR THE CARCINOGENICITY OF ACETALDEHYDE TO HUMANS.

IIARMB8 MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICAL 36,120,1985
§ TO MAN IARC

REC: 912

EVALUATION-APPRAISAL:
CLASSIFIED AS "POSSIBLY CARCINOGENIC TO HUMANS".

IIARMB8 MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICAL SUPPL.7,32,1987
§ TO MAN IARC

REC: 1396

- - - - T E S T D E S C R I P T I O N - - - -

ORGANISM: HAMST
LIFESTAGE,AGE: 6WK
SEX: F M
NUMBER EXPOSED: 36/DOSE 36/DOSE
NUMBER CONTROL: 36 36
EXPOSURE
ROUTE: INL
DOSE: 2970 - 4500 MG/M3 AIR
TYPE: LONG
PERIOD: 52WK
FREQUENCY: 7H/D 5D/WK

- - - - T E S T C O N D I T I O N S - - - -

STUDY TYPE: LAB

SPECIES-STRAIN-SYSTEM:
SYRIAN GOLDEN
EXPOSURE:
CONCENTRATION DECREASED FORM 4500 TO 2970 MG/M3
TEST METHODS:
6 ANIMALS WERE KILLED AND EXAMINED FROM EACH GROUP AT WEEK 52. THE REMAINING WERE OBSERVED TILL 81 WEEK AND KILLED

- - - - E F F E C T - - - -

ORGAN	EFFECT	REV	ONSET	SEX	AFFECTED IN EXPOSED	AFFECTED IN CONTROLS	COMMENTS ON RESULT
	NEF						6 ANIMALS FROM EACH GROUP HAD NO TUMOUR
PULMO	NEO			M	8/29	0/30	RESPIRATORY TRACT TUMOUR (P<0.05)
PULMO	NEO			F	5/29	0/28	RESPIRATORY TRACT TUMOUR (P<0.05)
PULMO	CAR						COMPOUND-INDUCED TUMORS WERE PREDOMINANTLY LARYNGEAL CARCINO
	NEO						MAS WITH A FEW LARYNGEAL POLYPS, & NASAL POLYPS & CARCINOMAS

CHEMICAL NAME: ACETALDEHYDE
COMMON NAME: ACETALDEHYDE

RTECS RN: AB1925000
CAS RN: 75-07-0

REC: 333

AB1925000 ACETALDEHYDE
75-07-0

EVALUATION-APPRAISAL:
NO DATA WERE AVAILABLE ON THE GENETIC AND RELATED EFFECTS OF ACETALDEHYDE IN HUMANS.

HARMBS MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICAL SUPPL.7,77,1987
S TO MAN IARC REC: 965

EVALUATION-APPRAISAL:
NO DATA WERE AVAILABLE ON THE GENETIC AND RELATED EFFECTS OF ACETALDEHYDE IN HUMANS.
ACETALDEHYDE INCREASED THE INCIDENCE OF SISTER CHROMATID EXCHANGES IN BONEMARROW CELLS OF MICE AND HAMSTER TREATED IN VI
VO AND INDUCED CHROMOSOMAL ABERRATIONS IN RAT EMBRYOS EXPOSED IN VIVO. IF INDUCED DNA CROSS-LINKS, CHROMOSOMAL ABERRATIO
NS AND SISTER CHROMATID EXCHANGES IN HUMAN CELLS IN VITRO AND CHROMOSOMAL ABERRATIONS, MICRONUCLEI AND SISTER CHROMATID
EXCHANGES IN CULTURED RODENT CELLS. IT INDUCED CHROMOSOMAL ABERRATIONS, MICRONUCLEI AND SISTER CHROMATID EXCHANGES IN PL
ANTS AND DNA DAMAGE AND MUTATION IN BACTERIA. ACETALDEHYDE INDUCED CROSSLINKS IN ISOLATED DNA.
EVALUATION BASED ON IARC MONOGRAPH 36, 1985.

HARMBS MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICAL SUPPL. 6,21,1987
S TO MAN REC: 1340

IIARMB8 MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICAL 36,101,1985
S TO MAN
EJCODS EUROPEAN JOURNAL OF CANCER & CLINICAL ONCOLOGY 18,13,1982
FERON, V.J. ET AL REC: 669

AB1925000 ACETALDEHYDE
75-07-0

TREATMENT & DISPOSAL METHODS:	FROM THIS REFERENCE	RECOMMENDED	RECOMMENDABLE	NOT RECOMMENDABLE
			INCINERATION	

DISSOLVE IN A COMBUSTIBLE SOLVENT SUCH AS ALCOHOL OR BENZENE, THEN SPRAY THE SOLUTION INTO THE FURNACE WITH AFTERBURNER.

ITIIT* TOXIC AND HAZARDOUS INDUSTRIAL CHEMICALS SAFETY MANUAL FOR HANDLI -,1,1979
NG AND DISPOSAL WITH TOXICITY AND HAZARD DATA.

REC: 346

AB1925000 ACETALDEHYDE
75-07-0

MEDIUM	ANALYTICAL METHOD	DETECTION LIMIT	SAMPLE SIZE	COMMENTS
AIR	HPLC-UV (245NM)	LESS THAN 0.325UG	60L	

COMMENTS:
AIR IS DRAWN THROUGH A MIDGET BUBBLER CONTAINING A BUFFERED SOLUTION OF GIRARD T REAGENT. THE ACETALDEHYDE-GIRARD T DERI
VATIVE IS THEN ANALYSED. THE METHOD WAS VALIDATED OVER THE RANGE OF 170-670MG/M3 AT T.= 21C AND P.= 756MM HG.
HPLC EQUIPPED WITH A VARIABLE WAVELENGTH UV DETECTOR SET AT 245NM AND A SAMPLE INJECTION VALUE WITH A 50UL EXTERNAL SAMP
LE LOOP.
COLUMN PACKED WITH ZIPAX SCX- STAINLESS STEEL CONDITIONS: COLUMN T.= AMBIENT. FLOW RATE = 0.75ML/MI, MOBILE PHASE =
0.022M NA2HPO4 AND 0.019M NAH2PO4 IN 20% ETHANOL.

NSHAM* NIOSH MANUAL OF ANALYTICAL METHODS 5,S-345,1979 REC: 402

AB1925000 ACETALDEHYDE
75-07-0

AREA	TYPE	SUBJECT		DESCRIPTOR	LEVELS,REMARKS AND REFERENCE	
ARG	REG	AIR	OCC	MPC	TWA : 180 MG/M3 (100 PPM), STEL : 270 MG/M3 (150 PPM) ARGENTINIAN LEGISLATION, DECRETO. , 351,-,1979	EFFECTIVE DATE: 22MAY1979 ENTRY DATE IN IRPTC: MAY1985
AUS	REC	AIR	OCC	TLV	TWA: 180MG/M3 (100PPM) STEL: 270MG/M3 (150PPM) APPROVED OCCUPATIONAL HEALTH GUIDE THRESHOLD LIMIT VALUES , -,-,1983	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985
BEL	REC	AIR	OCC	TLV	TWA: 180MG/M3 (100PPM); STEL: 270MG/M3 (150 PPM). THRESHOLD LIMIT VALUES (VALEURS LIMITES TOLERABLES) , -,-,1984	EFFECTIVE DATE: ENTRY DATE IN IRPTC: JUL1987
CAN	REG	AIR	OCC	TLV	TWA: 100PPM (180MG/M3). STEL: 150PPM (270MG/ M3) CONSOLIDATED REGULATIONS OF CANADA , 1978*10(997),7749,1978	EFFECTIVE DATE: 24APR1980 ENTRY DATE IN IRPTC: SEP1986
CAN	REG	TRNSP LABEL PACK		CLASS RQR ,	PIN (PRODUCT IDENTIFICATION NO.): 1089. CLASS (3.1): FLAMMABLE LIQUID WITH FLASHPOINT LESS THAN -18C. CLASS (9.2): HAZARDOUS TO THE ENVI RONMENT. SPECIAL PROVISIONS: (46),(56),(90), (99). PACK GROUP I (I=GREAT DANGER, III=MINOR DANGER). MAXIMUM AMOUNT PER PACKAGE THAT MAY BE TRANSPORTED ON A PASSENGER AIRCRAFT, TRAIN OR ROAD VEHICLE :PROHIBITED. MAXIMUM AMOUNT PER PACKAGE THAT MAY BE TRANSPORTED ON A CAR GO AIRCRAFT: 30L (CANADA GAZETTE PART II 1985*119(77),393,1985 AS LAST AMENDED BY THE REFERENCE GIVEN. THE REGULATIONS FALL UNDER THE TRANSPORTATION OF DANGEROUS GOODS ACT). CANADA GAZETTE PART II , 1987*121(13),2304,1987	EFFECTIVE DATE: 11JUN1987 ENTRY DATE IN IRPTC: MAY1988
CHE	REG	AIR	OCC	MAK	TWA: 90MG/M3 (50PPM) ZULAESSIGE WERTE AM ARBEITSPLATZ (PERMITTED VALUES IN THE WORKPLACE) , -,-,1987	EFFECTIVE DATE: ENTRY DATE IN IRPTC: DEC1987
CSK	REG	AIR	OCC	MAC	TWA = 200.0 MG/M3 ; CLV = 400.0 MG/M3 HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR (HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR) , 50,-,1985	EFFECTIVE DATE: MCH1985 ENTRY DATE IN IRPTC: AUG1985
DDR	REG	AIR	OCC	MAC	STEL: 100MG/M3 (IRRITANT TO THE RESPIRATORY SYSTEM). MAXIMALE ZULAESSIGE KONZENTRATIONEN GESUNDHEITSGEFAERDENDER STOFF E IN DER LUFT AM ARBEITSPLATZ (MAXIMUM ALLOWABLE CONCENTRATIONS OF NOXIOUS SUBSTANCES IN THE AT , -,1,1987	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1988

DEU	REC	AIR	OCC	MAK	8H-TWA: 90MG/M3 (50 PPM); 5MI-STEL: 180MG/M3 (100PPM) CEILING VALUE, 8X/SHIFT. LOCAL IRRITANT. (VP=100KPA AT 20C). SUBSTANCE SUSPECT OF CARCINOGENIC POTENTIAL. THE MAK VALUE IS THEREFORE TENTATIVELY RETAINED. DEUTSCHE FORSCHUNGSGEMEINSCHAFT, "MAXIMALE ARBEITSPLATZKONZENTRATIONEN UND BIOLOGISCHE ARBEITSSTOFFTOLERANZWERTE" (MAXIMUM WORKSITE CONCENTRATION AND BIOLOGICAL TOLERANCE VALUES , XXIII,15,1987	EFFECTIVE DATE: ENTRY DATE IN IRPTC: SEP1987
DEU	REG	AIR	EMI	MXL	THE SUBSTANCE BELONGS TO CLASS I THE AIR EMISSIONS OF ORGANIC COMPOUNDS MUST NOT EXCEED (AS THE SUM OF ALL COMPOUNDS IN ONE CLASS) THE FOLLOWING MASS CONCENTRATIONS: CLASS I: 20MG/M3 AT A MASS FLOW OF >=0.1KG/H CLASS II: 100MG/M3 AT A MASS FLOW OF >=2KG/H CLASS III: 150MG/M3 AT A MASS FLOW OF >=3KG/H IF COMPOUNDS FROM DIFFERENT CLASSES ARE PRESENT THE MASS CONCENTRATION MUST NOT EXCEED 0.15G/M3. GEMEINSAMES MINISTERIALBLATT (JOINT MINISTERIAL PAPERS) , 7,93-143,1986	EFFECTIVE DATE: 28FEB1986 ENTRY DATE IN IRPTC: JUN1986
DEU	REC	AQ STORE TRNSP		CLASS	THIS SUBSTANCE IS CLASSIFIED AS HARMFUL TO WATER (CLASS 2). (THE DIFFERENT CLASSES ARE: CLASS 0 = IN GENERAL NOT HARMFUL; CLASS 1 = SLIGHTLY HARMFUL; CLASS 2 = HARMFUL; CLASS 3 = VERY HARMFUL). IN ORDER TO PROTECT WATER, APPROPRIATE SECURITY MEASURES SHOULD BE TAKEN ACCORDINGLY DURING STORAGE, LOADING AND TRANSPORT. GEMEINSAMES MINISTERIALBLATT (JOINT MINISTERIAL PAPERS) , 11(G3191A),173,1985	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1986
DEU	REG	LABEL PACK USE	- - OCC	RQR RQR RSTR	FOR LABEL AND PACKAGING SEE EEC (OJEC L106, 18,1982). HANDLING OF SOME GROUPS OF CHEMICALS (INCL. CARCINOGENIC, MUTAGENIC, POISONOUS, TERATOGENIC, EXPLOSIVE AND EASILY INFLAMMABLE COMPOUNDS) IS PROHIBITED OR RESTRICTED FOR PREADULTS AND PREGNANT OR NURSING WOMEN. (BGBL I.S.1071,1536/2159,1980, AND BGBL I.S. 2069,1980 AS LAST AMENDED BY THE REFERENCE GIVEN). BUNDESGESETZBLATT , I.S.140,140,1982	EFFECTIVE DATE: 10CT1980 ENTRY DATE IN IRPTC: JUN1986
EEC	REG	LABEL PACK		RQR RQR	F - FLAMMABLE. XI - IRRITANT. EXTREMELY FLAMMABLE (R 12). IRRITATING TO EYES AND RESPIRATORY SYSTEM (R 36/37). KEEP CONTAINER IN A WELL-VENTILATED PLACE (S 9). KEEP AWAY FROM SOURCES OF IGNITION - NO SMOKING (S 16). DO NOT EMPTY INTO DRAINS (S 29). TAKE PRECAUTIONARY MEASURES AGAINST STATIC DISCHARGES (S 33). OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES , L.106,18,1982	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1986

FIN	REC	AIR	OCC	MPC	TWA: 90MG/M3 (50PPM) STEL: 135MG/M3 (75PPM) LUFTFOEORENINGAR PAA ARBETSPLATSEN (AIR POLLUTANTS AT THE WORKPLACE) , -,-,1982	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985
GBR	REC	AIR	OCC	RECL	8H-TWA: 180MG/M3 (100PPM). STEL(10MI-TWA): 270MG/M3 (150PPM) GUIDANCE NOTE FROM THE HEALTH AND SAFETY EXECUTIVE , EH40/87,8,1987	EFFECTIVE DATE: ENTRY DATE IN IRPTC: JUN1987
GBR	REG	AIR	EMI	RQR	PROVISIONS HAVE BEEN MADE WITH A VIEW TO CONTROLLING THE EMISSION INTO THE ATMOSPHERE OF NOXIOUS OR OFFENSIVE SUBSTANCES FROM ALDEH YDE WORKS IN WHICH FORMALDEHYDE, ACETALDEHYDE OR ACROLEIN OR THE METHYL, ETHYL OR PROPYL DERIVATIVES OF ACROLEIN ARE MADE. STATUTORY INSTRUMENTS , 943,-,1983	EFFECTIVE DATE: 5AUG1983 ENTRY DATE IN IRPTC: APR1986
GBR	REG	AIR	EMI	RQR	IT SHALL BE THE DUTY OF THE PERSON HAVING CON TROL OF ANY PREMISES OF A CLASS PRESCRIBED ELSEWHERE UNDER THIS REFERENCE TO USE THE BES T PRACTICABLE MEANS FOR PREVENTING THE EMISSI ON INTO THE ATMOSPHERE FROM THE PREMISES OF NOXIOUS OR OFFENSIVE SUBSTANCES SUCH AS ACETALDEHYDE AND FOR RENDERING HARMLESS AND INOFFENSIVE SUCH SUBSTANCES AS MAY BE SO EMITTED. (APPLIES TO ACETALDEHYDES). STATUTORY INSTRUMENTS , 943,1,1983	EFFECTIVE DATE: 5AUG1983 ENTRY DATE IN IRPTC: APR1986
GBR	REG	TRNSP LABEL		CLASS RQR	LABELLING OF ROAD TANKERS : FLAMMABLE LIQUID. , EMERGENCY ACTION CODE : 2YE STATUTORY INSTRUMENTS , 1702,1,1978	EFFECTIVE DATE: 28MCH1979 ENTRY DATE IN IRPTC: JAN1983
GBR	REG	LABEL PACK USE	- - OCC	RQR RQR RSTR	FOR LABEL AND PACKAGING, SEE EEC (OJEC** L.106,18,1982) STATUTORY INSTRUMENTS , 17,1,1983	EFFECTIVE DATE: 1SEP1978 ENTRY DATE IN IRPTC: APR1986
HUN	REG	AIR	OCC	MAC	TWA: 50MG/M3; STEL(30 MIN): 250MG/M3 HUNGARIAN STANDARD MSZ NO. , 21461-78,-,1978	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985
ITA	REC	AIR	OCC	TLV	100MG/M3 (55PPM) VALORI LIMITE PONDERATI (THRESHOLD LIMIT VALUES) , -,-,	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985
JPN	REC	AIR	EMI	MXL	EMISSION STANDARD BECAUSE OF OFFENSIVE ODOR : 0.05-0.5PPM (0.09-0.9 MG/M3) QUALITY OF THE ENVIRONMENT IN JAPAN , -,396,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: DEC1982
NLD	REC	AIR	OCC	MXL	TWA: 180MG/M3 (100PPM) NATIONALE MAC-LIJST (NATIONAL MAC-LIST) , -,-,1986	EFFECTIVE DATE: ENTRY DATE IN IRPTC: JUN1987
POL	REG	AIR	OCC	MPC	TWA: 5MG/M3	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985

ROM	REG	AIR	OCC	MPC	ORDINANCE OF THE MINISTER OF LABOUR, WAGES AND SOCIAL AFFAIRS , 22DEC,-,1982 TWA: 100MG/M3; CLV: 200MG/M3 ORDINANCE OF THE MINISTRY OF HEALTH , 60,-,1975	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985
SUN	REG	AIR	OCC	MAC	CLV : 5.0 MG/M3 (VAPOUR) GOSUDARSTVENNYI STANDART SSSR (STATE STANDARD OF USSR) , 12.1.005,-,1976	EFFECTIVE DATE: JAN1977 ENTRY DATE IN IRPTC: JUN1982
SUN	REG	AIR	AMBI	MAC	0.01 MG/M3 1X/D, 0.01 MG/M3 AV/D PREDELNO DOPUSTIMYE KONTSENTRATSII (PDK) ZAGRYAZNYAYUSHCHIKH VESH CHESTV V ATMOSFERNOM VOZDUKHE NASELENNYKH MEST (MAXIMUM ALLOWABLE CONCENTRATIONS (MAC) OF CONTAMINANTS IN THE , 3086-84,-,1984	EFFECTIVE DATE: AUG1984 ENTRY DATE IN IRPTC: SEP1985
SUN	REG	AQ	SURF	MAC	0.2 MG/L PREDELNO DOPUSTIMYE KONSENTRATSII (PDK) I ORIENTIROVOCHNYE BEZOPA SNYE UROVNI VOZDEISTVIA (OBUV) UREDMYKH VESHCHESTV V VODE VODNYKH OBIEKTOV KHOZIAISTVENNO-PITIEVOGO I KULTURNO-BYTOVOGO VODOPOLZOV , 2932-83,-,1983	EFFECTIVE DATE: OCT1983 ENTRY DATE IN IRPTC: SEP1985
SUN	REG	SOIL		MAC	10.0 MG/KG PREDELNO DOPUSTIMYE KONTSENTRATSII (PDK) KHIMICHESKIKH VESHCHESTV V POCHVE (MAXIMUM ALLOWABLE CONCENTRATIONS (MAC) OF CHEMICAL SUBSTANCES IN , 3210-85,-,1985	EFFECTIVE DATE: FEB1985 ENTRY DATE IN IRPTC: OCT1985
SWE	REG	AIR	OCC	HLV	TWA: 45MG/M3 (25PPM), STEL: 90MG/M3 (50PPM). ARBETARSKYDDSSTYRELSENS FOERFATTNINGSSAMLING , 1987:12,13,1987	EFFECTIVE DATE: 01JUL1988 ENTRY DATE IN IRPTC: FEB1988
SWE	REG	CLASS		CLASS	GIVEN AS AN EXAMPLE OF A HAZARDOUS SUBSTANCE STATENS NATURVARDSVERKS FORFATTNINGSSAMLING , 1983:6,1,1983	EFFECTIVE DATE: 23NOV1983 ENTRY DATE IN IRPTC: OCT1984
USA	REG	AIR	OCC	TLV	TWA: 180MG/M3(100PPM); STEL: 270MG/M3(150PPM) AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS , 1987-88,11,1987	EFFECTIVE DATE: ENTRY DATE IN IRPTC: OCT1987
USA	REG	AIR	OCC	PEL	TWA : 360 MG/M3 (200 PPM) CODE OF FEDERAL REGULATIONS , 29(1910),653,1986	EFFECTIVE DATE: ENTRY DATE IN IRPTC: DEC1987
USA	REG	AQ	EMI	CLASS	THE SUBSTANCE, INCLUDING ANY ISOMERS, HYDRATE S, AND SOLUTIONS AND MIXTURES CONTAINING THE SUBSTANCE, IS DESIGNATED AS A HAZARDOUS SUBST ANCE FOR PURPOSES OF DISCHARGE (INCLUDING SPI LLING, LEAKING, ETC.) UNDER THE WATER POLLUTI ON CONTROL ACT. CODE OF FEDERAL REGULATIONS , 40(116),33,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MAY1986
USA	REG	AQ	EMI	RQR RSTR	UNLESS IN COMPLIANCE WITH A SPECIFIED PERMIT OR PROCEDURE, OWNERS/OPERATORS OF VESSELS OR ON- OR OFFSHORE FACILITIES MUST NOTIFY THE US GOVERNMENT OF ANY DISCHARGE OF THIS SUBSTANCE IN OR ON NAVIGABLE WATERS, ADJOINING SHORELIN ES OR THE CONTIGUOUS ZONE IN AN AMOUNT EQUAL TO OR GREATER THAN 454KG IN ANY 24-HOUR PERIOD. SUCH A DISCHARGE IS A VIOLATION OF THE FEDERAL WATER POLLUTION CONTROL ACT.	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MAY1986

					CODE OF FEDERAL REGULATIONS , 40(117),44,1981	
USA	REG	AQ	EMI WASTE	RQR	PERMITS ARE REQUIRED FOR DISCHARGE OF ANY POL LUTANT FROM ANY POINT SOURCE INTO U.S.WATERS. THE FOLLOWING APPLICANTS MUST REPORT QUANITTA TIVE DATA FOR THE SUBSTANCE IN THEIR APPLICAT IONS: 1) EVERY APPLICANT WHO HAS REASON TO BELIEVE THAT THE SUBSTANCE IS CONTAINED IN ANY OF HIS OUTFALLS INSPECTION, MONITORING AND REPORTING REQUIREM ENTS AFTER THE ISSUE OF THE PERMIT ARE SPECIF IED. EVEN IF NOT REQUIRED IN THE PERMIT, DISC HARGE OF THE SUBSTANCE MUST BE REPORTED IF IT EXCEEDS THE HIGHEST OF THE FOLLOWING LEVELS: A) 100UG/L B) 5 TIMES THE MAXIMUM CONC. REPORTED IN THE APPLICATION C) THE LEVEL ESTABLISHED BY THE EPA DIRECTOR. CODE OF FEDERAL REGULATIONS , 40(122.53),121,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MAY1986
USA	REG	AQ TRNSP	EMI	RQR	WHEN CERTAIN SPECIFIED VESSELS CARRYING ACETALDEHYDE IN BULK ARE BOUND FOR OR DEPARTING FROM U.S. PORTS, THE CAPTAIN OF THE PORT MUST BE NOTIFIED AT LEAST 24 HOURS IN ADVANCE AND BE GIVEN CERTAIN INFORMATION. CODE OF FEDERAL REGULATIONS , 33(161),813,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MAY1986
USA	REG	FOOD FEED		ARL	EXEMPTIONS FROM RESIDUE TOLERANCE REQUIREMENT S IS MADE FOR THIS FUNGICIDE, WHEN USED POSTH ARVEST AS A STORAGE FUMIGANT, IN OR ON CERTAI N SPECIFIED PLANT PRODUCTS. CODE OF FEDERAL REGULATIONS , 40(180),269,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1986
USA	REG	TRNSP		RSTR RQR CLASS	ACETALDEHYDE, WHEN CARRIED IN BULK, IS CLASSIFIED AS A 'CARGO OF PARTICULAR HAZARD' FOR PURPOSES OF REGULATIONS GOVERNING HANDLIN G OF DANGEROUS CARGOES IN OR CONTIGUOUS TO WA TER-FRONT FACILITIES. A PERMIT IS REQUIRED FOR HANDLING SUCH CARGO. OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES , 33(126),613,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1986
USA	REG	USE	OCC	RSTR	NO POWER OPERATED INDUSTRIAL TRUCK MAY BE USE D IN ATMOSPHERES WHERE A HAZARDOUS CONCENTRAT ION OF THE SUBSTANCE IS PRESENT. CODE OF FEDERAL REGULATIONS , 29(1910),419,1981	EFFECTIVE DATE: ENTRY DATE IN IRPTC: APR1986
USA	REG	WASTE		CLASS RSTR RQR	THE SUBSTANCE, IF IT IS A COMMERCIAL CHEMICAL PRODUCT, IS IDENTIFIED AS A 'TOXIC WASTE' SUB JECT TO REGULATION AND NOTIFICATION REQUIREME NTS. CODE OF FEDERAL REGULATIONS , 40(261),360,1981	EFFECTIVE DATE: 19NOV1980 ENTRY DATE IN IRPTC: MAY1986
USA	REG	WASTE		CLASS	IN ACCORDANCE WITH THE LAW REQUIRING THE PRES IDENT TO IDENTIFY THE 400 HAZARDOUS WASTE FAC ILITIES IN THE USA WARRANTING THE HIGHEST PRI ORITY FOR REMEDIAL ACTION, EPA HAS ESTABLISHE D A HAZARD RANKING SYSTEM TO SET PRIORITIES. A CRITERION FOR ESTABLISHING THE RELATIVE RIS K OR DANGER IS THE CHARACTERISTICS OF WASTES IN A GIVEN FACILITY. FOR EXAMPLE ACETALDEHYDE IS RATED AS A NON-PERSISTENT COMPOUND.	EFFECTIVE DATE: ENTRY DATE IN IRPTC: JUN1983

					FEDERAL REGISTER , 47,31219,1982	
USA	REG	WASTE		CLASS	IN ACCORDANCE WITH THE LAW REQUIRING THE PRES IDENT TO IDENTIFY THE 400 HAZARDOUS WASTE FAC ILITIES IN THE USA WARRANTING THE HIGHEST PRI ORITY FOR REMEDIAL ACTION, EPA HAS ESTABLISHE D A HAZARD RANKING SYSTEM TO SET PRIORITIES. A CRITERION FOR ESTABLISHING THE RELATIVE RIS K OR DANGER IS THE CHARACTERISTICS OF WASTES IN A GIVEN FACILITY. FOR EXAMPLE, FOR ACETALD EHYDE THE TOXICITY VALUE IS 3, THE PERSISTENC E VALUE IS 0, THE IGNITION VALUE IS 3 AND THE REACTIVITY VALUE IS 2. (ALL RATINGS RANGING FROM 0 TO 3) FEDERAL REGISTER , 47,31219,1982	EFFECTIVE DATE: ENTRY DATE IN IRPTC: JUN1983
YUG	REG	AIR	OCC	MAC	TWA: 360MG/M3 (200PPM) ORDINANCE , 24-3698/1,-,1971	EFFECTIVE DATE: ENTRY DATE IN IRPTC: MCH1985

APPENDIX G

HEALTH EFFECTS REQUEST LETTER TO DEPARTMENT OF HEALTH SERVICES AND LETTER OF RESPONSE

State of California

MEMORANDUM

To : Ed Mendoza, Assistant Deputy Director
Public Health
Department of Health Services
714 P Street
Sacramento, CA 95814

Date : June 22, 1989

Subject : Health Effect Evaluation of Acetaldehyde

From : James D. Boyd
Executive Officer
Air Resources Board

This memorandum is a formal request that the Department of Health Services evaluate the health effects of acetaldehyde as a candidate toxic air contaminant in accordance with Health and Safety Code Section 39650 et seq.

Attached for your staff's consideration in evaluating acetaldehyde are the references on acetaldehyde health effects which were identified in an Air Resources Board (ARB) letter of public inquiry and provided by the public in response to that letter.

Ambient air monitoring of acetaldehyde began earlier this year. Although we do not have specific data at this time, we will provide ambient levels data for your staff later this year.

According to Health and Safety Code Sections 39660-62, the Department of Health Services has 90 days from receipt of this letter to submit a written evaluation to the ARB with recommendations on the health effects of acetaldehyde. If necessary, the Department of Health Services may request a 30 day extension.

If you have questions regarding this request, please contact me at 445-4383 or have your staff contact Robert D. Barham, Chief of the Toxic Air Contaminant Identification Branch at 322-7072.

Attachment

cc: Jananne Sharpless, Chairwoman, ARB
George Alexeeff, DHS, w/Atchs
Richard Jackson, DHS, w/Atchs
Jack Parnell, DFA
Members of the Scientific Review Panel
Assemblywoman Sally Tanner
Senator Ralph Dills
Senator Art Torres

State of California

Office of Environmental Health Hazard Assessment

Memorandum

→ lon

To : Peter Venturini, Chief
Stationary Source Division
Air Resources Board
1102 Q Street
Sacramento, CA 95814

Date : August 12, 1991

RECEIVED
AUG 16 1991
Stationary Source Division
Air Resources Board

From : Office of the Director
714 P Street, Room 460
Sacramento, CA 95814
(916) 324-7572

Subject : Health Effects of Acetaldehyde

Attached is the document prepared in response to your request for the assistance of the Office of Environmental Health Hazard Assessment in evaluating the health effects of acetaldehyde as a potential toxic air contaminant.

Steven A. Book, Ph.D.
Acting Director

Attachment

cc: Jim Wells, Acting Director
Department of Pesticide Regulation
1220 N Street
Sacramento, CA 95814

Jananne Sharpless, Chairwoman
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

The Honorable Sally Tanner
Member of the Assembly
State Capitol, Room 4146
Sacramento, CA 95814

Copies of document can be requested from:

Office of Environmental Health Hazard Assessment
Air Toxicology and Epidemiology Section
2151 Berkeley Way, Annex 11, Room 235
Berkeley, CA 94704

APPENDIX H

GLOSSARY

Glossary

Aldehyde: Any of a class of highly reactive organic chemical compounds obtained by oxidation of primary alcohols, characterized by the common group CHO.

Aliphatic: Organic chemical compounds in which the carbon atoms are linked in open chains rather than rings.

Ambient air: Outdoor air.

Annual averaged concentrations: The yearly mean value of monitored ambient air concentrations from the sum of the monthly means. This is a mechanism to smooth data from seasonal and diurnal variations. Can apply to either one specific site or on a statewide basis.

Annual average population-weighted concentration: The annual average population-weighted exposure divided by the total population exposed.

Annual average population-weighted exposure: The sum of the annual average outdoor concentration (C) estimated for each census tract multiplied by the population (P) exposed in each census tract,

e.g. $E = (C_1 \times P_1) + (C_2 \times P_2) \ldots\ldots\ldots$

Areawide exposure: The average exposure the general population experiences in a large area surrounding sources of TAC's. This is generally based on ambient air monitoring data for populated areas.

Atmospheric Lifetime: The atmospheric lifetime τ of a chemical is defined as the time to decay to a concentration of 1/e (= 0.368) of the initially present concentration of that chemical.

Bioaccumulation: The process by which a chemical becomes more concentrated in an organism than it is in the environment of the organism.

Carcinogenic effects: Effects that cause cancer.

Catalyst: A substance, usually present in small amounts relative to the reactants, that modifies, especially increases, the rate of chemical reaction without being consumed in the process.

Catalytic converter: A reaction chamber typically containing a finely divided platinum-iridium catalyst into which exhaust gases from an automotive engine are passed together with excess air so that carbon monoxide and hydrocarbon pollutants are oxidized to carbon dioxide and water

Catalytic cracking: Using heat, pressure and catalysts to convert heavy oils from distillations, coking and deasphalting processes into lighter products such as gasoline.

Coefficient of variation (CV): The CV is the precision relative to the mean of the population expressed in percentages. The CV is equal to the standard deviation of all observations divided by the mean of all observations multiplied by 100.

Coking operation: Coke is the solid carbon residue obtained from carbon compounds after removal of volatile material by destructive distillation.

Dispersion Modeling: Technique for estimating the annual average concentration of a pollutant resulting from emissions from a specific source. We provide emission rate data to modeling staff which combine these data with data on wind speed and other meteorological conditions impacting the source to estimate the annual average concentration attributable to the source's emissions. The concentration predicted from dispersion modeling is assumed to be in addition to background concentrations measured by ambient air monitoring.

Dose: The concentration of the pollutant and the length of time that the subject is exposed to that pollutant.

Emission factor: An estimate of the rate at which a pollutant is released into the atmosphere as a result of some activity.

Emission rate: The weight of a pollutant emitted per unit of time (e.g. tons/year).

Excess carcinogenic risk: The number of potential excess lifetime cancer cases occurring per million persons continuously exposed for 70 years to a given concentration of a TAC; e.g. the excess carcinogenic risk from acetaldehyde exposure = 7 to 75 potential lifetime cancer cases per million persons continuously exposed to 1 ppb acetaldehyde (7 - 75 potential lifetime cancer cases / 10^6 ppb persons). In this case, 7 would be the risk based on the lower bound potency and 75 would be the risk based on the upper bound potency.

Exposure (E): The concentration (C) of the pollutant in the air multiplied by the population (P) exposed to that concentration over a specified time period, e.g. E = C X P (typical units are millions of ppb-persons averaged over one year).

Humic: Derived from humus. A brown or black organic substance consisting of decayed vegetable matter.

Individual cancer risk: The probability, expressed as chances in a million, that a person experiencing 70 years of continuous areawide outdoor exposure to a TAC will get cancer.

Limit of Detection (LOD): The levels at or above which compound concentrations are not only detectable, but are also quantifiable. LOD = A + 3S : A is the least squares intercept calculated from the multipoint data: S is the standard deviation of replicate determinations of the lowest standard. At least 3 replicates are required. The lowest standard must be run at 1 to 5 times the estimated detection limit. If data is not available in the concentration range near the detection limit, S may be estimated by: S = RSD X A where RSD is the relative standard deviation of the lowest standard analyzed.

Log normal distribution: A random variable's distribution is log normal if the distribution of the log of the variable is a normal distribution.

Mean: A number that represents a set of numbers in any of several ways determined by a rule involving all members of the set; average.

Median: The middle value in a distribution, above and below which lie an equal number of values; midpoint.

Method of Detection: The method used by which the laboratory staff estimates the LOD.

Mutagenic: The ability of a chemical or physical agent to produce inheritable changes in the genetic information stored in the DNA of living cells.

Non-carcinogenic effects: A finite dose, or threshold, below which adverse effects will not occur. Non-cancer effects include birth defects, organ damage, death and many others.

Octanol/water partition coefficient: A laboratory measure of the partitioning of a chemical between n-octanol and water provides Kow, which is related to water solubility

Organic precursor: Carbon compounds that are utilized in the synthesis of further chemicals

Oxidation: The combination of a substance with oxygen. A reaction in which the atoms in an element lose electrons and its valence is correspondingly increased.

Photolysis: Chemical decomposition induced by light or other radiant energy.

Photo-oxidation: Oxidation under the influence of radiant energy (as photochemical oxidation)

Polymer: Any of numerous natural and synthetic compounds of unusually high molecular weight consisting of up to millions of repeated linked units, each a relatively light and simple molecule.

Pyrolysis: Chemical change caused by heat.

Radical: An atom or group of atoms with at least one unpaired electron.

Secondary acetaldehyde: Acetaldehyde formed as a result of photo-oxidation of organic precursors

Sidestream tobacco smoke: Smoke which arises mainly from the passive burning of the cigarette and is released into the environment.

Standard Deviation: A statistic used as a measure of dispersion in a distribution, the square root of the arithmetic average of the squares of the deviations from the mean.

Stationary source: A non mobile source which can be either a point or area source.

Thermal catalytic cracking: Thermal decomposition with catalysis of petroleum to extract low -boiling fractions such as gasoline

Topography: The exact physical configuration of a place or region.

Toxic air contaminant (TAC): An air pollutant which may cause or contribute to an increase in serious illness, or which may pose a present or potential hazard to human health. Substances which have been identified by EPA as hazardous air pollutants (e.g. benzene, asbestos) shall be identified by the Board as toxic air contaminants.

Travel Blank: Used in estimating concentrations of measured substances. A travel blank is a blank system that tells us that our instruments and methods are working properly and that our filled test samples are accurate. It also provides an estimate of the level of contamination due to transport and handling of the cartridges.

Troposphere: The lowest region of the atmosphere between the earths' surface and the tropopause, characterized by decreasing temperature with increasing altitude, about 15 kilometers

Unit Risk: The number of potential excess cancer cases from a lifetime exposure to 1 microgram per cubic meter (ug/m^3) of a given substance; e.g. a unit risk value of 5.5×10^{-6} (ug/m^3) would indicate an estimated 5.5 cancer cases per million people exposed to an average concentration of 1 ug/m^3 of a specific carcinogen for 70 years.

Vapor pressure: The pressure exerted by a vapor in equilibrium with its solid or liquid phase.

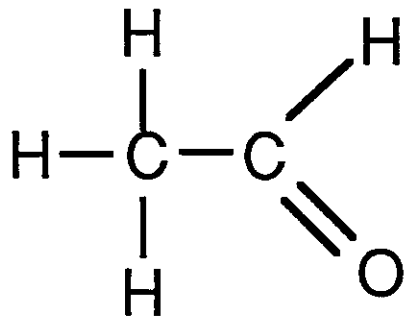
Volatile: Evaporating readily at normal temperatures and pressures. Capable of being readily vaporized.

California Environmental Protection Agency

Air Resources Board

Acetaldehyde

as a Toxic Air Contaminant



Part B

Health Assessment

Stationary Source Division

November 1993

PART B

HEALTH EFFECTS OF ACETALDEHYDE

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November 1993

TABLE OF CONTENTS

	Page
LIST OF FIGURES	v
LIST OF TABLES	vi
AUTHORS, CONTRIBUTORS, REVIEWERS	viii
1.0 SUMMARY	**1-1**
2.0 METABOLISM AND PHARMACOKINETICS	2-1
2.1 Introduction	2-1
2.2 Absorption	2-1
2.2.1 Inhalation Studies	2-1
2.2.2 Oral Studies	2-2
2.3 Distribution	2-5
2.4 Metabolism	2-7
2.4.1 Aldehyde Dehydrogenase Enzyme System	2-7
2.4.2 Extrahepatic Metabolism	2-9
2.4.3 Acetaldehyde Binding and Antibody Formation	2-12
2.4.4 Acetaldehyde Binding to DNA	2-13
2.5 Excretion	2-13
2.6 Conclusions	2-14
3.0 ACUTE TOXICITY	3-1
3.1 Human Health Effects	3-1
3.2 Animal Studies	3-1
3.2.1 Inhalation Exposure	3-1
3.2.2 Oral	3-4
3.2.2 Parenteral Administration	3-4
3.3 Toxicity of Peroxyacetyl Nitrate	3-4
3.4 Conclusions	3-5
4.0 SUBCHRONIC TOXICITY	4-1
4.1 Inhalation Studies	4-1
4.2 Oral Studies	4-2
4.3 Conclusions	4-3
5.0 CHRONIC TOXICITY	5-1
5.1 Introduction	5-1
5.2 Inhalation	5-1
5.3 Inhalation with Intratracheal Instillation of Benzo[a]pyrene	5-2
5.4 Intratracheal Instillation	5-3
5.5 Conclusions	5-3

TABLE OF CONTENTS (cont.)

	Page
6.0 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS	6-1
6.1 Introduction	6-1
6.2 *In vivo* Studies	6-1
6.2.1 Developmental Toxicity	6-1
6.2.2 Reproductive Toxicity	6-2
6.2.3 Reporductive Toxicity	6-3
6.3 *In vitro* Studies	6-3
6.3.1 Developmental Toxicity	6-3
6.3.2 Reproductive Toxicity	6-4
6.4 Conclusions	6-4
7.0 GENOTOXICITY	7-1
7.1 Introduction	7-1
7.2 Gene Mutations	7-1
7.2.1 Bacteria	7-1
7.2.2 Yeast	7-1
7.2.3 Nematodes	7-3
7.2.4 Insects	7-3
7.2.5 Mammalian Cells	7-3
7.3 Chromosomal Aberrations	7-3
7.3.1 Plants	7-3
7.3.2 Insects	7-4
7.3.3 Mammalian Cell Cultures	7-4
7.3.4 Whole Mammals	7-5
7.4 Sister Chromatid Exchanges	7-5
7.4.1 CHO Cells	7-5
7.4.2 Human Lymphocytes	7-6
7.4.3 Whole-Mammal Bone Marrow Cells	7-7
7.5 DNA Damage	7-7
7.5.1 Bacteria	7-7
7.5.2 Mammalian Cell Culture	7-7
7.6 Cell Transformation	7-8
7.7 Conclusions	7-8
8.0 CARCINOGENICITY	8-1
8.1 Introduction	8-1
8.2 Epidemiological Study	8-1
8.3 Animal Studies	8-2
8.3.1 Inhalation	8-2
8.3.2 Inhalation + Intratracheal Instillation	8-8
8.3.3 Intratracheal Instillation	8-18
8.4 Carcinogenicity of Ethanol	8-18
8.5 Conclusions	8-22

9.0 QUANTITATIVE RISK ANALYSIS 9-1
9.1 Noncarcinogenic Risks 9-1
9.2 Carcinogenic Risks 9-1
9.2.1 Thresholds 9-2
9.2.2 Rat Nasal Carcinomas and the Multistage Model 9-2
9.2.3 Interspecies Scaling and Rat Nasal Carcinomas 9-6
9.2.4 Rat Nasal Carcinomas and Contact Scaling 9-8
9.2.5 Hamster Laryngeal Carcinomas and Multistage Model 9-9
9.2.6 Risk Estimate using the Gaylor-Kodell Approach 9-9
9.2.7 Population Risk from Acetaldehyde in Ambient Air 9-10
9.2.8 Selection of Best Value for Risk Assessment 9-10

APPENDIX A: Results of Reproductive and *in vivo* Developmental Toxicity Studies with Acetaldehyde A-1

APPENDIX B: Mutagenicity-Genotoxicity Testing of Acetaldehyde B-1

APPENDIX C: IARC and USEPA Classification Schemes for Carcinogens .. C-1

REFERENCES R-1

LIST OF FIGURES

Figure No.		Page
2-1	The retention of acetaldehyde with the open system design at three respiratory rates and three concentration ranges	2-3
2-2	The retention of acetaldehyde with the closed system design	2-4
2-3	The effect of increasing amounts of oral ethanol upon acetaldehyde and ethanol concentrations in alveolar air in one subject	2-8

LIST OF TABLES

Table No.		Page
2-1	Tissue Distribution of Acetaldehyde Following Acetaldehyde Inhalation and Intragastric Ethanol Administration	2-6
2-2	Estimated Kinetic Constants for the NAD^+-Dependent Oxidation of Acetaldehyde to Acetate Catalyzed by Homogenates of Respiratory and Olfactory Mucosa from Fischer-344 rats	2-10
3-1	Acute Toxicity Studies Conducted with Acetaldehyde	3-2
7-1	Genotoxicity of Acetaldehyde in Various Test Systems	7-2
8-1	Summary of Carcinogenicity Studies of Acetaldehyde in Rats and Hamsters	8-3
8-2	Summary of Respiratory Tract Hyperplastic and Preneoplastic Lesions in Rats Exposed to Acetaldehyde by Inhalation	8-5
8-3	Sites, Types, and Incidences of Respiratory Tract Tumors in Rats Exposed to Acetaldehyde by Inhalation	8-7
8-4	Incidence of Respiratory Tract Tumors in Hamsters Exposed to Either Air or Acetaldehyde Vapor	8-9
8-5	Types and Incidences of Respiratory Tract Tumors in Male Hamsters After 52 Weekly Intratracheal Instillations of B[a]P and Exposure to Air or Acetaldehyde Vapor	8-11
8-6	Treatment Protocol for Hamsters Exposed to Either Air or Acetaldehyde Vapor	8-13
8-7	Sites and Incidences of Respiratory Tract Tumors in Hamsters Exposed to Air or Acetaldehyde Vapor and Treated Intratracheally with B[a]P or Subcutaneously with DENA	8-14
8-8	Sites, Types, and Incidences of Respiratory Tract Tumors in Hamsters Exposed to Air or Acetaldehyde Vapor and Treated Intratracheally with B[a]P or Subcutaneously with DENA	8-16

LIST OF TABLES (continued)

Table No.		Page
8-9	Treatment of Hamsters in the Various Groups Used in the Intratracheal Instillation Study	8-19
8-10	Types and Incidences of Respiratory Tract Tumors in Hamsters Given Intratracheal Instillations of 0.9% NaCl Solution, Acetaldehyde, B[a]P, B[a]P + Acetaldehyde, DENA, or DENA + Acetaldehyde	8-20
8-11	Classification of Acetaldehyde's Carcinogenicity	8-24
9-1	Tumor Incidences in Male and Female Rats After 28 Months of Acetaldehyde Exposure	9-3
9-2	Carcinogenic Potency Determination by GLOBAL86: Inhalation Unit Risk/PPB Based on Rat Nasal Tumors	9-5

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This document is based in part on a review of the literature on the toxicology of acetaldehyde prepared under contract with the Air Toxicology and Epidemiology Section by Dynamac Corporation. The Dynamac Corporation personnel involved in the preparation of the review were: Aisar Atrakchi, Ph.D. (Principal Author); Jess Rowland, M.S. and Dawn Webb, B.S. (Authors); William L. McLellan, Ph.D. and Allan Gray, Ph.D. (Reviewers); Karen Swetlow, B.S. (Technical Editor); and Nicolas P. Hajjar, Ph.D. (Department Manager). This document was prepared under contract with the California Department of Health Services, Hazard Evaluation Section, Berkeley, CA, Ms. Michelle Sabel, Project Officer. Melanie A. Marty, Ph.D. of the Air Toxicology and Epidemiology Section also reviewed the document.

Additionally, the authors gratefully acknowledge the assistance of Gloria Harrell and Laurie Bliss in preparation of this document.

1.0. SUMMARY

The health effects of acetaldehyde have been reviewed and evaluated to determine if acetaldehyde may be a toxic air contaminant, i.e., an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

At ambient temperatures acetaldehyde is a gas. In vivo acetaldehyde is rapidly distributed throughout the body. Acute exposure leads to eye, skin, and respiratory tract irritation, as well as to other pathologic changes. At high doses acetaldehyde cause embryotoxicity and fetal malformations in rats. At current ambient levels of acetaldehyde, no acute or noncarcinogenic chronic effects are expected; however, hot spots have not been evaluated.

Acetaldehyde (CH_3CHO), a saturated, aliphatic aldehyde with a pungent, suffocating odor, is a colorless liquid that is volatile at room temperature. Since acetaldehyde is the immediate oxidation product of ethyl alcohol, its metabolic fate and toxic effects have been studied primarily in conjunction with the effects of alcohol.

Acetaldehyde is readily absorbed through the lungs into the blood following inhalation exposure and from the gastrointestinal tract following oral administration. Following inhalation exposure, it is transported by the blood to various organs for metabolism. Acetaldehyde undergoes transplacental transport when present at relatively high concentrations in the blood of pregnant rats. Following oral administration, it undergoes extensive first-pass metabolism in the liver; only 5% remains unchanged. Acetaldehyde is metabolized by aldehyde dehydrogenase to acetate and is eliminated in the urine, in expired air, and through the skin. When acetaldehyde is administered orally to rats at low concentrations, the elimination kinetics are first order but nonlinear when concentrations greater than 100 μM are reached. Because acetaldehyde is a reactive molecule, it is mostly bound to proteins and other blood components while in the bloodstream. Acetaldehyde causes lipid peroxidation and free radical formation resulting in cellular injury. It can also act as a hapten, and antibodies against acetaldehyde conjugates have been isolated from human serum.

The major effects of acetaldehyde vapor in humans consist of irritation to the eyes, skin, and respiratory tract. Information in the available literature is inadequate to assess the chronic effects of acetaldehyde exposure in humans. The American Conference of Governmental Industrial Hygienists (ACGIH) Time-Weighted Average Threshold Limit Value (TLV) for exposure 8 hours/day, 5 days/week, is 100 ppm. This is also the Occupational Safety and Health Administration's Permissible Exposure Level (PEL) for workers.

From the LD_{50} and LC_{50} values, acetaldehyde is considered to produce low acute toxicity in laboratory animals. Following single or repeated exposure, the entire respiratory tract is affected to varying degrees, depending on the concentration and length of exposure. Signs of toxicity include labored respiration, mouth breathing, weight loss, and liver damage.

Subchronic exposure to acetaldehyde caused varying degrees of inflammation and injury to the respiratory tract. Lesions included hyperplasia and metaplasia

of the olfactory mucosa. The NOAEL (No Observed Adverse Effect Level) and LOAEL (Lowest Observed Adverse Effect Level) from subchronic inhalation toxicity studies with rats are 150 ppm and 400 ppm, respectively.

In hamsters and rats, the chronic toxicity of acetaldehyde inhalation included increased mortality and growth retardation. Histopathological changes in the nose, larynx, and trachea included degeneration, hyperplasia, and metaplasia. A NOAEL for chronic toxicity could not be established. A LOAEL of 750 ppm was obtained for growth retardation.

The Office of Environmental Health Hazard Assessment (OEHHA) uses Reference Exposure Levels (RELs) to assess risk for noncancer health effects. The United States Environmental Protection Agency (USEPA) has developed a specific methodology to derive RELs and calls the resulting number the Reference Concentration (RfC) for the chemical. The RfC is an estimate, with an uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime of exposure. The RfC is derived from a no (NOAEL) or lowest (LOAEL) observed adverse effect level in human or animal exposure, to which uncertainty or "safety" factors are applied. The USEPA has determined an RfC for acetaldehyde of 0.009 mg/m^3 (5 ppb) which is based on studies in which degeneration of the olfactory epithelium of rats was the most sensitive endpoint. OEHHA staff agree that below this RfC there will be no significant noncancer health effects due to acetaldehyde. Since the annual average ambient air level of acetaldehyde in California is estimated by the Air Resources Board in part A of this document to be 0.004 mg/m^3 (2 ppb), noncarcinogenic effects are not expected to occur since the air level is one-half of the RfC. However, "hot spots" of acetaldehyde exposure have not been evaluated.

Acetaldehyde has been shown to cross the placenta and enter the fetus in laboratory studies. Acetaldehyde caused developmental and reproductive toxicity in some rodents. Several intraperitoneal and intravenous developmental studies, *in vitro* studies, and a single reproductive study in male mice were found. The *in vivo* studies provided insufficient information upon which to base finite conclusions regarding developmental toxicity. Both the single male reproductive toxicity study and the *in vitro* testicular cell culture tests revealed effects on testosterone production. Various studies showed similarities between human and animal effects. No reproductive or developmental toxicity studies were found in which acetaldehyde was given via the inhalation or oral route.

Genotoxicity studies indicate that acetaldehyde is mutagenic in somatic cells. Acetaldehyde induced gene mutations in *Drosophila* but not in *Salmonella* assays. Conflicting results were obtained for mitochondrial mutations in *Saccharomyces cerevisiae*. Mammalian cell cultures indicated that acetaldehyde induces aneuploidy, micronuclei, chromosomal aberrations, and sister chromatid exchange. *In vivo*, acetaldehyde induced chromosome gaps and breaks in rat embryos after intra-amniotic injection, and sister chromatid exchange in mouse and hamster bone marrow cells after intraperitoneal injection. Acetaldehyde also has the potential to initiate cell transformation.

Inhalation studies in rats and hamsters provided positive evidence for acetaldehyde carcinogenicity. Rats and hamsters exposed to acetaldehyde via

inhalation of 750-3000 and 1500 ppm, respectively, developed nasal and respiratory tract tumors, and hamsters exposed via inhalation to 1650-2500 ppm also developed nasal and respiratory tract tumors. Nasal tumors found in rats were mainly squamous cell carcinomas and adenocarcinomas originating in the respiratory and olfactory epithelium, respectively. In hamsters, acetaldehyde-induced tumors were predominantly in the larynx. No useful epidemiologic data were available.

The International Agency for Research on Cancer has concluded that there is sufficient evidence for the carcinogenicity of acetaldehyde in animals; in humans, the evidence for carcinogenicity is inadequate. Overall, based on both the animal and human data, IARC considers that acetaldehyde is possibly carcinogenic to humans. The Environmental Protection Agency (U.S. EPA, 1991) has classified acetaldehyde in class B2, a probable human carcinogen, "based on increased incidence of nasal tumors in male and female rats and laryngeal tumors in male and female hamsters after inhalation exposure." Office of Environmental Health Hazard Assessment (OEHHA) staff concurs with these conclusions. In addition, OEHHA staff found no evidence for a carcinogenic threshold level for acetaldehyde.

OEHHA staff recommends that the range of risks for ambient exposures to acetaldehyde be based on the range of upper 95% confidence limits predicted from fitting a linearized multistage model to the male and female rat nasal tumor data after application of one of three plausible interspecies scaling factors: one which assumes that ppb concentrations are equivalent between species (i.e., a scaling factor of 1), a second which is a standard surface area correction factor, and a third which is a contact area correction factor. The range of estimated excess lifetime cancer risk is 0.97 to 27 x 10^{-6} per ppb (0.54 to 15 x $10^{-6}/\mu g/m^3$). The risk from continuous exposure for a 70 year lifetime to average ambient airborne concentrations in California, estimated by the Air Resources Board to be 2 ppb (4 $\mu g/m^3$), is 2 to 54 cases per million persons exposed. The lower and upper ends of the range are from female rat nasal tumors with no scaling factor and male rats with a contact area scaling factor, respectively. Within this range OEHHA staff believe that the best upper bound value is 4.8 x 10^{-6} per ppb, based on nasal tumors in male rats. Using the best value exposure to the ambient value of 2 ppb could result in up to 288 excess lifetime cancers (Upper 95% Confidence Limits) among the 30 million residents of the state. However, potential "hot spots" have not been evaluated.

The range of risk values represents several sources of uncertainty, including statistical uncertainty due to the relatively small number of animals used in the bioassay (less than the usual 50 per group). Other general sources of uncertainty, include the choice of the animal-to-human scaling factors, the choice of the extrapolation model, and the large range of extrapolation (five orders of magnitude) from the acetaldehyde concentrations used in the animal experiments to current ambient levels. In addition there is the possibility in light of the absence of an epidemiological connection between exposure to acetaldehyde and cancer that the risks in rats and hamsters may not be applicable to humans, i.e., acetaldehyde is only a potential human carcinogen. While a portion of the population is exposed to concentrations of acetaldehyde greater than 2 ppb, others will be exposed to less and thus have a lower risk.

Based on the findings of carcinogenicity and the results of the risk assessment, OEHHA staff finds that ambient acetaldehyde is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

2.0 METABOLISM AND PHARMACOKINETICS

2.1 Introduction

Acetaldehyde is the immediate oxidation product of ethyl alcohol. Most of the toxicity induced by alcohol consumption in humans has been related to the accumulation of acetaldehyde in various tissues. Consequently, the metabolic fate and effects of acetaldehyde have been generally studied in conjunction with the effects of alcohol. Acetaldehyde is also an intermediate byproduct of many metabolic cycles (Krebs and Perkins 1970). The small amount of acetaldehyde generated in the body is rapidly oxidized to acetate, primarily in the liver; therefore, a significant amount of acetaldehyde is seldom found in the body unless it is introduced exogenously or through ingestion of large amounts of alcohol (Krebs and Perkins 1970).

The following sections discuss acetaldehyde absorption, distribution, metabolism, and excretion. The absorption studies include both the inhalation and oral routes of exposure. The varied routes of exposure in the distribution and metabolism studies include the use of ethanol as a precursor. A search of the available literature revaled no data on dermal exposure.

2.2 Absorption

2.2.1 Inhalation Studies

Acetaldehyde is a volatile liquid with a boiling point of 20.6°C, a vapor pressure of 1.23 atm at 25°C, and a vapor density of 1.52 (air = 1). These properties allow rapid exchange and equilibration between blood entering the lungs and alveolar air (Ridge 1963). Watanabe et al. (1986) exposed male Sprague-Dawley rats to acetaldehyde vapor concentrations in air ranging from 9 to 1000 mg/l for 1 hour. Acetaldehyde inhalation resulted in blood concentrations considerably higher than liver levels; at a blood level greater than 10 ug/ml, the concentration of acetaldehyde in the liver was less than 2.5 ug/g. Moreover, following acetaldehyde inhalation, levels in arterial blood were higher than in peripheral venous blood (data not given). This latter finding led the study authors to suggest that acetaldehyde is rapidly absorbed from and metabolized by the lungs, which possess aldehyde dehydrogenase. Acetaldehyde also undergoes extrahepatic metabolism, and only minor amounts reach the liver.

Two inhalation studies were conducted with humans and dogs to determine the percent retention of inhaled acetaldehyde in the respiratory tract under given experimental conditions (Egle 1970, 1972a). Retention was defined as the percent difference between the amount of acetaldehyde inhaled in a given exposure period and the amount exhaled. In the first study, Egle (1970) measured the total respiratory tract retention in relation to respiratory frequency, duration of exposure, and concentration of acetaldehyde inhaled. Volunteers (males and females aged 23-60 years) inhaled acetaldehyde vapors through nose and mouth breathing. Acetaldehyde vapors (average concentration between 0.4 and 0.6 ug/ml) were inhaled from a respirometer. Two breathing systems, open and closed, were used. In the open system, acetaldehyde vapor was inhaled from a respirometer and exhaled into a collecting bag; in the closed system, acetaldehyde vapor was circulated through the system by a fan,

and exhaled air was returned to the respirometer. The closed system permitted a record of the entire ventilatory pattern, and from this, an estimate of the contact time. In a sine-wave breathing pattern, contact time was determined by measuring the base of the triangular pattern, dividing by two, and converting millimeters to seconds. The contact time of a square-wave breathing pattern was determined as the sum of parallel sides of a trapezoid divided by two and converted to seconds.

The results of both the open and closed systems indicated an inverse relationship between ventilatory rate and percent retention of acetaldehyde (Figures 2-1 and 2-2). Moreover, in the open system (Figure 2-1), percent uptake (the difference between the amount inhaled and the amount retained) declined as the concentration of acetaldehyde increased. No differences in uptake were noted among the volunteers with regard to the absolute uptake under given conditions or the pattern of change in uptake when conditions were varied. The uptake was defined as the difference between the amount in the system before and after the inhalation period (these values were derived from the initial and final concentrations and the volume of the system). Total acetaldehyde retention was the same for mouth and nose breathing. In humans, the total respiratory tract retention was 60% under the given experimental conditions; the physiological respiratory rate was 10 to 20 ml/min, and the tidal volume was 500-2000 ml. The results also showed that total retention in multiple breath experiments was independent of tidal volume, and that uptake was controlled by frequency and duration of ventilation. For example, the uptake at acetaldehyde concentrations ranging between 0.4 and 0.6 ug/ml was 78% at an average contact time of 10.1 seconds and only 59% at an average contact time of 1.4 seconds ($p < 0.02$).

In a followup study to compare the effects of acetaldehyde vapors on the total respiratory tract in dogs and humans and to test (in dogs only) the effects of high acetaldehyde vapor concentrations on different parts of the respiratory tract, Egle (1972a) exposed male and female mongrel dogs to acetaldehyde vapors ranging from 0.4 to 0.8 ug/ml. The authors concluded that the total respiratory tract retention of acetaldehyde in dogs was similar to human retention values and inversely related to the ventilatory rate. In the dog-only studies, the results showed higher uptake in the upper respiratory tract than in the lower tract; these results were independent of the inhaled concentrations or the tidal volume.

2.2.2 Oral Studies

Because of its small molecular size and lipophilic and water-miscibile nature, acetaldehyde is readily absorbed from the gastrointestinal tract following oral administration. Once absorbed, acetaldehyde enters the bloodstream; a large portion reaches the hepatic circulation and becomes metabolized by the liver, the major organ of acetaldehyde breakdown (Ridge 1963). Data describing the dose-absorption relationship are not available (Barry and Williams 1988).

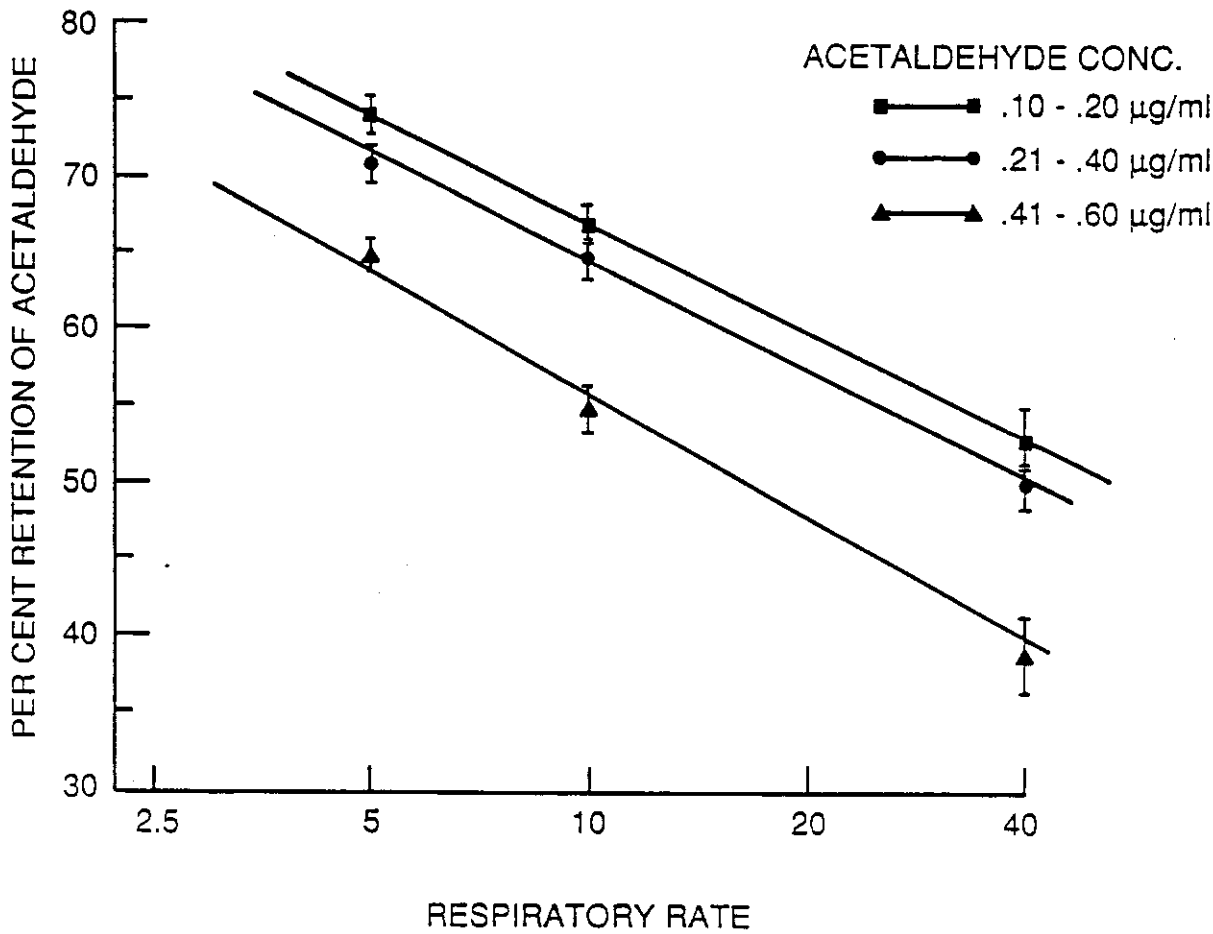

Figure 2-1. The retention of acetaldehyde with the open system design at three respiratory rates and three concentration ranges. Each point represents the average of 10 or more experiments.

SOURCE: Egle 1970.

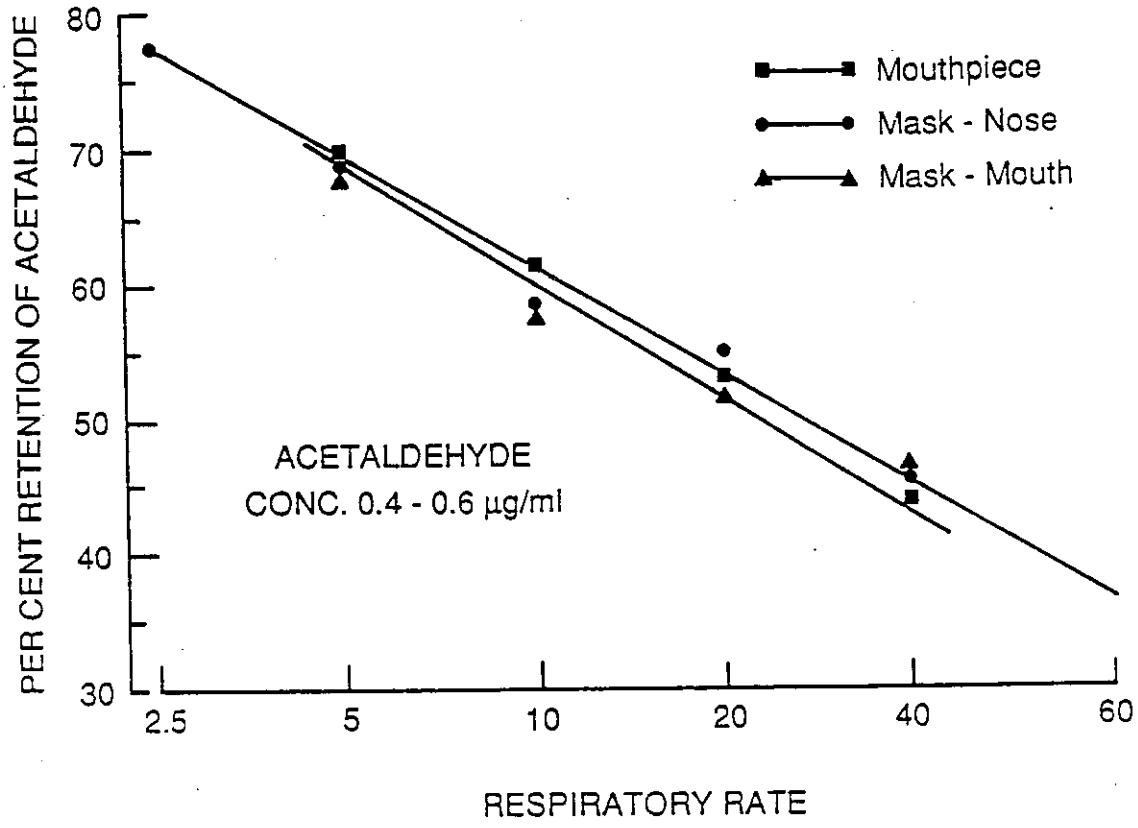

Figure 2-2. The retention of acetaldehyde with the closed system design. Three different types of breathing are compared. The overall average tidal volumes for each rate were 2.5/min, 2295 ml; 5/min, 1092 ml; 20/min, 762 ml; 40/min, 530 ml; and 80/min, 480 ml.

SOURCE: Egle 1970.

2.3 Distribution

Acetaldehyde readily diffuses through cellular membranes and is distributed to various organs for metabolism. It has been suggested that a normal endogenous level of acetaldehyde exists in blood from intestinal bacterial action and breakdown (Thurman and Pathman 1975). However, other studies have failed to detect such levels (Cohen and MacNamee 1976).

Hobara et al. (1985) exposed three male Sprague-Dawley rats to acetaldehyde air concentrations ranging from 1 to 20 mM for 1 hour. Within minutes postexposure, acetaldehyde was found in the blood, liver, kidneys, spleen, heart, and skeletal muscle, indicating rapid distribution. Immediately postexposure, the highest level of acetaldehyde was found in peripheral blood; at 15 minutes, arterial blood levels were 55% higher than peripheral venous blood levels. The lowest value was found in the liver (Table 2-1). These findings are in contrast to those reported by Watanabe et al. (1986), who reported that acetaldehyde levels were highest in arterial blood immediately following exposure. Hobara et al. (1985) reported that acetaldehyde disappeared rapidly from the blood; the half-life was 3.1 minutes. In contrast to findings related to inhalation of acetaldehyde, intragastric administration of ethanol at 3 g/kg produced blood and tissue acetaldehyde concentrations considerably lower than the values reported for inhalation exposure; the highest concentration was found in the liver (Table 2-1).

Shiohara et al. (1984) exposed rats by inhalation to 0.3 mmol acetaldehyde/l air (7000 ppm), 2 hours/day for 7 days, and measured blood levels at the end of the last exposure period. They found that acetaldehyde was rapidly removed from the blood; half-life was 10 minutes, and time to total body clearance was 40 minutes. Mean acetaldehyde blood concentration was 0.7, 0.2, and 0.1 mM at 5, 15, and 20 minutes, respectively, after inhalation was terminated. Following ingestion of 0.8 g/kg ethanol, acetaldehyde concentration in the hepatic blood of control nonalcoholics was 15.4 uM. Acetaldehyde could not be detected in the antecubital blood of controls (Nuutinen et al. 1984). A concentration-dependent increase was seen in acetaldehyde disappearance rate, which exhibited first-order Michaelis-Menten kinetics at acetaldehyde concentrations below 50 uM; the Michaelis constant (K_m) was 30-40 umol/l, and the V_{max} was 7 umol/l blood/minute. However, at blood acetaldehyde concentrations higher than 100 uM, the elimination kinetics followed a nonlinear pattern.

To demonstrate the rapid exchange of acetaldehyde between blood and exhaled air in humans, Freund and O'Hollaren (1965) used gas chromatography and detected acetaldehyde in alveolar air following ingestion of 0.5 ml ethanol/lb (859 mg/kg) body weight. Acetaldehyde could not be detected in alveolar air in a subject who consumed 1 ppm acetaldehyde in 500 ml orange juice (0.5 mg) containing no ethanol. However, it would seem highly unlikely that a dose this low (0.5 mg) would be detected in alveolar air, since acetaldehyde is extensively metabolized by the liver before it enters the blood circulation and the lung.

The results showed that acetaldehyde concentrations rose in proportion to ethanol intake when ethanol concentrations were less than 15-25 ug/100 ml. However, at higher ethanol concentrations, acetaldehyde values remained at a

TABLE 2-1

TISSUE DISTRIBUTION OF ACETALDEHYDE FOLLOWING ACETALDEHYDE INHALATION AND INTRAGASTRIC ETHANOL ADMINISTRATION

Tissue	Acetaldehyde Inhalation (nmol/g)	Ethanol Administration (nmol/g)
Blood[a]	1210	4.2
Liver	55	9.4
Kidney	213	2.1
Spleen	183	2.1
Heart muscle	277	2.3
Skeleton-muscle	345	1.7

[a]Blood levels were expressed as nmol/ml. Rats were exposed to 1-20 mM acetaldehyde vapor (in air) for 1 hour. The acetaldehyde levels were determined immediately after discontinuation of inhalation and 3 hours after the intragastric administration of ethanol at 3 g/kg body weight.

SOURCE: Hobara et al. 1985.

relatively constant level. As ethanol concentration dropped to 25 ug/100 ml or below, acetaldehyde concentration decreased rapidly (Figure 2-3).

Johannsson-Brittebo and Tjalve (1979) have used whole-body autoradiography to show the distribution of ^{14}C-acetaldehyde injected intravenously in mice. Within 1 minute, high radioactivity was detected in the heart muscle, diaphragm, kidney cortex, gastrointestinal mucosa, pancreas, salivary and lacrimal glands, bone marrow, nasal and bronchial mucosa, brown fat, plexus chorioidus, Harder's gland, and skeletal muscle. Low radioactivity was detected in the liver. After 5 minutes, the radioactivity in the heart, diaphragm, and skeletal muscle had decreased to low levels. Similar radioactivity distribution patterns were found in tissues 30 minutes to 24 hours postadministration. After 6 days of ^{14}C-acetaldehyde administration, radioactivity was high in the adrenal cortex, ovaries, bile, kidney cortex, nasal and bronchial mucosa, and skin; this was attributed to the incorporation of the 2-carbon moieties into other biosynthetic pathways, such as incorporation of acetyl-CoA into the citric acid cycle. Thus, acetaldehyde is rapidly distributed throughout the body and is incorporated into the body's metabolic cycles.

2.4 Metabolism

The liver is the main site of acetaldehyde metabolism. There is a strong "first pass" effect for ingested acetaldehyde and only 5% leaves the liver unchanged; this portion of acetaldehyde is transported by peripheral blood into other organs for its metabolism (Lubin and Westerfeld 1945; Westerfeld 1949). Inhaled acetaldehyde does not undergo a first pass effect and is distributed to all tissues including the liver. Acetaldehyde is oxidized by the enzyme aldehyde dehydrogenase to acetate. At least four additional enzymes can utilize acetaldehyde as a substrate. Xanthine oxidase, which occurs in the liver and in the blood and milk of some species, oxidizes acetaldehyde to acetate. Aldehyde mutase, found predominantly in the liver, preferentially reacts with one mole of acetaldehyde and one mole of pyruvate to produce acetate and lactate. Aldehyde aldolase and carboxylase, both of which are found in muscle, can metabolize acetaldehyde but apparently do not play a significant role in acetaldehyde breakdown *in vivo*.

Acetaldehyde blood concentrations have not been determined in persons exposed to the vapor, but have been determined following alcohol and paraldehyde administration; they were found not to exceed 0.2 mg/l.

The following sections discuss the aldehyde dehydrogenase enzyme system responsible for acetaldehyde metabolism, extrahepatic metabolism of acetaldehyde, and the compound's chemical reactivity.

2.4.1 Aldehyde Dehydrogenase Enzyme System

Aldehyde dehydrogenase is the main enzyme responsible for the breakdown of acetaldehyde. Its properties and subcellular locations have been extensively studied in the rat liver. This enzyme is found in both the cytosol and the mitochondria. The mitochondrial aldehyde dehydrogenase, which is the primary site of acetaldehyde oxidation in the rat, accounts for 80% of the

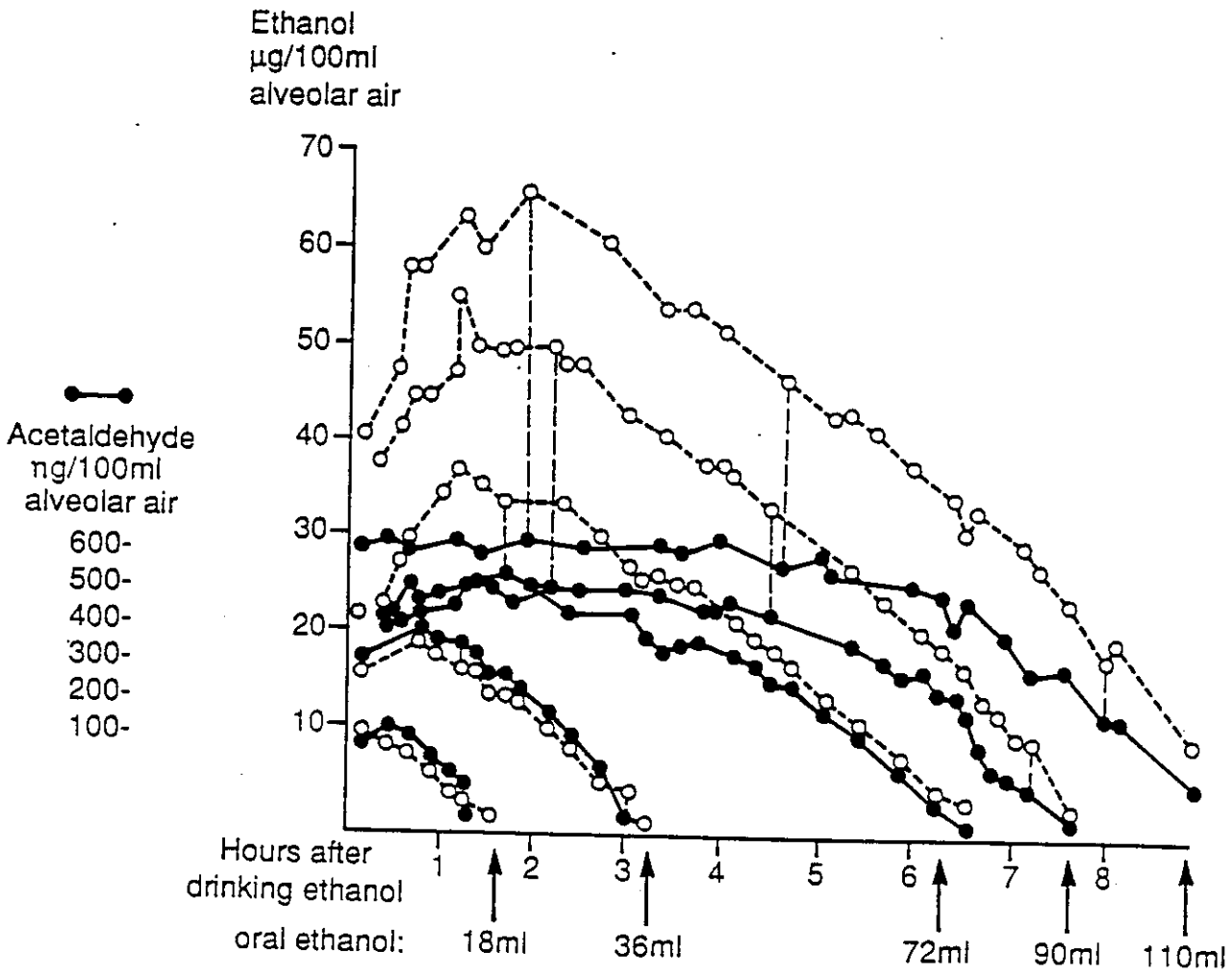

Figure 2-3. The effect of increasing amounts of oral ethanol upon acetaldehyde and ethanol concentrations in alveolar air in one subject. The circles represent ethanol, and the solid dots represent acetaldehyde concentrations. Each acetaldehyde curve is connected with its corresponding ethanol curve by three vertical lines.

SOURCE: Freund and O'Hollaren 1965.

acetaldehyde metabolizing activity in the mitochondria (Lindros et al. 1972; Horton and Barrett 1975, 1976). Two isozymes of aldehyde dehydrogenase are present in rat liver mitochondria. The first isozyme, designated as aldehyde dehydrogenase-I-NAD^+, has a K_m value for acetaldehyde oxidation of <5 uM (high affinity site); the second isozyme, designated as aldehyde dehydrogenase-II-NAD^+, has a K_m value of 1.5 mM (low affinity site). Acetaldehyde oxidation in the rat is linked to the mitochondrial electron transport chain at the NAD-aldehyde dehydrogenase site (Hasumura et al. 1976). Koivula et al. (1975) found two separable enzyme activities in both the cytosol and the microsomal fractions of the liver with properties similar to the mitochondrial enzymes with high K_m values.

Shiohara et al. (1984) exposed Sprague-Dawley rats to 0.3 mM acetaldehyde concentration in air for 2 hours/day for 7 or 14 successive days and killed them 24 hours after the last exposure. The authors found a significant ($p < 0.05$) decrease in liver mitochondrial low-K_m aldehyde dehydrogenase activity. They found similar results in the high-K_m aldehyde dehydrogenase of both mitochondrial and microsomal liver fractions. Acetaldehyde oxidation by intact liver mitochondria was decreased to 60% of that of controls. In contrast, brain mitochondrial aldehyde dehydrogenase activity and oxidation properties were unaffected by acetaldehyde inhalation. The authors suggested that only a small concentration of acetaldehyde had reached the brain.

The subcellular location of acetaldehyde oxidation in humans is debated. It has been suggested that the cytosol, not the mitochondria, is the primary site of acetaldehyde oxidation. However, more recently Cao et al. (1988), using beef and pig liver slices, showed that 60% of acetaldehyde oxidation was catalyzed by mitochondrial aldehyde dehydrogenase and only 20% by the high-K_m cytosolic enzyme. These findings are similar to those obtained in rats. Cao et al. concluded that the mitochondria appear to be the main site of acetaldehyde oxidation in all mammalian tissues including humans.

2.4.2 Extrahepatic Metabolism

In addition to hepatic mitochondrial metabolism, acetaldehyde is also metabolized by the respiratory-olfactory epithelium, kidneys, blood, brain, and spleen. Michoudet and Baverel (1987a) showed that in human and baboon renal cortex, acetaldehyde is oxidized to acetate by the kidney aldehyde dehydrogenase in a dose-dependent and linear manner with time. Acetaldehyde also crosses the blood-brain barrier and is metabolized by the brain aldehyde dehydrogenase (Shiohara et al. 1983). Forsander et al. (1969) showed a five- to sixfold higher level of acetaldehyde in peripheral blood as compared with that in the intact rat liver and hepatic vein. This was expected, since the former represents the total amount of acetaldehyde metabolized by all the extrahepatic organs. Oxidation rates of acetaldehyde were reported to be 2.0 umol/minute/g in the perfused rabbit liver and 1.1 umol/minute/g in the rat liver.

Casanova-Schmitz et al. (1984) exposed male F344 rats to 1500 ppm acetaldehyde for 6 hours/day for 5 days. At least two isozymes of aldehyde dehydrogenase were found in the nasal mucosa, differing with respect to their apparent V_{max} and K_m values (Table 2-2 shows these parameters in both the respiratory and olfactory mucosa). It is clear from the table that oxidation of acetaldehyde

occurred more rapidly in the homogenates of the respiratory than the olfactory mucosa. The nasal tissue is the first to contact acetaldehyde vapors upon inhalation. The presence of aldehyde dehydrogenase in the respiratory mucosa, as demonstrated in mice, rats, and hamsters, is important in the detoxification of acetaldehyde following inhalation. The aldehyde dehydrogenase acts as a defense mechanism, helping to minimize or prevent toxic injury to nasal tissues exposed to airborne compounds such as acetaldehyde (Kerns et al. 1983; Feron et al. 1982).

Michoudet and Baverel (1987b) prepared renal cortex tubules from the dog, rat, and guinea pig and incubated them with various concentrations of acetaldehyde. They found that acetaldehyde was metabolized at high rates in the tubules and in a dose-dependent fashion when high concentrations of acetaldehyde (5-10 mM) were tested. The rate of acetate accumulation was high in the dog and guinea pig but not in the rat, and exceeded the rate of conversion of acetate to acetyl-CoA by acetyl-CoA synthetase. These species differences were due to differences in the activities of these two enzymes. In rat renal cortex, acetyl-CoA synthetase was suggested to be the rate-limiting enzyme in acetaldehyde breakdown. The ratio of aldehyde dehydrogenase to acetyl-CoA synthetase in the dog, rat, and guinea pig was 1.13, 0.65, and 2.24, respectively. The acetaldehyde carbon removed but not accounted for by acetate was converted into carbon dioxide (CO_2). When concentrations of acetaldehyde (0.1-0.2 mM) closer to the physiological range were used, acetate did not accumulate. This study indicates that in vivo, the kidneys have high capacity to remove acetaldehyde from the circulation. Similarly, Marchner and Tottmar (1976) showed 50% lower acetaldehyde concentrations in renal venous blood of the rat after ethanol ingestion as compared with concentrations in the arterial blood. From all these findings, it is clear that the kidneys play a significant role in removing acetaldehyde from the circulation.

Results similar to those obtained in the above studies have been reported in the human and baboon renal cortex (Michoudet and Baverel 1987a). Acetaldehyde, 1-20 mM, was metabolized at high rates, in a dose-dependent fashion, and was completely oxidized to CO_2 and water in isolated human and baboon kidney cortex tubules. This indicated that the kidneys in vivo play a significant role in metabolism of acetaldehyde.

Pietruszko and Vallari (1978) were the first to demonstrate the presence of aldehyde dehydrogenase in human blood. Total catalytic enzyme activity was 0.017 umol/minute/ml blood incubated with 680 uM acetaldehyde. The enzyme was suggested to be located in the intracellular fraction of the blood.

In a recent study, Solomon (1988) investigated the effects of acetaldehyde on human red blood cell (RBC) enzyme activities in vivo. He tested 26 different enzymes and found that incubation of undiluted RBC lysates with 10 mM acetaldehyde at 37°C for 4 hours decreased aldolase activity by 42%, glutamic-pyruvic transaminase (GPT) by 52%, and glutamic-oxaloacetic transaminase (GOT) by 37%. In intact RBCs under identical incubation conditions, 10 mM acetaldehyde decreased GPT, GOT, and aldolase by 26%, 17%, and 53%, respectively. The acetaldehyde-mediated enzyme inhibition was both time- and temperature-dependent. There was no inhibition at 4°C, and in the first half hour there was no detectable inhibition of enzyme activity; however, within 3.5 hours, inhibition was significant. The findings were different with diluted hemolysate. Acetaldehyde had no effect on GPT, GOT, or aldolase

TABLE 2-2

ESTIMATED KINETIC CONSTANTS FOR THE NAD^+-DEPENDENT OXIDATION OF ACETALDEHYDE TO ACETATE CATALYZED BY HOMOGENATES OF RESPIRATORY AND OLFACTORY MUCOSA FROM FISCHER-344 RATS

AldDH isozyme	Tissue[a]	V_{max}[b] [nmol·min^{-1}·(mg protein)$^{-1}$]	K_m[b] (mM)
		Control	
I	Respiratory mucosa	128 ± 10	20 ± 3
	Olfactory mucosa	28 ± 4	22 ± 7
II	Respiratory mucosa	0.8 ± 0.9	$3 \times 10^{-4} \pm 9 \times 10^{-2}$
	Olfactory mucosa	2.2 ± 0.6	$1 \times 10^{-1} \pm 5 \times 10^{-2}$
		Exposed[c]	
I	Respiratory mucosa	140 ± 7	21 ± 2
	Olfactory mucosa	17.8 ± 0.6	14 ± 1
II	Respiratory mucosa	1.5 ± 1.1	$1 \times 10^{-1} \pm 2 \times 10^{-1}$
	Olfactory mucosa	1.3 ± 0.2	$7 \times 10^{-2} \pm 3 \times 10^{-2}$

[a]Mucosal samples from eight rats were combined for the measurement of the enzyme activity.
[b]Estimates shown are mean ± S.D., calculated by nonlinear regression analysis of the inital velocity on the substrate concentration; df = 13.
[c]Rats were exposed to 1500 ppm of acetaldehyde (6 hours/day, 5 days).

SOURCE: Casanova-Schmitz et al. 1984.

activities, suggesting the requirement of other metabolic conditions. The inhibition of aldolase was due to acetaldehyde oxidation, whereas transaminase inhibition seemed to require a nonoxidative pathway of acetaldehyde. It was suggested that acetaldehyde-mediated enzyme inhibition may play a role in the toxicity of alcoholics. Acetaldehyde-mediated transaminase inhibition was prevented by blocking glycolysis with sodium fluoride (Feig et al. 1971); therefore, some glycolytic intermediates may play a role in acetaldehyde-mediated transaminase inhibition. This was supported by Hoberman (1979a,b), where acetaldehyde was shown to react with glycolytic intermediates forming metabolites that bind to RBC proteins.

2.4.3 Acetaldehyde Binding and Antibody Formation

In addition to its metabolism by enyzmes, acetaldehyde is very reactive chemically. It has been reported to bind to proteins, the peptide glutathione, individual amino acids, and DNA. Schiff base formation appears to be the preferred initial reaction for acetaldehyde (Tuma and Sorrell, 1985) but other reactions are possible (USEPA, 1987).

Reaction of acetaldehyde with proteins was reported as early as 1949 (Mohammad et al. 1949). Acetaldehyde in the blood is found mostly in the bound form. It binds to albumin, hemoglobin, and other blood proteins (Donohue et al. 1983; Eriksson et al. 1977; Gaines et al. 1977; Mohammad et al. 1949). The maximum amount of acetaldehyde bound to rat erythrocytes is reported to be equivalent to 1.2 umol/ml of blood (Hagihara et al. 1981). Controversy exists concerning the presence of significant binding of acetaldehyde in human blood. Eriksson et al. (1977) reported 60% binding of acetaldehyde to whole blood in ethanol-dosed rats (different strains) that produced 20-300 uM acetaldehyde in the blood. Yet no significant binding was found in blood obtained from the antecubital vein of male and female human volunteers.

Gaines et al. (1977) reported that acetaldehyde irreversibly binds to erythrocyte membrane proteins such as hemoglobin in a manner similar to the binding of formaldehyde and glutaraldehyde (Stek 1972). They reacted isolated human erythrocyte ghosts with ^{14}C-acetaldehyde (1 mM containing 5 uCi of ^{14}C) and found that free acetaldehyde constituted 16% of the initial amount of label added; the remaining 84% was bound and remained in the suspension.

The binding of acetaldehyde to liver membrane proteins is known to alter the morphological and structural conformation of the membrane and perhaps the immunogenicity without having an effect on membrane function (Barry et al. 1984). Since the nonenzymatic browning of many foods involves, as a first step, an aldehyde-amine addition or condensation reaction, this phenomenon was used to demonstrate the interaction of acetaldehyde with various proteins (Mohammad et al. 1949). The reaction of acetaldehyde with bovine serum albumin (BSA) was temperature-, pH-, and substrate concentration-dependent and was evident by the appearance of the brown color and gelation of the reaction mixture. When proteins were isolated, they showed decreased solubility, lowered total nitrogen content, and a significant reduction in free amine content. This indicated the reaction of acetaldehyde with the amino groups of BSA. Acetaldehyde also reacted with guanidyl groups but to a lesser extent than with those of the amino groups of BSA.

Gelation of BSA by acetaldehyde was attributed to the formation of cross-links between the different reactive sites of protein molecules. Direct proof of BSA-acetaldehyde cross-linking was determined by osmotic pressure measurements, which revealed a large increase in the average molecular weight of soluble derivatives.

Acetaldehyde also reacted with some amino acids, such as alanine, serine, and threonine. The results were similar to those found with proteins. The reaction of acetaldehyde with proteins has been described as irreversible and covalent in nature. Such strong binding is due to the electrophilic properties of acetaldehyde, which can form both stable and unstable Schiff bases with the free amino groups of BSA and hepatic proteins (Donohue et al. 1983).

Acetaldehyde is well known to cause lipid peroxidation either directly through oxidation, or indirectly as a glutathione (GSH) conjugate (Shaw et al. 1981). Acetaldehyde binds to cysteine, one of the three amino acids constituting the GSH tripeptide. Depletion of GSH can reduce the scavenging of toxic free radicals by GSH. Although depletion of GSH per se is not enough to produce liver injury (Siegers et al. 1977), it should be accompanied by free radical formation. Williams and Barry (1986) showed that incubation of rat liver membranes with acetaldehyde led to the formation of products that activated neutrophils to degranulate and to produce cytotoxic superoxide ions. Tuma et al. (1984) incubated 200 uM ^{14}C-acetaldehyde with 6 mg/ml BSA with or without 5 mM ascorbate, a strong antioxidant. In the absence of ascorbate, acetaldehyde-BSA adduct formation reached a maximum after 24 hours of incubation and plateaued thereafter up to 240 hours. The percent acetaldehyde converted to stable adducts increased progressively with time and ranged from 35 to 70% after 240 hours. On the other hand, in the presence of ascorbate, there was a gradual and continuous increase in the formation of total acetaldehyde-BSA adducts throughout the reaction period. The total adducts formed were stable. Similar enhancement of stable adduct formation was seen in the reaction of acetaldehyde with cytochrome c, histones, and poly-L-lysine. Based on these findings, it was suggested that possible liver injury due to formation of stable hepatotoxic adducts may occur in individuals who consume megadoses of vitamin C and drink alcohol.

Fleisher et al. (1988) found that rabbits immunized with acetaldehyde-rabbit serum albumin (A-RSA) generated high titers of serum antibodies against A-RSA. The induced antibodies reacted negligibly against untreated RSA, indicating that A-RSA can serve as an antigen and immunize the host. In addition, A-RSA-immunized rabbits produced antibodies against acetaldehyde conjugates of human serum albumin, human gamma globulin, BSA, and bovine gamma globulin. These results suggest a role for immune mechanisms in the pathogenesis of alcohol liver disease. Indeed, Hoerner et al. (1988) found that the majority of alcoholic patients studied had elevated circulatory antibody titers against acetaldehyde-human hemoglobin and acetaldehyde-human serum albumin adducts.

2.4.4 Acetaldehyde Binding to DNA

Lam et al. (1986) reported the ability of acetaldehyde to crosslink DNA to protein in rat nasal respiratory mucosa. Crosslinking was demonstrated both in vitro, in homogenates of nasal respiratory mucosa incubated with acetaldehyde, and in vivo, after inhalational exposure of rats to

acetaldehyde. Such crosslinking indicates that acetaldehyde can react with DNA.

2.5 Excretion

The data on the disposition and elimination kinetics of acetaldehyde are scarce. Acetaldehyde can be excreted unchanged in urine, expired air, and skin (Baselt and Cravey 1989). Truitt and Walsh (1971) suggested that during periods of elevated blood levels, acetaldehyde metabolites would be excreted in the urine. Kallama and Hemminki (1983) injected Wistar rats with 120 uCi of ^{14}C-acetaldehyde and found that only 6% of the initial radioactivity was excreted in urine over a 7-day period. The main urinary products were acetate and two cysteine adducts constituting 2% of the radioactivity in urine collected 48 hours after ^{14}C-acetaldehyde administration. When a complex mixture of ^{14}C-cysteine and acetaldehyde was injected into the rats, 13.6% of radioactivity was detected in urine throughout 4 days in the form of 2-methylthiazolidine-4-carboxylic acid. This was in agreement with other studies, indicating that cysteine is a relatively poor trapping agent for acetaldehyde *in vivo*.

2.6 Conclusions

From the three inhalation studies investigating absorption, acetaldehyde was found to undergo rapid absorption and to reach equilibrium between the alveolar air and blood entering the lungs. Inhalation of 0.4 and 0.6 ug/ml acetaldehyde vapors in humans caused a decrease in tissue retention of vapors as the respiratory rate was increased. The total retention was 60% under physiological conditions of rate and tidal volume. No difference in total retention was found between nose and mouth breathing in humans. Total retention was independent of tidal volume, but uptake was dependent on frequency and duration of respiration. Similarity was found in total retention between the dog and human; in the dog, uptake was greater in the upper than in the lower tract, and it was independent of tidal volume and inhaled concentration.

Acetaldehyde is rapidly distributed to various organs when administered through inhalation, oral, or parental routes. At low concentrations, the acetaldehyde disappearance rate follows a first-order Michaelis-Menten kinetics with a K_m of 30-40 mM and a V_{max} of 7 umol/l blood/minute. At concentrations higher than 100 uM, the elimination kinetics are nonlinear.

The liver is the main site of acetaldehyde metabolism; extrahepatic metabolism also occurs in kidneys, lungs, blood, brain, and spleen. Aldehyde dehydrogenase is the enzyme system responsible for the metabolism of acetaldehyde into acetate. This enzyme is found in at least two isozyme forms in the cytosol and the mitochondia of various tissues. The mitochondrial aldehyde dehydrogenase is the main site of acetaldehyde oxidation both in rat liver and mammalian tissues including man. Oxidation occurs more rapidly in the respiratory mucosa than in the olfactory mucosa. Aldehyde dehydrogenase in the nasal tissue acts as a defense mechanism in detoxification of various airborne compounds, including acetaldehyde entering via inhalation. Acetaldehyde can be excreted unchanged in urine, expired air, and skin.

Acetaldehyde is a highly reactive molecule; it binds to amino acids and blood and membrane proteins. It causes lipid peroxidation leading to adduct formation and free radical-induced cell injury. Acetaldehyde can act as a hapten, and antibodies against acetaldehyde conjugates have been detected in human serum.

In conclusion, more complete studies are needed to examine the detailed pharmacokinetics of acetaldehyde metabolism, particularly via the inhalation route. The studies presented in this chapter have shown acetaldehyde to be rapidly absorbed, distributed, metabolized, and excreted. No accumulation in tissues occurs when administered via the various routes. At concentrations less than 100 uM, the elimination kinetics follow a first-order Michaelis-Menten linear relationship; the elimination kinetics are nonlinear at concentrations greater than 100 uM when acetaldehyde is given orally.

3.0 ACUTE TOXICITY

3.1 Human Health Effects

Inhalation of acetaldehyde vapors is the main route of occupational exposure in humans. The Occupational Safety and Health Administration's Time-Weighted Average (TWA) Permissible Exposure Limit (PEL) is 100 ppm (180 mg/m^3) for an exposure period of 8 hours/day, 5 days/week (OSHA 1989). The American Conference of Governmental Industrial Hygienists (ACGIH 1986) recommends a Threshold Limit Value (TLV) of 100 ppm (180 mg/m^3) for an exposure period of 8 hours/day, 5 days/week. OSHA has also promulgated a Short Term Exposure Limit (STEL) of 150 ppm.

The major effects of human exposure to acetaldehyde vapors consist of irritation to the eyes, skin, and respiratory tract. Low to moderate air concentrations (50-200 ppm) cause eye irritation and upper respiratory tract discomfort. Concentrations greater than 200 ppm may cause dyspnea and central nervous system depression (Baselt and Cravey 1989). Other clinical manifestations include erythema, coughing, pulmonary edema, and narcosis (Dreisbach 1980).

Human volunteers exposed to 50 ppm for 15 minutes experienced mild eye irritation (Silverman et al. 1946). Exposure to 134 ppm for 30 minutes produced mild upper respiratory tract irritation, and exposure to 200 ppm for 15 minutes produced transient conjunctivitis in all subjects. Sim and Pattle (1957) exposed 14 men, aged 18-45 years, to 133 ppm acetaldehyde for 30 minutes. Only mild irritation of the upper respiratory tract was evident.

When splashed in the eye, acetaldehyde liquid causes lacrimation and blurred vision (MCA, Inc. 1952). Prolonged exposure of the skin to liquid acetaldehyde causes erythema and burns; repeated contact may lead to dermatitis due to primary irritation or sensitization (ACGIH 1986).

3.2 Animal Studies

The acute animal toxicity studies discussed in this section include inhalation, oral, parenteral, and subcutaneous routes of administration with emphasis on the first three routes.

The acute LD_{50} values for acetaldehyde are summarized in Table 3-1. The acute inhalation LC_{50} is 20,000 ppm in rats exposed to acetaldehyde for 30 minutes (Skog 1950) and 13,300 ppm in rats exposed for 4 hours (Appleman et al. 1982). However, in another study inhalation of either 8,000 or 16,000 ppm acetaldehyde vapors for 8 hours caused no mortality in rats at 14 days postexposure (Smyth et al. 1951). The acute oral LD_{50} was reported to be 1232 mg/kg in mice and ranged from 1900 to 5300 mg/kg in rats. The LD_{50} for subcutaneous injection ranged from 560 to 640 mg/kg.

3.2.1 Inhalation Exposure

Following single or repeated exposure to acetaldehyde, the entire respiratory tract responds to varying degrees. The severity generally depends on the

TABLE 3-1

ACUTE TOXICITY STUDIES CONDUCTED WITH ACETALDEHYDE

Species	Number and Sex/Dose	Route of Administration	Dosage Eliciting Toxic Effects	Reference
Rat	5 males, 5 females	inhalation	LC_{50} 13,300 ppm/4 hr	Appleman et al. 1982
	--[a]	inhalation	LC_{50} 20,000 ppm 30 min	Skog 1950
	--	inhalation	LC_{Lo} 4000 ppm/4 hr	Lewis and Tatkin 1983
	--	inhalation	8000-16,000 ppm/8 hr; no deaths 14 days later	Smyth et al. 1951
Mouse	4 males	inhalation	RD_{50} 4946 ppm	Kane et al. 1980
	--	inhalation	RD_{50} 2845 ppm	Barrow 1982
Rat	--	oral	LD_{50} 1900 mg/kg	Windholz et al. 1983
	--	oral	LD_{50} 1930 mg/kg	Smyth et al. 1951
	--	oral	LD_{50} 5300 mg/kg	Omel'yanets et al. 1978
Mouse	--	oral	LD_{50} 1232 mg/kg	NRC 1977
	--	subcutaneous	LD_{50} 560 mg/kg	Skog 1950
Rat	--	subcutaneous	LD_{50} 640 mg/kg	Skog 1950

[a]Data were not reported in the literature.

concentration and exposure time. Appelman et al. (1982) exposed 20 SPF albino Wistar rats of each sex for 4 hours to acetaldehyde concentrations in air ranging from 10,436 to 16,801 ppm and observed the rats for 14 days. During the first 30 minutes of exposure, the animals were restless; they exhibited labored respiration with closed eyes. After 1 hour, the rats exhibited prostration with open eyes and severe mouth breathing. The 4-hour acute inhalation LC_{50} was estimated to be 13,300 ppm. Death occurred 2 to 6 days after exposure to the 15,683-ppm concentration.

Kane et al. (1980) studied the sensory irritant effect of acetaldehyde in male Swiss-Webster mice by recording the degree of respiratory rate depression. Groups of four animals were subjected to head-only exposures at varying concentrations for 10 minutes. Within a few seconds, the respiratory rate was reduced, and a pattern typical of sensory irritants was seen (Alarie 1966). Moreover, after 3 to 4 minutes, the animals exhibited a further reduction in rate as pronounced as the first. From the concentration-response relationship, the RD_{50} (the concentration that produced a 50% decrease in respiration rate) was calculated to be 4946 ppm. Concentrations of 1500 ppm and above resulted in respiratory rate depression. In another study, the RD_{50} of acetaldehyde in mice was calculated to be 2845 ppm (Barrow 1982). Neither of these studies reported histopathology but other studies have correlated RD_{50} concentrations with histopathology (Jiang et al. 1983, Buckley et al. 1984). The RD_{50} value indicates an irritation response to the chemical; it is useful in comparing relative potencies of chemicals as irritants and in establishing TLVs.

Unlike mice, F344 rats are not a good model for predicting acceptable occupational exposure concentrations to prevent sensory irritation in humans. Babiuk et al. (1985) exposed male Fischer 344 rats head only to various aldehydes. Both naive (no pretreatment) and formaldehyde-pretreated rats were used to determine whether pretreatment with formaldehyde could cause sensory irritation and cross-tolerance. All pretreated rats were exposed to 15 ppm formaldehyde 9 hours/day for 9 days; on the 10th day, the animals were exposed to acetaldehyde. The sensory irritant response was quantified by measuring respiratory rate depression using plethesmography. Acetaldehyde alone showed an RD_{50} value of 2991 ppm. After formaldehyde pretreatment, acetaldehyde showed cross-tolerance. The concentration response curve for acetaldehyde shifted to the right with a 3.5-fold increase in the RD_{50} from 2,991 to 10,601 ppm. They speculated that the mechanism of cross-tolerance is either a nonspecific injury to the nasal mucosa or modulation of a specific receptor in the trigeminal nerve endings.

Changes in arterial blood pressure and heart rate were measured in anesthetized rats exposed to 278-16,680 ppm (0.5-30 ug/ml) acetaldehyde (Egle 1972b). Blood pressure was significantly increased at concentrations of 1668 ppm (3 ug/ml) and greater, whereas heart rate was increased at 6672 and 13,900 ppm (12 and 25 ug/ml), respectively.

Liver damage is known to occur upon inhalation of large amounts of acetaldehyde. Tanaka et al. (1988) showed that acetaldehyde potentiates adenylate cyclase activity, which in turn stimulates cyclic adenosine 3',5'-monophosphate (cAMP) release in rats exposed to acetaldehyde for 2 hours (concentration not reported). This elevated cAMP increased the synthesis and release of biogenic amines that caused the liver damage.

3.2.2 Oral

Severe hypomotility (reduction of norman physical movements) was induced by intragastric administration of 100 mg/kg of acetaldehyde to male albino rats (Durlach et al. 1988). This almost immediate and severe hypomotility partially decreased after 5 minutes and plateaued for the remainder of the 15-minute test period. It could be reversed by calcium-N-acetylhomotaurine, the taurine analog having the greatest anti-acetaldehyde activity.

Mixed-breed male dogs dosed orally with 600 g/kg acetaldehyde showed frequent and severe bloody vomiting lasting for several hours (Booze and Oehme 1986). Only two of the acetaldehyde-dosed dogs exhibited slight tremors, and the remaining four dogs did not show any neurological or muscular symptoms. The two dogs exhibiting tremors had high acetaldehyde levels in their blood, whereas acetaldehyde either could not be detected or remained near the detection limit of 2 ng/ul in the other four dogs. All dogs appeared normal at 24 hours postdosing.

3.2.3 Parenteral Administration

Condouris and Havelin (1987) showed that intravenous injection of acetaldehyde at 1 to 10 mg/kg or infusion at 0.1 to 100 mg/kg/min to anesthetized cats resulted in increased mean arterial blood pressure and heart rate. Ventricular arrhythmias in the form of premature ventricular beats, bigeminy, and multifocal rhythms were seen at a threshold dose of 1-2.5 mg/kg. These effects of acetaldehyde were indirectly induced via the release of endogenous catecholamines from the heart. Similar results were found in guinea pigs (Mohan et al. 1981).

In mice, acetaldehyde injected intraperitoneally at 250 mg/kg three times, 10 minutes before 1-methyl-4-phenyl-1,2,3,4 tetrahydropyridine (MPTP), and 10 and 30 minutes after MPTP, potentiated the neurotoxicity of MPTP injected intraperitoneally at 36 mg/kg. This potentiation occurred through enhancement of striatal dopamine depletion and destruction of dopaminergic neurons in the substantia nigra (Corsini et al. 1987; Zuddas et al. 1987).

Acetaldehyde has been shown *in vitro* or following intravenous administration to cause cardiomyopathies by impairing protein synthesis (Lieber 1988) and by increasing the epinephrine content in the heart (Fujiwara et al. 1988). It stimulates the adrenal glands and hence increases the synthesis and release of biogenic amines (Lieber 1988). Acetaldehyde also impairs vitamin metabolism, particularly that of vitamin B (Veitch et al. 1975), and it affects the synthesis of vascular prostacyclin (Guivernau et al. 1987).

3.3 Toxicity of Peroxyacetyl Nitrate

Airborne acetaldehyde in the presence of nitrogen oxides can be converted to peroxyacetyl nitrate (PAN). PAN causes eye irritation in humans in the 1 ppm range (Stephens et al., 1961). In male A-strain mice, an LC_{50} (2 hours) of 106 ppm has been estimated (Campbell et al., 1967). Younger mice had a higher

LC_{50} (more resistant to PAN) than older mice. No lethality was seen at 97 ppm which indicates a very steep dose response curve. In rats the 4 hour LC_{50} was 95 ppm (Kruysse et al., 1977). Additional studies were done in rats for 4 and 13 weeks with exposures of 6 h/day, 5 days/week (Kruysse et al., 1977). In the 4 week study a NOEL of 4.1 ppm was obtained based on minimal behavioral disturbances, transient growth depression, slightly increased lung weights, and mild changes in the histopathology of the respiratory tract. The NOEL was 0.9 ppm. In the 13 week study the LOEL was 1 ppm, based on minimal irritation of the mucous membranes of the nasal cavity. The NOEL was 0.2 ppm. The toxic effects of PAN need to be considered as possible sequelae of acetaldehyde emissions.

3.4 Conclusions

In humans, the primary route of exposure to acetaldehyde is vapor inhalation. Acetaldehyde vapor is irritating to the skin, eyes, and respiratory tract. In animal studies, the 4-hour LC_{50} value in rats is 13,300 ppm, and the LD_{50} value ranges from 1900 to 5300 mg/kg. The RD_{50} is 2845 ppm in mice and the lowest observed effect level reported is 1500 ppm for a 10 minute exposure based on respiratory rate depression. It is hepatotoxic in rats when inhaled in large amounts. Acetaldehyde affects the cardiovascular system. It affects blood pressure and heart rate, causes cardiac arrhythmias through the release of catecholamines, and at high concentrations, acts as a depressant to the central nervous system and causes narcosis when administered via different routes. Acetaldehyde indirectly caused liver damage in rats by stimulating the synthesis and release of catecholamines. Oral administration of 100 mg/kg to rats caused severe hypomotility. Dogs orally dosed at 600 g/kg developed severe bloody vomiting. In mice, the neurotoxicity of MPTP was potentiated by acetaldehyde injected intraperitoneally at 250 mg/kg.

4.0 SUBCHRONIC TOXICITY

4.1 Inhalation Studies

Three subchronic inhalation studies in rats and one in hamsters were found in the literature. Appelman et al. (1982) exposed SPF rats to 0, 400, 1000, 2200, or 5000 ppm of acetaldehyde (0, 720, 1800, 3960, or 9000 mg/m^3, respectively) for 6 hours/day, 5 days/week for 4 weeks. Rats exposed to 5000 ppm exhibited severe dyspnea and marked excitation during the first 30 minutes of exposure. No significant clinical signs were observed at the lower exposure levels. Decreased body weight occurred in males dosed at 1000, 2200, and 5000 ppm and in females dosed at 5000 ppm. The percentage of lymphocytes was lower and that of neutrophils was higher in males and females exposed to 5000 ppm relative to the controls. No treatment-related changes were seen in clinical chemistry values. At the high dose, liver weights were significantly decreased in both sexes, and lung weights were increased only in males. Histopathological changes were seen at all doses tested, with the nose being more sensitive than the larynx, trachea, or lungs. The dorsal region of the nose exhibited the most severe changes, such as loss of microvilli, disarrangement of the epithelium, occasional loss of sensory cells at 400 ppm, and severe atrophy of the epithelium at 5000 ppm. At the two highest exposure concentrations, focal hyperplasia and stratified squamous metaplasia were seen. Damage to the larynx at 2200 and 5000 ppm consisted of hyperplastic and metaplastic stratified squamous epithelia. Metaplastic and hyperplastic changes in the tracheal epithelium were seen only at the highest exposure level.

The most severe effects appeared to occur in the posterior portion of the nose. The authors speculated that a combination of factors, including the impact of acetaldehyde due to the airstream through the nose, the polarity and solubility of acetaldehyde, and the higher sensitivity of the epithelium in this area, could explain the severity of the damage. The LOAEL was 400 ppm, but a NOAEL was not determined. The EPA has used this LOAEL to determine a Reference Concentration (RfC) for acetaldehyde (see Section 9.1).

In a later study, Appelman et al. (1986) tested intermittent and peak exposure effects of acetaldehyde vapor in groups of 10 male SPF Wistar rats. Two 4-week studies were performed using either (1) continuous exposure to 150 ppm or 500 ppm (270 or 900 mg/m^3, respectively) for 6 hours/day, 5 days/week; (2) two 3-hour exposures to 150 or 500 ppm for 5 days/week, interrupted by a nonexposure period of 1.5 hours between the first and second exposure; or (3) same as in (2) with four 5-minute peaks of 6 times the basic concentrations of 111 or 500 ppm per 3-hour exposure period. The peak exposure levels were 668 or 3043 ppm, respectively. A control group received fresh air only. Only rats exposed to 500 ppm with peak exposures of 3043 ppm showed irritation, displayed as eye blinking, excessive running, and nose twitching. In addition, the mean body weight of this group was significantly reduced compared to the controls. No effects on condition, behavior, or body weights were reported for animals exposed to 150 ppm with or without interruption or for those exposed to 111 ppm with or without peak exposures.

Histopathology revealed lesions of the epithelium from the dorsal part of the nose at 500 ppm (uninterrupted), but not at 150 or 111 ppm (interrupted). The effects noted in the respiratory tract at 500 ppm were comparable to those

noted at 404 ppm in the Appelman et al. (1982) study. In addition, a reduced phagocytic index was seen at the highest dose. Interruption of 500 ppm with peak concentrations of 3043 ppm caused a further reduction in the phagocytic index; nevertheless, there were no marked changes on the nasal epithelium. The NOAEL in this study was 150 ppm, and the LOAEL was 500 ppm.

Saldiva et al. (1985) exposed male Wistar rats via inhalation to 243 ppm acetaldehyde, 8 hours/day, 5 days/week for 5 weeks. Various pulmonary function tests were carried out in addition to gross and microscopic examinations of the respiratory system. The results revealed significant increases in functional residual capacity, residual volume, total lung capacity, and respiratory frequency. The authors excluded the possibility of emphysema or obstructive bronchial disease and suggested that the damage to the distal airways was unrelated to acetaldehyde. They suggested that these changes were the result of forced expiratory maneuvers such as applying negative pressure to simulate forced expiration, which can cause a premature collapse of the bronchioli.

The authors suggested that the increase in respiratory frequency was due to irritation of the airways. Gross examination did not reveal any differences between the control and acetaldehyde-treated groups. In contrast, histopathology showed an intense subacute inflammatory reaction in the nasal cavity characterized by hyperplasia of the olfactory epithelium and polymorphonuclear and mononuclear infiltration of the submucosa. The trachea and larynx were not examined.

Kruysse et al. (1975) exposed groups of Syrian golden hamsters to acetaldehyde vapor at concentrations of 0, 390, 1340, and 4560 ppm (0, 702, 2412, and 8208 mg/m^3, respectively), 6 hours/day, 5 days/week for 13 weeks. This study showed that more severe damage occurred in the upper rather than the lower respiratory tract, as was seen in rats (Saldiva et al. 1985). This suggested that the hamster is a less sensitive species than the rat. At 4560 ppm, a significant decrease in body weight and increase in relative heart, kidney, brain, testes, and lung weights were seen. Except for an increased relative kidney weight in males exposed to 1340 ppm, no other changes in organ or body weights were seen at the 390- and 1340-ppm doses. Lesions of the nasal cavity, larynx, trachea, bronchi, and lungs were seen at the highest dose, 4560 ppm. These lesions consisted of necrosis, inflammation, hyperplasia, and keratinizing squamous metaplasia. The NOAEL in this study was 1340 ppm, and the LOAEL was 4560 ppm.

4.2 Oral Studies

Both sexes of SPF Wistar rats received acetaldehyde in a test solution containing 25, 125, or 675 mg acetaldehyde/kg body weight/day for 4 weeks (Til et al. 1988). The only observed adverse effects were noted in rats receiving 675 mg/kg. These effects included hyperkeratosis of the forestomach, a significant decrease in food and liquid intake, and a slight increase in the relative weight of the kidneys in male rats compared to controls. No significant changes occurred in hematology values. The NOAEL was 125 mg/kg/day.

4.3 Conclusions

Few subchronic studies were found in the available literature. Acetaldehyde was found to be highly toxic to the entire respiratory tract. The effects included lesions such as hyperplasia and metaplasia of the olfactory mucosa and varying degrees of inflammation. The nose, trachea, and larynx were affected. Following oral administration, the NOAEL value in the rat was 125 mg/kg/day. Exposure of rats to acetaldehyde via inhalation gave a LOAEL value of 400 ppm and a NOAEL value of 150 ppm. The hamster appeared to be more resistant than the rat to the effects of acetaldehyde inhalation.

5.0 CHRONIC TOXICITY

5.1 Introduction

Limited information is available on the effects of acetaldehyde following chronic exposure. This chapter discusses chronic toxicity with relationship to two inhalation and two intratracheal instillation carcinogenicity studies in rats and hamsters. These studies are divided into three sections for clarity: inhalation, inhalation and intratracheal instillation, and intratracheal instillation. See Table 8-1 for a summary of these studies with regard to animal species, sex, number, dose, duration, and effects. The neoplastic changes observed in these studies are discussed in detail in Chapter 8 on carcinogenicity; only the nonneoplastic and/or preneoplastic lesions are presented in this chapter.

5.2 Inhalation

Woutersen et al. (1984, 1986) and Woutersen and Feron (1987) exposed male and female Wistar rats to acetaldehyde at concentrations of 0, 750, 1500, or 3000/1000 ppm (0, 1350, 2700, or 5400/1800 mg/m^3, respectively) 6 hours/day, 5 days/week for up to 28 months. The concentration in the high-dose group was gradually reduced from 3000 to 1000 ppm because of severe growth retardation, occasional loss of body weight, and early mortality. Animals in the high-dose group exhibited signs of severe respiratory distress, including salivation, labored breathing, and mouth breathing.

Mortality increased with dose; a clear dose-response relationship was evident. By day 715, all high-dose rats had died. Very few animals in the mid-dose group lived to study termination at day 844. Treatment caused dose-dependent growth retardation in males at all exposure concentrations and in females at the two highest concentrations. Consequently, the LOAEL was 750 ppm and a NOAEL could not be determined from this study.

The rats in the high-dose group showed signs of excitation, salivation, piloerection, and labored respiration; blood was seen around the nares of several animals. Despite a further reduction in the acetaldehyde concentration, a greater number of animals developed these symptoms after 12 months. In almost every high-dose rat that died early or was sacrificed moribund, the nose was partially or completely occluded by excessive amounts of keratin and inflammatory exudate. Several male and female rats also developed acute bronchopneumonia, occasionally accompanied by tracheitis.

Feron et al. (1982) exposed male and female Syrian golden hamsters to decreasing concentrations of acetaldehyde. The initial concentration was 2500 ppm (4500 mg/m^3); this was gradually decreased (between weeks 9 and 44) to 1650 ppm (2970 mg/m^3), 6 hours/day, 5 days/week for 52 weeks. The animals were sacrificed following a 29-week recovery period (at week 81). Mortality was slightly higher in hamsters exposed to acetaldehyde vapor than in controls. Body weights were recorded every 2 weeks during the first 6 weeks and monthly thereafter. Beginning at week 4, hamsters exposed to acetaldehyde had substantially lower body weights ($p < 0.05$) than those exposed to air. During the postexposure period

(53 to 81 weeks), differences in the body weights of exposed and control hamsters generally diminished but did not disappear. Except for a slight increase in alkaline phosphatase activity in females exposed to acetaldehyde, no significant differences in hematological or biochemical properties were observed between treated and control animals. The relative kidney and lung weights were higher in treated hamsters as compared with controls; the difference was statistically significant (p value not provided) only in treated females.

5.3 Inhalation with Intratracheal Instillation of Benzo[a]pyrene

Male Syrian golden hamsters exposed to air or 1500 ppm (2700 mg/m^3) acetaldehyde vapor, 7 hours/day, 5 days/week for 52 weeks, also received concurrent weekly intratracheal instillations of 0, 0.0625, 0.125, 0.25, 0.5, or 1.0 mg benzo[a]pyrene (B[a]P) for the same duration (Feron 1979). No differences in mortality rate were observed in hamsters exposed to acetaldehyde alone or air for up to 39 weeks; thereafter, the mortality of treated hamsters increased more rapidly than that of the control group (12 deaths as compared with 5 deaths at week 78, respectively). Hamsters exposed to acetaldehyde alone were generally more restless and had slightly lower body weights (maximum 10%) than controls. The hemoglobin, hematocrit, and red blood cell count values were significantly (p value not provided) lower in hamsters exposed to acetaldehyde than in controls exposed to air. In addition, in the acetaldehyde-exposed group, the urine contained more protein and the kidney weights were increased significantly as compared with the air-control groups (p value not provided). The mortality of hamsters exposed to acetaldehyde and receiving the high dose (52 mg) of B[a]P increased more rapidly than the B[a]P + air-exposed group when compared with respective controls ($p < 0.001$ in both groups).

In a similar experiment (Feron et al. 1982), male and female hamsters were exposed to air or to acetaldehyde vapor (initial concentration = 2500 ppm; final concentration = 1650 ppm; see Section 5-2 above) for 7 hours/day, 5 days/week for 52 weeks, and were given simultaneous weekly intratracheal instillations of 0.32 ml of 0.175% or 0.35% B[a]P (total dose, 18.2 or 36.4 mg/hamster, respectively) in saline, or subcutaneous injections once every 3 weeks of 0.2 ml of 0.0625% diethylnitrosamine (DENA) (total volume injected, 2.1 ul). The experiment was terminated after 81 weeks. Mortality was slightly higher in acetaldehyde-exposed hamsters relative to controls; also, these hamsters exhibited lower body weights than those exposed to air from week 4 onward. During the recovery period (53 to 81 weeks), the significant ($p < 0.05$) differences in body weights between exposed and control hamsters generally diminished but did not disappear.

There was a significant increase in mortality ($p < 0.05$) in animals treated with B[a]P and exposed to acetaldehyde or air over those exposed to acetaldehyde or air alone. In addition, mortality was considerably higher in animals, particularly in males, treated with the highest dose of B[a]P and exposed to acetaldehyde than in those given the same dose of B[a]P but exposed to air. There was low mortality in the DENA-treated group exposed to air.

5.4 Intratracheal Instillation

Feron (1979) gave male and female hamsters weekly or biweekly intratracheal instillations of 4 or 8 ul of acetaldehyde in 0.2 ml saline (approximately 32 to 73 mg/kg) for 52 weeks. Vehicle controls received 0.2 ml saline. The experiment was terminated at 104 weeks. Intratracheal instillation of acetaldehyde had no significant effect on mortality or body weight gain.

5.5 Conclusions

The major treatment-related chronic toxicity following inhalation exposure was increased mortality and growth retardation in hamsters and rats. Rats exposed to high concentrations (>1600 ppm) exhibited acute bronchopneumonia, occasionally accompanied by tracheitis and severe respiratory distress that included salivation, labored breathing, and mouth breathing. Inhalation of acetaldehyde resulted in histopathological alterations in the respiratory tract. NOAELs were not established for chronic toxicity. A LOAEL of 750 ppm can be reported for chronic toxicity. However, since the LOAEL for subchronic toxicity is lower (400 ppm), this putative chronic LOAEL does not reflect a likely LOAEL for acetaldehyde.

6.0 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

6.1 Introduction

Clinical and experimental studies have shown that ethyl alcohol causes developmental and reproductive toxicity. Ethyl alcohol (in alcoholic beverages) is a chemical known to the State of California to cause reproductive toxicity. Acetaldehyde, the primary metabolite of ethyl alcohol, has been suggested as a possible etiological agent in fetal alcohol syndrome. Its precise mode of action remains unknown. However, it has been shown to cross the placenta in mice (Blakely and Scott 1984b) as well as in rats (Zorzano and Herrera 1989) (see discussion above in Section 2.3, Distribution). A number of studies have been conducted to elucidate the mechanism of action of ethyl alcohol/acetaldehyde in causing developmental toxicity. This chapter summarizes studies in rodents that have evaluated *in vivo* and *in vitro* developmental and reproductive toxicity of direct exposure to acetaldehyde (as opposed to ethanol-mediated exposure). No studies were found in which acetaldehyde was administered via the inhalation or oral route; *in vivo* studies were limited to the intraperitoneal (ip) and intravenous (iv) routes of exposure. Only one reproductive toxicity study was found. *In vitro* studies include whole mouse and rat embryo culture systems for detecting developmental effects and various testicular cell culture systems for detecting effects on testosterone production.

6.2 In vivo Studies

6.2.1 Placental Transfer

Acetaldehyde is distributed to embryos via the placenta (Randall et al. 1978). Blakley and Scott (1984b) administered intraperitoneal injections of acetaldehyde to pregnant CD-1 mice at 200 mg/kg on day 10 of gestation. Within 5 minutes postadministration, acetaldehyde reached maximal concentrations in the maternal blood and liver, embryo, and yolk sac. The acetaldehyde rapidly disappeared; it was undetectable 2 hours after treatment.

Zorzano and Herrera (1989) found that acetaldehyde freely crossed the placenta in Wistar rats when present in maternal blood at high concentrations (100 uM or 4.4 mg/l). At all times following intravenous injection of acetaldehyde at 10 mg/kg to pregnant rats on gestation day 21, acetaldehyde concentrations in maternal blood were similar to those in fetal blood and amniotic fluid, and they reached equilibrium within 2 minutes of dosing. Peak concentrations were reached within 5 minutes of dosing; these were 1355, 1332, and 1913 uM in maternal blood, fetal blood, and amniotic fluid, respectively. However, at maternal blood concentrations below 80 uM, acetaldehyde was metabolized by fetal tissues or by the placenta and was not detected in fetal blood. The above studies indicate that acetaldehyde crosses the placenta and therefore can present an exposure to the fetus.

6.2.2 Developmental Toxicity

Studies in rodents that have examined the developmental toxicity of acetaldehyde following ip or iv administration of a single injection or multiple injections on different days during gestation are summarized in Appendix A (Table A-1).

In studies with rats, acetaldehyde has been shown to be teratogenic and embryolethal and has been shown to cause growth retardation. Sreenathan et al. (1982) evaluated the developing embryos and their membranes on gestation day (gd) 21 after a single ip injection of 50, 75, or 100 mg/kg acetaldehyde on gd 10, 11, or 12, or daily injections on gd 10-12 in Charles Foster (CF) rats. They found a significant ($p < 0.05$) increase in the number of resorptions. The incidence of litters with malformations was increased in the higher single-injected dose groups as well as in all triple-injected dose groups. Significant ($p < 0.05$) growth retardation was evidenced by reduced fetal body weights, crown-rump and tail length, transumbilical distance, umbilical cord length, and delayed skeletogenesis. In fetuses from dams dosed on gd 12 or 10-12, the placental weight was significantly ($p < 0.05$-0.001) reduced. No obvious dose-dependency was noted for these effects. In a time-course study, these same authors (Sreenathan et al. 1984) studied delayed ossification in gd 16-21 fetuses from CF rats that had received 50 mg/kg acetaldehyde ip on gd 8-15. Their results indicated that ossification of selected bones in the forelimbs, hindlimbs, and skull was significantly ($p < 0.05$-0.001) delayed by 1 to 2 days. An additional study (Padmanabhan et al. 1983) reported similar findings; CF rats were examined on gd 21 after ip administration of 50, 75, 100, or 150 mg/kg acetaldehyde on gd 8-15. Significant ($p < 0.01$-0.001) and dose-dependent increases were observed in the number of resorptions and the incidence of malformations. In addition, ossification was significantly ($p < 0.001$), but not dose-dependently, delayed in selected skull bones and in the axial skeleton.

Ali and Persaud (1988) investigated the effects of ip administration of 100 mg/kg acetaldehyde on gd 9-12 in Sprague-Dawley rats. Of the 16 recognizable morphologic endpoints evaluated on gd 12, only head length was significantly ($p < 0.05$) reduced in the treated animals when compared with the controls. Dreosti et al. (1981) examined the fetal development in Wistar rats on gd 20 after exposure to acetaldehyde (0.5 ml of a 3% saline solution, twice daily) throughout gestation. Slight but nonsignificant changes were noted in fetal body weight (decrease) and in the number of resorptions (increase). No increase in the incidence of malformations was observed.

In studies with CD-1 mice, acetaldehyde produced no effects on body weight and number of resorptions and malformations in gd 18 fetuses after five ip injections of 200 mg/kg each, administered during a 10-hour period on gd 10 (Blakley and Scott 1984a). No histopathological changes were observed in gd 10 fetuses from mice of the LACA strain after a single ip injection of approximately 60-480 mg/kg on gd 9 (Bannigan and Burke 1982). In C57Bl/6J mice, after one or two ip injections of 320 mg/kg acetaldehyde on gd 6, 7, 8, or 9, a nonsignificant decrease in fetal body weight and a slight increase in percent malformed fetuses (head and limb defects) were observed (Webster et al. 1983). However, in this latter study, control groups were not always used. Consequently, the slight increase in percent malformed fetuses that was observed cannot be compared with the spontaneous malformation rate normally

present in this mouse strain. Interpretation of these results is difficult.

In contrast, in CFLP mice given multiple iv injections of 40-80 mg/kg/day acetaldehyde on gd 7-9 (O'Shea and Kaufman 1979) or a single or multiple iv injections of 50 mg/kg on gd 6-9 (O'Shea and Kaufman 1981), a significant ($p < 0.05$-0.001) dose-related increase in the number of resorptions (days 10 and 19), decrease in the crown-rump length (days 10 and 19), and decrease in gd 19 fetal body weight were observed. In addition, slight increases (no statistical analysis reported) in the incidence of malformations (neural tube) and number of embryos failing to turn into a fetal position were noted on gd 10 only.

6.2.3 Reproductive Toxicity

In a male reproductive toxicity study (Lähdetie 1988), hybrid male mice (C57BL/6J x C_3H/He)F_1 were given daily ip injections of saline solution containing 62.5, 125, or 250 mg/kg acetaldehyde for 5 days. Animals were sacrificed 5 weeks after the beginning of treatment, and the testicular genotoxic effects were evaluated. No significant effects were observed on frequency of meiotic micronuclei, sperm count and morphology, and testicular and seminal vesicle weights. However, this study evaluated only selected end-points and, therefore, is not a representative study for male reproductive toxicity (see Conclusion for further discussion).

6.3 In vitro Studies

6.3.1 Developmental Toxicity

Several studies examined the embryotoxic properties of acetaldehyde utilizing whole mouse and rat embryos. These studies are summarized in Appendix A (Table A-2). Evaluations were conducted on cultures of postimplantation embryos recovered between gd 7 and 10.

In C_3H 8-day-old mouse embryos, acetaldehyde at doses of 7.4, 19.7, and 39.4 mg/l induced alterations in somite count, heartbeat, DNA synthesis, CNS development, and neural tube defects at all or some dose levels, while no consistent (and dose-related) response was noted in 9-day-old embryos (Thompson and Folb 1982). Exposure of ICR mouse embryos to acetaldehyde (range 17.6 ug/l to 1.7 g/l) resulted in increased embryolethality and incidence of malformations (cranial, facial, and limb effects) at all dose levels as well as dose-related growth retardation (Higuchi and Matsumoto 1984).

Albino rat embryos exposed to acetaldehyde on gd 9 at doses ranging from 0.20 to 1,980 mg/l caused significant ($p < 0.05$) growth retardation and an increased incidence of malformations. The lowest effective dose was 1.1 mg/l, and the no-effect level was 0.22 mg/l (Popov et al. 1982). Campbell and Fantel (1983) demonstrated similar results in 11-day-old Sprague-Dawley rat embryos after exposure to 5, 25, 50, 75, and 100 uM acetaldehyde on gd 10. The highest concentration was lethal; the no-effect level was 5 uM; and 25, 50, and 75 uM caused significant ($p < 0.01$) growth retardation and decreased total protein content.

In contrast, Priscott (1985) observed no significant effects in 11- and 12-day-old Wistar rat embryos previously exposed to 100 and 260 uM acetaldehyde on gd 10. At 800 uM, there was a rapid cessation of growth and development resulting in "an unrecognizable necrotic mass."

Preimplantation 2-cell stage embryos from CF-1 mice exposed to acetaldehyde at concentrations of 5, 10, 50, 100 and 500 mg/100 ml culture medium (Kalmus and Buckermaier 1989) resisted the lower concentrations of acetaldehyde, while doses of ≥50 mg/100 ml medium were lethal. These lethal doses are considered by some authors to be unusually high. Consequently, the 2-cell stage embryos are regarded as highly resistant to acetaldehyde.

6.3.2 Reproductive Toxicity

Reproductive in vitro toxicity studies have shown that acetaldehyde is a potent inhibitor of testicular steroidogenesis. Cicero et al (1980) exposed dispersed testicular cell cultures from 55- to 60-day-old Sprague-Dawley rats to acetaldehyde at concentrations of 0.02 to 1.0 mM. At acetaldehyde concentrations of 50 uM, testicular steroidogenesis was significantly inhibited. Johnson et al. (1981) examined the effects of acetaldehyde on three enzymes involved in the conversion of pregnenolone to testosterone. Testicular microsomal fractions were prepared from 60-day-old Wistar rats; 600 uM acetaldehyde, in the presence of androstenedione, significantly inhibited this conversion.

To assess potential acute impairment of testicular testosterone, Boyden et al. (1981) conducted a study in dogs with isolated blood-perfused testes. Acetaldehyde, at a dose level corresponding to blood levels of 0.2 mg/dl (approximately 50 uM, which is frequently found in humans), inhibited hCG-stimulated testosterone production.

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. Small sample numbers and evaluation of a limited number of endpoints are evident in most studies; nevertheless, certain general conclusions may be drawn. Different species and strains respond differently to acetaldehyde exposure. All rat strains examined, when given approximately the same ip dose of acetaldehyde, exhibited similar effects for number of resorptions, incidence, and type of malformations, and/or growth retardation. Some mouse strains exhibit resistance to acetaldehyde, and others show effects similar to those observed in rats. Mode and duration of administration (as observed in mice) influenced the degree (but not the type) of developmental toxicity. Some, but not all, studies show a dose-related response for the endpoints studied. As discussed by several authors, these studies demonstrate a great inter-litter variability in embryolethality; some litters were highly affected and others not at all. It has been suggested that this indication of great differences in susceptibility to acetaldehyde within a strain is due to genetic makeup; this has been observed in human offspring and their susceptibility to ethanol.

Only one male reproductive toxicity study for acetaldehyde exposure was found. Only a selected number of endpoints in one sex was examined, since the authors' intentions were to study the testicular genotoxic effects of acetaldehyde. Therefore, the negative results of the study should not be interpreted as evidence of acetaldehyde not being a male reproductive toxicant. For example, to cover the entire spermatogenic cycle in mice, sperm count/morphology, testicular weight/morphology, hormone levels, fertility, etc., should be examined periodically over a 35- to 42-day period. This study evaluated some endpoints at one time only (at the end of one complete spermatogenic cycle). In fact, in support of male reproductive toxicity are the results from studies with various testicular cell culture systems. Acetaldehyde seems to affect testosterone production; one author suggests that it does so by inhibiting one of four enzymes necessary for conversion of pregnenolone to testosterone.

The effects observed on embryos in culture are in agreement with those observed in in vivo studies. Both test systems have demonstrated similar types of malformations and growth retardation as well as embryolethality; species and strain differences exist in both; and some (but not all) results exhibit a dose-related response. Two-cell stage preimplantation embryos appear to be more resistant to acetaldehyde than are postimplantation embryos.

Acetaldehyde crosses the placenta and enters the fetal circulation. Acetaldehyde equilibrated within 2 minutes of injection of a high concentration into pregnant rats; it reached peak concentration within 5 minutes of dosing in maternal blood, fetal blood, and amniotic fluid.

Acetaldehyde has been shown to cause adverse developmental effects in some rodent species when administered at high doses via i.p. or i.v. injection. There is also evidence for toxicity to the embryo and to testicular function when there is direct exposure to acetaldehyde in vitro. In all but one of the in vivo studies discussed, maternal toxicity parameters were not reported and the authors did not discuss or determine the maternal versus the developmental no-effect and low-effect levels of acetaldehyde toxicity. However, several authors have emphasized the similarities between the types of effects observed in humans and those observed in rodents. The mechanisms by which acetaldehyde causes developmental and reproductive toxic effects in vitro and following high i.p. and i.v. doses in vivo are not known. There are also no data available to indicate the relevance of adverse effects under the conditions investigated to possible human exposures. It is, therefore, not possible at present to determine if acetaldehyde poses 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.

7.0 GENOTOXICITY

7.1 Introduction

Acetaldehyde has been tested for genotoxicity in a variety of *in vitro* and *in vivo* assays designed to detect gene mutations, chromosomal aberrations, sister chromatid exchanges, DNA damage, and cell transformation. Formation of Schiff bases and other adducts may be involved at the molecular level (see Section 2.4). Table 7-1 summarizes the findings for acetaldehyde genotoxicity as demonstrated in each test. The table in Appendix B summarizes the protocols and specific results for each individual study.

7.2 Gene Mutations

Acetaldehyde has been tested for the potential to induce gene mutations in bacteria, yeast, nematodes, insects, and mammalian cells.

7.2.1 Bacteria

Acetaldehyde was nonmutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, TA102, or TA104 both in the presence and absence of metabolic activating systems (Laumbach et al. 1976; Rosenkranz 1977; Pool and Wiessler 1981; Marnett et al. 1985; Mortelmans et al. 1986). In one study, acetaldehyde (7793 ug/plate) caused a slight increase in mutant colonies of strain TA1535 without activation (16 revertants in the treated group versus 4 revertants in the water control); however, the very low background frequency made the results inconclusive (Rosenkranz 1977). It is unclear why acetaldehyde produces consistently negative results in the *Salmonella* assays while producing positive results in other test systems. It is possible that the standard Ames test is not suitable for detecting the mutagenicity of acetaldehyde because the compound is volatile, and precautions may not have been taken to prevent its evaporation (Dellarco 1988).

Conflicting results were obtained when acetaldehyde was tested for mutagenicity in liquid suspension assays with *Escherichia coli* WP2 uvrA. Nonactivated acetaldehyde was mutagenic at a concentration of 38.8 ug/ml (880 uM) when incubated in sealed tubes at 0°C for 30 minutes (Veghelyi et al. 1978), but was nonmutagenic in the same strain at concentrations ranging from 0.9 to 441 ug/ml without metabolic activation (20 to 10,000 uM) when incubated in capped tubes at 37°C for 18 hours (Hemminki et al. 1980). It has been suggested that the positive results obtained by Veghelyi et al. may be due to the lower incubation temperature, which would reduce the evaporation of acetaldehyde during treatment and the oxidation of acetaldehyde to acetic acid (Dellarco 1988).

7.2.2 Yeast

Bandas (1982, as cited in Dellarco 1988) reported that nonactivated acetaldehyde exhibited a weakly mutagenic effect on mitochondrial DNA (petite mutations) of the yeast *Saccharomyces cerevisiae*. A twofold increase in the spontaneous

TABLE 7-1

GENOTOXICITY OF ACETALDEHYDE IN VARIOUS TEST SYSTEMS

Endpoint	Test Systems	Results		
		Positive	Negative	Equivocal
Gene mutation	*Salmonella typhimurium*		X	
	Escherichia coli			X
	Caenorhabditis elegans			X
	Drosophila melanogaster sex-linked recessive lethal test	X		
	Human lymphocytes	X		
Chromosomal aberrations	*Vicia faba*	X		
	Drosophila melanogaster reciprocal translocation		X	
	Rat fibroblasts	X		
	Chinese hamster ovary cells	X		
	Human lymphocytes	X		
	In vivo bone marrow cells	X		
Sister chromatid exchange	Chinese hamster ovary cells	X		
	Human lymphocytes	X		
	In vivo bone marrow cells	X		
DNA damage	*Escherichia coli* pol A			X
	Mammalian cells (mouse lymphoma, rat hepatocytes, human lymphocytes, and human bronchial epithelial cells)		X	
Mammalian cell transformation	Kidney cells (HRPT[4])	X		

frequency of petite mutants was seen after treatment of cells with 23,490 ug/ml acetaldehyde for 90 minutes. However, this response was considered to be equivocal because it occurred at an extremely cytotoxic dose (96% of the cells were killed) and no dose-response was demonstrated. Dellarco (1988) considered the interpretation of the response (increase in mitochondrial mutations) to be uncertain because cytoplasmic mutations are less defined genetically than the nuclear mutations used in standard assays.

7.2.3 Nematodes

Acetaldehyde (783 or 7,830 ug/ml for 2 hours) was tested in the nematode *Caenorhabditis elegans* for its ability to induce mutations in the genes affecting the egg-laying system. The frequency of mutations (reduction in brood size) was increased at the lower (783 ug/ml) concentration ($1x10^{-4}$ in treated nematodes versus $6x10^{-6}$ in untreated controls); acetaldehyde was toxic at the higher concentration (Greenwald and Horvitz 1980).

7.2.4 Insects

Woodruff et al. (1985) tested acetaldehyde in the sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster* by adult feeding and injection. Acetaldehyde was nonmutagenic after feeding (25,000 ppm), but 22,500 ppm given by injection produced 0.21% lethals versus 0.06% in the untreated control group.

7.2.5 Mammalian cells

He and Lambert (1990) used acetaldehyde to induce mutations at the hypoxanthine-guanine phosphoribosyl transferase (hprt) locus in freshly isolated human T-cell lymphocytes. Cells were incubated for 24 h with 1.2 to 2.4 mM acetaldehyde or for 48 h with 0.2 to 0.6 mM acetaldehyde. Cells showed decreasing survival with increasing acetaldehyde and a 3 to 16 fold increase in mutation frequency at the hprt locus relative to background (background mutation rate = 3.2 to $6.2x10^{-6}$). Several of the mutations involved partial deletions of the hprt gene. This study is the first demonstration of induction of mutations by acetaldehyde in human somatic cells.

7.3 Chromosomal Aberrations

Acetaldehyde has been tested for its ability to induce chromosomal aberrations in plant, insect, and mammalian cells.

7.3.1 Plants

Acetaldehyde produced a dose-dependent increase in the frequency of chromosomal aberrations (breaks and translocations) in cells of the root-tip meristem of *Vicia faba*. The clastogenic effect was seen following treatment with 220.5 to 2,205 ug/ml (5 to 50 mM) acetaldehyde for 24 hours at 12°C; higher temperatures

reduced the clastogenic effects of acetaldehyde (Rieger and Michaelis 1960).

7.3.2 Insects

As part of the full investigation of acetaldehyde in D. melanogaster, Woodruff et al. (1985) evaluated the brood-yielding results in the SLRL assay for the induction of reciprocal translocations. Acetaldehyde (22,500 ppm administered by injection) was negative.

7.3.3 Mammalian Cell Cultures

Bird et al. (1982) studied the production of micronuclei and chromosomal aberrations in primary rat skin fibroblasts exposed to concentrations of 4.4 to 441 ug/ml acetaldehyde for 12, 24, or 48 hours (micronucleus test) or 0.44 to 44.1 ug/ml acetaldehyde for 12 or 24 hours (chromosomal aberrations). Treatment resulted in a dose-dependent production of micronuclei; the lowest effective concentration was 22 ug/ml (2.4% cells with micronuclei versus 0.5% in control cultures after 12-hour treatment). In the chromosomal aberration assay, the 12-hour exposure to acetaldehyde induced an increase in aberrations (14% aberrant cells compared with 2% in control cultures) only at the 44.1 ug/ml concentration; chromatid breaks and gaps and acentric fragments were observed. Treatment for 24 hours increased the frequency of aberrations (12% at 4.4 ug/ml and 20% at 44.1 ug/ml as compared with 4% in control cultures), and the number of metaphases with specific aberrations (chromatid and chromosomal breaks, gaps, deletions, and fragmentation) was also increased. An increase in aneuploid cells was also seen at the 4.4- and 44.1-ug/ml dose levels; however, only the total incidences of aneuploidy were reported rather than the incidences of hyperploidy and hypoploidy.

Dulout and Furnus (1988) determined that the most notable cytogenetic effect of acetaldehyde in cultured Chinese hamster ovary (CHO) cells was aneuploidy and not chromosomal breakage. Acetaldehyde added for 24 hours to cultures at concentrations of 15.66, 31.32, or 46.98 ug/ml produced an increased frequency of aneuploidy compared to controls ($p < 0.001$). Aneuploidy was due mainly to an increase in the number of hypodiploid cells; the ratio of hypodiploid/hyperdiploid cells was 0.81 in the controls and 2.72, 2.73, and 3.57 in the 15.66-, 31.32-, and 46.98-ug/ml acetaldehyde-treated cells, respectively. In contrast to the induction of aneuploidy at all assayed levels, the frequency of structural aberrations (chromatid or isochromatid breaks, chromatid exchanges, and dicentric chromosomes) was significantly increased only at the two highest concentrations: 31.32 ug/ml (3.6% abnormal cells, $p < 0.025$) and 46.98 ug/ml (30.38% abnormal cells, $p < 0.001$). Acetaldehyde was not clastogenic at 15.66 ug/ml. These results suggested that acetaldehyde can elicit an aneuploidy effect at nonclastogenic concentrations. To a lesser degree, acetaldehyde also induced polyploidy as indicated by the significant increase in polyploidy cells at 15.66 ug/ml ($p < 0.001$) and 31.32 ug/ml ($p < 0.05$); concentrations were severely cytotoxic.

Obe et al. (1979) studied the chromosome-breaking activity of acetaldehyde in peripheral lymphocytes of a patient with Fanconi's anemia (deficiency in repairing DNA cross-links) and three normal individuals. After 24 hours of

treatment, acetaldehyde (7.83 or 15.7 ug/ml) caused a non-dose-related increase in the frequency of gaps, breaks, exchange-type aberrations, and acentric fragmentation in the cells from the subject with Fanconi's anemia. No clastogenicity was observed in the cells of the normal subjects.

Böhlke et al. (1983) examined the cytogenetic effects of acetaldehyde in cultured lymphocytes of German and Japanese subjects having different aldehyde dehydrogenase (ALDH) phenotypes. Cells, derived from the German subjects possessing both ALDH isozymes I and II and from the Japanese subjects possessing either isozyme II or isozymes I and II, were exposed for 72 hours to acetaldehyde concentrations ranging from 0.09 to 1.08 ug/ml. Cells from both populations showed dose-dependent increases in chromatid aberrations (especially achromatic lesions, chromatid breaks, and exchange-type aberrations) following exposure to acetaldehyde concentrations of 0.72 and 1.08 ug/ml; no significant differences were seen among the different ALDH phenotypes.

7.3.4 Whole Mammals

Barilyak and Kozachuk (1983) conducted a cytogenetic analysis of embryonic cells harvested 24 hours after a single intra-amniotic injection of 7830 ug/ml acetaldehyde was administered on gd 13 to female Wistar rats. A higher frequency of chromosome aberrations (mostly gaps and breaks) was seen in treated rat embryos (16 ± 1.5% metaphases with breaks) as compared with controls (3.8 ± 0.8%).

Lähdetie (1988) observed no significant increase in the frequency of meiotic micronuclei in early spermatids harvested from hybrid mice (C57Bl/6J x C3H/He)F1 given single intraperitoneal injections of 0, 125, 250, or 375 mg/kg acetaldehyde in saline and sacrificed 13 days posttreatment. No mice survived treatment with the highest dose (500 mg/kg).

7.4 Sister Chromatid Exchanges

A number of studies have shown acetaldehyde to be a strong inducer of sister chromatid exchanges (SCEs) in CHO cells and human peripheral blood lymphocytes *in vitro*.

7.4.1 CHO Cells

Obe and Ristow (1977) treated CHO cells once each day for 8 days with nonactivated acetaldehyde concentrations ranging from 3.92 to 31.32 ug/ml. Cells incubated with concentrations greater than 7.83 ug/ml were cytotoxic. Lower concentrations (3.92 and 7.83 ug/ml) caused dose-dependent increases in SCEs, which ranged from 13.56 SCEs/cell at 3.9 ug/ml to 28.35 SCEs/cell at 7.83 ug/ml. The background central frequency was 4.69 SCEs/cell.

Following a 24-hour exposure of CHO cells to nonactivated acetaldehyde concentrations ranging from 1.96 to 11.75 ug/ml, Obe and Beek (1979) found that the lowest effective concentration was 3.92 ug/ml, which produced 18.89 SCEs/cell

compared with 8.24 SCEs/cell in controls. The maximum response (22.08 SCEs/cell) was seen at the highest (11.75 ug/ml) concentration.

De Raat et al. (1983) reported that acetaldehyde (7.8 to 39.4 ug/ml for 24 hours) induced dose-related increases in SCEs both in the presence and absence of metabolic activation. The lowest concentration tested, 7.8 ug/ml, produced 17.25 SCEs/cell without activation and 15.40 SCEs/cell with S9 activation; corresponding values in control cultures were 9.20 and 13.45 SCEs/cell, respectively.

7.4.2 Human Lymphocytes

Ristow and Obe (1978) observed a dose-related increase in SCEs in cultured human whole-blood lymphocyte cultures exposed to 3.92 to 15.7 ug/ml acetaldehyde. The highest concentration (15.7 ug/ml) produced 14.18 SCEs/cell compared with 4.02 SCEs/cell in control cultures at 24 hours; when treated for 48 hours, the SCE frequency increased to 23.95 SCEs/cell.

Similarly, Norppa et al. (1985) observed statistically significant ($p < 0.001$) dose-related increases in SCEs following treatment of peripheral lymphocytes with 2.8 to 88.2 ug/ml acetaldehyde (-S9) for 48 hours.

In another study, exposure of lymphocytes to 3.92 or 7.83 ug/ml acetaldehyde (-S9) for 90 hours caused significant ($p < 0.01$), dose-dependent increases in SCEs; approximately 17 or 28 SCEs/cell were produced, respectively, in treated cells compared to 11 SCEs/cell in control cultures (Jansson 1982).

Böhlke et al. (1983) treated lymphocytes derived from German subjects possessing both ALDH isozymes and from Japanese subjects possessing either isozyme II or isozymes I and II with nonactivated acetaldehyde (3.97 to 47.6 ug/ml) for 72 hours. A dose-dependent increase in SCE frequencies was observed for both populations; no differences that could be related to the different ALDH phenotypes were observed.

Obe et al. (1986) showed that SCE induction was slightly reduced when ALDH was added directly to the culture medium. Exposure of human peripheral lymphocytes to 78.3 ug/ml acetaldehyde for 3 hours without metabolic activation produced approximately 28.2 SCEs/cell compared to 10 SCEs/cell in control cultures. When ALDH and NAD (required cofactor for ALDH) were added, the SCE frequency was reduced to 14.5 SCEs/cell. Treatment with acetaldehyde at 15.66 ug/ml for 3 hours (without added ALDH and NAD) produced approximately two- and threefold increases in SCE frequencies over the control values.

He and Lambert (1985) examined the SCE-inducing effect of acetaldehyde in human lymphocytes treated at different phases of the cell cycle. Exposure of cells to 4.4, 8.8, or 13.2 ug/ml resulted in a twofold increase of SCEs when acetaldehyde was added in the late G_1 phase of the cell cycle (23 hours post-mitogen stimulation) as compared to an earlier G_1-cell (at the time of mitogen stimulation) exposure. In addition, the authors demonstrated that the length of exposure affected SCE induction. For a 1-hour exposure, a 24-fold higher concentration (105.6 ug/ml) of acetaldehyde was required to elicit an SCE

response equivalent to that seen following a 70-hour exposure of the cells to 4.4 ug/ml.

7.4.3 Whole-Mammal Bone Marrow Cells

Obe et al. (1979) reported a significant ($p < 0.001$) increase in the SCE frequency of a single male mouse administered an intraperitoneal injection of acetaldehyde at either 0.01 (2.88 SCEs/cell) or 0.02 (6.40 SCEs/cell) mg/kg. However, the number of animals used was lower than the minimum of three animals/dose required for an *in vivo* study (Latt et al. 1981). Therefore, the positive results observed in this study are considered to be suggestive rather than definitive evidence of a genotoxic effect (Dellarco 1988).

Korte and Obe (1981) administered single intraperitoneal injections of acetaldehyde at 0.01, 0.1, or 0.5 mg/kg to groups of six or seven male and six or seven female Chinese hamsters. Doses equal to or greater than 0.6 mg/kg were lethal, and animals died within 30 minutes of injection. The SCE frequency was elevated only in the 0.5-mg/kg dose group (6.1 SCEs/cell) as compared with untreated controls (3.5 SCEs/cell, $p < 0.01$).

It is of note that the route of exposure in these two *in vivo* studies was intraperitoneal. It is uncertain, therefore, whether similar responses would be observed if a route relevant to human exposure (inhalation or oral) were used.

7.5 DNA Damage

Acetaldehyde-induced DNA damage was studied in DNA repair-deficient bacteria and in cultured mammalian cells.

7.5.1 Bacteria

Rosenkranz (1977) observed a weakly positive response in the *E. coli* pol A assay after exposure of the bacteria to 7938 ug/ml acetaldehyde in the absence of metabolic activation; the zone of inhibition for the DNA repair-deficient strain (pol A^-) was only slightly greater (12 mm) than that for the DNA repair-proficient (pol A^+) strain (8 mm). However, conditions may not have been ideal for the testing of a volatile material.

7.5.2 Mammalian Cell Culture

Results from *in vitro* alkaline elution assays showed that acetaldehyde did not produce detectable DNA damage in mouse lymphoma L5178Y/$TK^{+/-}$ cells exposed to 66 to 1936 ug/ml for 3 hours (Garberg et al. 1988); rat hepatocytes exposed to 1.3 to 132 ug/ml for 3 hours (Sina et al. 1983); human lymphocytes treated with 441 ug/ml for 4 hours (Lambert et al. 1985); or human bronchial epithelial cells receiving doses up to 44.1 ug/ml for 1 hour (Saladino et al. 1985). However, if acetaldehyde produces chromosomal aberrations and SCEs by DNA-DNA and/or DNA-protein cross-linking, it may not necessarily produce DNA strand breaks (Bradley

et al. 1979).

7.6 Cell Transformation

Eker and Sanner (1986) studied the potential of acetaldehyde to initiate transformation of the rat kidney cell line ($HRPT^4$) in a two-stage (initiation/promotion) cell transformation assay. The assay is based on anchorage-independent growth (i.e., transformed cells can grow in medium gelled with agar while "normal," anchorage-dependent cells cannot).

A 3-hour incubation with noncytotoxic concentrations of acetaldehyde up to 132 ug/ml was followed by continuous 6-day treatment with 0.1 ug/ml of the known tumor promoters: 12-O-tetradecanoyl-phorbol 13-acetate (TPA) or phorbol 12,13-didecanoate (PPD) or the non-tumor-promoting analogue, 4Á-phorbol 12,13-didecanoate (4Á-PPD). Cell viability was determined after 3 or 6 days; colonies growing in soft agar were scored after 14 days of incubation.

Exposure to acetaldehyde alone or TPA alone had no effect on cell survival; however, a significant increase (p value not provided) in viability was seen (10% above the control treated with solvent only) with the combined 4.4-ug/ml acetaldehyde/TPA-treatment. Viability was increased up to 70% above the control at the highest concentration (132 ug/ml acetaldehyde + TPA). Results further demonstrated that the promoter PPD was also effective in enhancing acetaldehyde-treated cell viability; however, the non-tumor-promoting phorbol analogue (4Á-PPD) had no effect. Transformation was confirmed by measuring colony growth in soft agar of the cells treated with 132 ug/ml acetaldehyde plus 0.1 ug/ml TPA. The number of colonies from acetaldehyde-treated cells (450 colonies) was approximately twofold higher than the control untreated cells (250 colonies). The results of this well-controlled but unconfirmed study indicate that acetaldehyde has the potential to act as an initiator of cell transformation.

7.7 Conclusions

The results of *in vitro* genotoxic assays indicate that acetaldehyde induces gene mutations in *Drosophila* and human cells but not in *Salmonella*. Positive gene mutation results were also reported in the nematode *Caenorhabditis*, but no dose-response was shown. Conflicting results were obtained for mitochondrial mutations in the yeast *Saccharomyces cerevisiae*. There is sufficient evidence indicating that acetaldehyde induces aneuploidy, micronuclei, chromosomal aberrations (breaks, gaps, and exchange-type aberrations), and sister chromatid exchanges in rat fibroblasts, CHO cells, and human lymphocytes. Chromosomal aberrations have also been detected in plants. Acetaldehyde has yielded negative results in tests for DNA strand breaks in cultured mammalian cells. *In vivo*, chromosome gaps and breaks were seen in rat embryos after a single intra-amniotic injection, and acetaldehyde-induced SCE have been detected in mice and hamster bone marrow cells after intraperitoneal injection. However, acetaldehyde did not increase the frequency of micronuclei in the early spermatids harvested from mice. Although unconfirmed, there is evidence from a well-controlled initiation/promoter cell transformation assay showing that acetaldehyde initiated transformation of rat kidney cells.

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

8.0 CARCINOGENICITY

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.

8.2 Epidemiological Study

Bittersohl (1974) conducted a morbidity survey to study the incidence of total cancer in an aldol and aliphatic aldehyde factory in the German Democratic Republic (GDR). The work force in this factory was potentially exposed to a product primarily consisting of acetaldol (70%) combined with smaller, but variable, amounts of acetaldehyde; butylaldehyde; crotonaldehyde; "large" condensed aldehydes such as hexatrial, hexatetral, and ethylhexal; traces of acrolein; and 20 to 22% water. The observation period extended from 1967 to 1972. The study cohort consisted of 220 people actively employed in the factory during the observation period; of these, approximately 150 were employed for more than 20 years. Air in the reduction process work site was sampled for various chemicals, including acetaldehyde. Acetaldehyde concentrations were found to range from 1 to 0.56 ppm; this level was far below the recommended GDR Maximum Allowable Concentration ("MAC value") of 55.6 ppm (100 mg/m^3) for this chemical.

Nine cases of cancer were identified in male workers during the 6-year study period. The distribution of cause-specific cancer was as follows: five squamous cell carcinomas of the bronchi, two squamous cell carcinomas of the mouth cavity, one adenocarcinoma of the stomach, and one adenocarcinoma of the cecum. An incidence rate of 6,000 per 100,000 population (9 cases/150 individuals employed for more than 20 years) for total cancer was calculated for this study cohort. In contrast, the incidence rate for cancer in the general population of the GDR during the same time period was 1,200 per 100,000. Analysis by latency showed that eight cases had an average latency period of 26 years (range $\pm$ 4 years), and one case (buccal cavity carcinoma) had a latency period of 13 years. Of the nine cases, five belonged to the 35- to 59-year age group, and the remaining four were over 65 years old. All had a history of smoking. One individual smoked 30 cigarettes per day and developed buccal cavity carcinoma with a latency period of 13 years; the remaining eight smoked between 5 and 10 cigarettes per day.

This study has the following major methodological limitations: the incidence rate was not age adjusted; concurrent exposure to other chemicals and cigarette smoke occurred; duration of exposure was short; a small number of subjects was studied; and information on subject selection, age, and sex distribution was lacking. Because of these limitations, IARC (1985) considered this study to be inadequate to evaluate the carcinogenicity of acetaldehyde.

8.3 Animal Studies

Four carcinogenicity studies with animals were found; acetaldehyde was administered by inhalation in all but part of one study, in which animals were dosed via intratracheal instillation. In the first two studies, one preliminary to the other and described together below, rats received acetaldehyde by inhalation alone. In the other two studies, hamsters received one or the other of two carcinogenic chemicals, either alone or simultaneously with acetaldehyde. In this test for the synergistic effects of acetaldehyde, the hamsters received each additional chemical via the noninhalation route previously found to produce malignancies. In part of one of these studies, hamsters received acetaldehyde by intratracheal instillation. Table 8-1 summarizes the experimental protocols and results of the animal studies.

8.3.1 Inhalation

Woutersen et al. (1984, 1986) exposed groups of 105 male and 105 female SPF-Wistar rats to atmospheres containing acetaldehyde concentrations of 0, 750, 1500, or 3000/1000 ppm (0, 1350, 2700, or 5400/1800 mg/m^3, respectively), 6 hours/day, 5 days/week for up to 28 months. The highest concentration was gradually decreased from 3000 ppm (days 0 to 141) to 1000 ppm (from day 313 forward) because of severe growth retardation, occasional loss of body weight, and early mortality.

Treatment-related nonneoplastic histopathological lesions observed in the nose, larynx, and lungs are summarized in Table 8-2. The most severe lesions were seen in the nose (degeneration, hyperplasia, and metaplasia) of animals in all test groups (except controls), and in the vocal cord region of the larynx (hyperplasia and squamous metaplasia) of several animals in the mid-dose (1500 ppm) and high-dose (3000 ppm) groups. Laryngeal lesions at the lower concentration (750 ppm) were comparable to controls.

The types and incidences of benign and malignant tumors of the respiratory tract are summarized in Table 8-3. Nasal tumors were mainly squamous cell carcinomas and adenocarcinomas originating from the respiratory and olfactory epithelium, respectively. The incidences of adenocarcinomas were significantly ($p < 0.01$) higher in both sexes of rats at all exposure concentrations when compared to controls; on the other hand, squamous cell carcinomas were significantly ($p < 0.01$) increased in males in the mid- and high-dose groups and in females in the high-dose group. No laryngeal or lung tumors were seen in male rats. In females, a carcinoma *in situ* was seen in the larynx in one animal in the mid-dose group, and a poorly differentiated adenocarcinoma of the lung was seen in one animal in the low-dose group. Tumors observed in the other organs of treated rats were comparable to those in the controls. The presence of nasal tumors at all exposure levels suggested that the latency period for nasal tumor induction was independent of the acetaldehyde concentration. The authors concluded that under the conditions of this study, acetaldehyde was carcinogenic to the nasal mucosa of rats.

In an extension of the above study, Woutersen and Feron (1987) examined the process of regeneration of damaged nasal mucosa. Rats exposed to acetaldehyde at concentrations described above for 52 weeks were sacrificed after a recovery

TABLE 8-1

SUMMARY OF CARCINOGENICITY STUDIES OF ACETALDEHYDE IN RATS AND HAMSTERS

Species/Strain	No./Sex/Group	Route of Exposure	Compound	Exposure Level	Duration of Exposure	Neoplastic and Nonneoplastic Lesions	Reference
Rat/Wistar	105/M 105/F	Inhalation	Acetaldehyde	0, 750, 1500, or 3000 decreasing to 1000 ppm	6 hr/day, 5 days/week for 28 months	Neoplasm: Squamous cell carcinomas and adenomas of the nose in males and females. Nonneoplastic lesions: Degeneration, hyperplasia, metaplasia, and squamous metaplasia in the nose and larynx in both sexes.	Woutersen et al. 1984, 1986
Hamster/Syrian golden	36/M 36/F	Inhalation	Acetaldehyde	0, 2500 ppm decreasing to 1650 ppm	7 hr/day, 5 days/week for 52 weeks	Neoplasm: Adenomas, adenocarcinomas, and anaplastic carcinomas of the nose and carcinomas in situ; squamous cell carcinomas and adeno-squamous carcinomas in the larynx of males and females. Nonneoplastic lesions: Rhinitis, hyperplasia, and metaplasia of the nasal, laryngeal, and tracheal epithelium in both sexes.	Feron et al. 1982
Hamster/Syrian golden	35/M 35/F	Intratracheal instillation	Saline Acetaldehyde B[a]P DENA Acetaldehyde + B[a]P	0.2 ml 4 or 8 ul 0.25% in 0.2 ml saline 0.25% in 0.2 ml saline 4 or 8 ul + 0.5% in 0.2 ml saline	1/week for 52 weeks	Neoplasm: Acetaldehyde alone did not induce respiratory tumors. Acetaldehyde neither enhanced nor inhibited the carcinogenicity of B[a]P or DENA. Noneoplastic lesions: Acetaldehyde alone induced peribronchiolar adenomatoid lesions.	Feron 1979

TABLE 8-1 (continued)

Species/Strain	Route of Exposure	No./Sex/Group	Compound	Level	Duration of Exposure	Neoplastic and Nonneoplastic Lesions	Reference
			Acetaldehyde + DENA	4 or 8 ul + 0.5% in 0.2 ml saline			
Hamster/Syrian golden	Inhalation + Intratracheal instillation	35/M + B[a]P	Acetaldehyde +	0 or 1500 ppm +week for 52 weeks	7 hr/day, 5 days/ respiratory tract tumors. A synergistic effect was	Neoplasm: Acetaldehyde alone did not induce seen in both benign and malignant tumor response in animals treated with acetaldehyde + the high dose (52 mg) of B[a]P. No synergistic effect of acetaldehyde was seen at lower doses. Nonneoplastic lesions: Hyper- and metaplastic lesions in the nasal, laryngeal, and tracheal epithelium.	Feron 1979
			B[a]P	0, 0.0625, 0.125, 0.25, 0.5, or 1.0 mg in 0.2 ml saline	1/week for 52 weeks		
Hamster/Syrian golden	Inhalation + Intratracheal instillation or Subcutaneous injection	30/M 30/F + B[a]P or DENA	Acetaldehyde +	0, 2,500-1,650 ppm week for 52 weeks	7 hr/day, 5 days/ laryngeal tumors. Combined treatment with high	Neoplasms: Acetaldehyde alone induced nasal and dose (36.4 mg) of B[a]P produced a synergistic effect in benign and malignant respiratory tract tumor response. No synergistic effects were seen with acetaldehyde + DENA treatment. Nonneoplastic lesions: Hyper- and metaplastic lesions in the nose and respiratory epithelium.	Feron et al. 1982
			B[a]P	0.35 or 0.70 mg in 0.2 ml saline	1/week for 52 weeks		
			DENA	0.625% in 0.2 ml saline	Once each week for a total of 17 injections		

TABLE 8-2

SUMMARY OF RESPIRATORY TRACT HYPERPLASTIC AND PRENEOPLASTIC LESIONS IN RATS EXPOSED TO ACETALDEHYDE BY INHALATION

Organ Examined and Site and Type of Lesion Observed	Incidence of Lesions in Rats Exposed to Acetaldehyde (ppm)							
	Males				Females			
	0	750	1500	3000	0	750	1500	3000
Nose	(49)[a]	(52)	(53)	(49)	(50)	(48)	(53)	(53)
Squamous metaplasia of respiratory epithelium								
Without keratinization	0	1	11[b]	1	0	3	14[b]	0
With keratinization	0	0	5	19[b]	0	1	16[b]	18[b]
Papillomatous hyperplasia with atypia and keratinization	0	0	0	2	0	0	0	6
Focal hyperplasia of respiratory epithelium	0	4	3	5	0	3	11[b]	2
Focal respiratory epithelial pseudoepitheliomatous hyperplasia	0	1	13[b]	3	0	0	20[b]	7
Focal olfactory epithelial squamous metaplasia								
Without hyperkeratosis	0	0	0	0	0	0	1	1
With hyperkeratosis	0	0	0	3	0	0	0	0
Focal basal cell hyperplasia of olfactory epithelium								
Without atypia	0	37[b]	9	0	0	42[b]	19[b]	0
With atypia	0	1	17[b]	0	0	0	5	0
Focal aggregates of (atypical) basal cells in the submucosa beneath the olfactory epithelium	0	0	23[b]	0	0	0	31[b]	2
Focal proliferation of glands in the loosely arranged submucosa beneath the olfactory epithelium	0	0	14[b]	5	0	4	18[b]	5[c]

TABLE 8-2 (continued)

Organ Examined and Site and Type of Lesion Observed	Incidence of Lesions in Rats Exposed to Acetaldehyde (ppm)							
	Males				Females			
	0	750	1500	3000	0	750	1500	3000
Larynx	(50)	(50)	(51)	(47)	(51)	(46)	(47)	(49)
Squamous metaplasia/hyperplasia								
Without hyperkeratosis	2	2	10[c]	9	1	0	6	9
With hyperkeratosis	1	4	13[b]	32[b]	0	3	17[b]	23[b]
Proliferation of dysplastic epithelium	0	0	1	0	0	1	4[c]	2
Lungs	(55)	(54)	(55)	(52)	(53)	(52)	(54)	(54)
Squamous metaplasia with hyperkeratosis of bronchial epithelium	0	0	0	1	0	0	0	0

[a]Numbers in parentheses represent numbers of animals examined.
[b]$p < 0.01$, according to Fisher's Exact test. All comparisons were made with the controls.
[c]$p < 0.05$, according to Fisher's Exact test. All comparisons were made with the controls.
All statistical analyses were done by the author.

SOURCE: Woutersen et al. 1986.

TABLE 8-3

SITES, TYPES, AND INCIDENCES OF RESPIRATORY TRACT TUMORS IN RATS EXPOSED TO ACETALDEHYDE BY INHALATION

Organ Examined and Site and Type of Lesion Observed	Incidence of Lesions in Rats Exposed to Acetaldehyde (ppm)							
	Males				Females			
	0	750	1500	3000	0	750	1500	3000
Nose	(49)[a]	(52)	(53)	(49)	(50)	(48)	(53)	(53)
Papilloma	0	0	0	0	0	1	0	0
Adenocarcinoma	0	16[b]	31[b]	21[b]	0	6[c]	26[b]	21[b]
Metastasizing adenocarcinoma	0	0	1	1	0	0	0	1
Carcinoma *in situ*	0	0	0	1	0	0	3	5
Squamous cell carcinoma	1	1	10[b]	15[b]	0	0	5	17[b]
Metastasizing squamous cell carcinoma	0	0	0	1	0	0	0	0
Larynx	(50)	(50)	(51)	(47)	(51)	(46)	(47)	(49)
Carcinoma *in situ*	0	0	0	0	0	0	1	0
Lungs	(55)	(54)	(55)	(52)	(53)	(52)	(54)	(54)
Poorly differentiated adenocarcinoma	0	0	0	0	0	1	0	0

[a]Numbers in parentheses represent numbers of animals examined.

[b]$p < 0.01$, according to Fisher's Exact test.

[c]$p < 0.05$, according to Fisher's Exact test.

SOURCE: Woutersen et al. 1986.

period of 26 weeks (10 males and 10 females) and 52 weeks (20 males and 20 females). During the recovery period, restoration of the olfactory epithelium was evident in the low-dose group (750 ppm), evident to a lesser degree in the mid-dose group (1500 ppm), and absent in rats in the high-dose group (3000/1000 ppm). During this period, the number of nasal tumors observed was almost the same as in the lifetime study, which indicated that proliferative epithelial lesions of the nose may develop into tumors even without continued acetaldehyde exposure. The authors concluded that the rat olfactory epithelium may regenerate after damage by acetaldehyde, provided that the mucosa is not completely devoid of basal cells and that Bowman's glands have not been totally destroyed.

Feron et al. (1982) exposed groups of 36 male and 36 female Syrian golden hamsters to room air (0 ppm) or to decreasing concentrations of acetaldehyde. The initial concentration was 2500 ppm (4500 mg/m^3), which was gradually decreased (between weeks 9 and 44) to 1650 ppm (2970 mg/m^3) 6 hours/day, 5 days/week for 52 weeks; the animals were sacrificed at 81 weeks. Acetaldehyde-induced nonneoplastic lesions were seen in the nose, larynx, and trachea. Nasal lesions consisted of rhinitis, thinning and degeneration of the layer of olfactory epithelium, hyperplasia and metaplasia of the respiratory epithelium, and thickening of the submucosa. Laryngeal and tracheal lesions characterized by slight to moderate focal hyperplasia and squamous metaplasia of the lining epithelium were seen in nearly all treated hamsters. Tumors were seen in both the nose (adenoma, adenocarcinoma, and anaplastic carcinoma) and the larynx (carcinoma in situ, squamous cell carcinoma, and adeno-squamous carcinoma, Table 8-4). The tumor incidences were 7 and 26% in males and 4 and 20% in females for the nose and larynx, respectively; only the increases in laryngeal tumors were statistically significant ($p < 0.05$) when compared with controls (see Table 8-4). In addition to tumors, hyperplasia and metaplasia with unequivocal nuclear cell atypia were seen in the larynx of males (17%) and females (15%); these lesions were not seen in control rats exposed to air. No nasal or respiratory tract tumors were seen in the control animals. Under the conditions of this study, acetaldehyde is considered to be carcinogenic in male and female hamsters.

These two studies (Woutersen et al. 1986; Feron et al. 1982) demonstrate that acetaldehyde is capable of inducing tumors in the nose and larynx of both hamsters and rats following chronic inhalation exposure. However, the localization of effects differs in these two species. In rats, the major tumor response occurred in the nose, and only one carcinoma was observed in the larynx. In contrast, the major tumor response in hamsters occurred in the larynx (10/43 developed laryngeal tumors), and only a few tumors (3/53) were found in the nose. This difference between the two species may be due to dissimilarities in their upper respiratory tract anatomy, breathing pattern (rats are obligatory nose-breathers, and hamsters may also breathe through the mouth), susceptibility of the epithelium to acetaldehyde, or a combination of these factors (Woutersen et al. 1984, 1986).

8.3.2 Inhalation + Intratracheal Instillation

In a second part of the above study (Feron 1979), groups of 35 male Syrian golden hamsters were exposed by inhalation to 0 or 1500 ppm (2700 mg/m^3) acetaldehyde vapor 7 hours/day, 5 days/week for 52 weeks. The animals also received a

TABLE 8-4

INCIDENCE OF RESPIRATORY TRACT TUMORS IN HAMSTERS EXPOSED TO EITHER AIR OR ACETALDEHYDE VAPOR

Site	Type of Tumor	Air		Acetaldehyde	
		Males	Females	Males	Female
Nose	Adenoma	0/24	0/23	1/27	0/26
	Adenocarcinoma	0/24	0/23	0/27	1/26
	Anaplastic carcinoma	0/24	0/23	1/27	0/26
Larynx	Polyp/papilloma	0/20	0/22	1/23	1/20
	Carcinoma *in situ*	0/20	0/22	3/23	0/20
	Squamous cell carcinoma	0/20	0/22	2/23	1/20
	Adeno-squamous carcinoma	0/20	0/22	0/23	2/20

SOURCE: Feron et al. 1982.

concurrent, weekly intratracheal instillation of 0, 0.0625, 0.125, 0.225, 0.5, or 1 mg benzo[a]pyrene (B[a]P) in saline for the same duration. Simultaneous exposure to acetaldehyde and B[a]P induced marked nonneoplastic lesions in the nasal cavity and trachea. However, after the 26-week recovery period, the lesions in the nasal cavity clearly diminished or completely disappeared. No treatment-related nonneoplastic lesions were seen in other areas of the respiratory tract or other organs. No respiratory tract tumors were seen in hamsters exposed to acetaldehyde alone. Various types of benign and malignant respiratory tract tumors were found in male hamsters treated with B[a]P or B[a]P plus acetaldehyde (Table 8-5). Combined treatment of acetaldehyde plus the high dose (52 mg) of B[a]P resulted in an increased tumor response; twice as many squamous cell carcinomas of the trachea (24/30 versus 11/28, $p = 0.002$) and bronchi (8/30 versus 4/28, $p = 0.20$) were seen as compared with those seen at the same dose of B[a]P without acetaldehyde. In addition, simultaneous exposure (at the high dose) also resulted in a distinct shortening of the latency period (28 weeks versus 50 weeks) for the induction of respiratory tract tumors as compared with those exposed to air plus B[a]P. This effect of acetaldehyde was not noticeable at any of the lower B[a]P levels. The results of this study indicate no evidence for carcinogenicity of acetaldehyde and limited evidence of co-carcinogenicity. This study had the following methodological limitations: only male hamsters were used, the duration of exposure was only 1 year, the study was terminated at 78 weeks, and only one exposure level of acetaldehyde was used. This single exposure level did exceed the maximum tolerated dose (MTD), since increased mortality and decreased body weight gain were noted (as described in Chapter 5.0, Chronic Toxicity). Moreover, cessation of treatment at 52 weeks might have caused regression in metaplastic lesions.

In an extension of the above study, Feron et al. (1982) exposed male and female hamsters to air or high concentrations (2500-1650 ppm, 4500-2970 mg/m^3) of acetaldehyde vapor 7 hours/day, 5 days/week for 52 weeks, and simultaneously treated the animals either with weekly intratracheal instillations of 0.35 or 0.70 mg B[a]P in saline for 2 weeks or with subcutaneous injections of 0.0625% DENA once every 3 weeks (total dose 2.1 ul/hamster) (Table 8-6). Following a 29-week recovery period, all hamsters were sacrificed (81 weeks). At the end of the exposure period, acetaldehyde-exposed animals displayed distinct nonneoplastic histopathological nasal changes similar to those observed in previous studies (e.g., thinning and degeneration of the layer of olfactory epithelium; hyperplasia and metaplasia of the respiratory epithelium). Table 8-7 shows the incidence of respiratory tract tumors in hamsters exposed to the various treatment regimens. Combined treatment of acetaldehyde and the high dose (36.4 mg) of B[a]P caused significant ($p < 0.05$) increases in the incidence of carcinomas in the trachea and bronchi of male hamsters compared with those treated with the same dose of B[a]P but exposed to air only (Table 8-8). The latency period of the tracheobronchial tumors was much shorter after combined exposure than after treatment with B[a]P alone. The enhancing effect of B[a]P-initiated respiratory tract tumor formation observed in this study was similar to that observed in the previous study (Feron 1979), in which inhalation at a lower concentration (1500 ppm) of acetaldehyde and intratracheal instillation of 52 mg of B[a]P produced a slight enhancing effect. There was no evidence that acetaldehyde exposure increased the incidence or affected the type of DENA-induced tumors in any part of the respiratory tract (see Tables 8-7 and 8-8). Based upon these findings, the authors concluded: "acetaldehyde is an irritant

TABLE 8-5

TYPES AND INCIDENCES OF RESPIRATORY TRACT TUMORS IN MALE HAMSTERS AFTER 52 WEEKLY INTRATRACHEAL INSTILLATIONS OF B[a]P AND EXPOSURE TO AIR OR ACETALDEHYDE VAPOR

	Incidence of Tumors											
	Air and B[a]P (mg)						1500 ppm Acetaldehyde and B[a]P (mg)					
Site and Type of Tumor	0	3.25	6.5	13	26	52	0	3.25	6.5	13	26	52
Animals killed after 52 weeks												
Number of animals examined	5	5	5	5	5	5	5	5	5	5	5	5
Number of animals with tumors	0	0	0	0	2	4	0	0	0	0	1	5
Total number of tumors	0	0	0	0	3	6	0	0	0	0	2	12
Trachea												
Papilloma	0	0	0	0	2	0	0	0	0	0	0	1
Squamous cell carcinoma	0	0	0	0	0	1	0	0	0	0	0	4
Bronchi												
Squamous cell carcinoma	0	0	0	0	0	0	0	0	0	0	1	1
Squamous adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	1
Anaplastic carcinoma	0	0	0	0	0	1	0	0	0	0	0	0
Bronchioli and alveoli												
Adenoma	0	0	0	0	1	3	0	0	0	0	1	4
Squamous cell carcinoma	0	0	0	0	0	0	0	0	0	0	0	1
Anaplastic carcinoma	0	0	0	0	0	1	0	0	0	0	0	0
Animals that died spontaneously or were killed after 78 weeks or when moribund												
Number of animals examined[a]	29	30	30	30	29	28	29	28	29	29	29	30
Number of animals with tumors	0	3	4	9	25	26	0	1	5	8	16	29
Total number of tumors	0	4	5	12	44	58	0	1	7	10	26	63
Larynx												
Papilloma	0	0	0	0	0	0	0	0	0	1	0	0
Squamous cell carcinoma	0	0	0	0	0	0	0	0	0	0	0	1
Adenocarcinoma	0	0	0	0	0	0	0	0	0	1	0	0
Trachea												
Polyp	0	0	0	0	2	0	0	0	0	1	0	0
Papilloma	0	3	1	5	9	6	0	0	4	3	6	3
Squamous cell carcinoma	0	0	0	0	5	11	0	0	0	0	4	24[b]
Squamous adenocarcinoma	0	0	0	0	1	1	0	0	0	0	1	0
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	1
Fibrosarcoma	0	0	0	0	1	0	0	0	0	0	0	0
Bronchi												
Polyp	0	0	0	0	2	1	0	0	0	0	1	1
Papilloma	0	0	0	0	1	2	0	0	0	0	0	0
Squamous cell carcinoma	0	0	0	0	2	4	0	0	0	0	2	8
Squamous adenocarcinoma	0	0	0	0	1	2	0	0	0	0	1	3

TABLE 8-5 (continued)

Site and type of tumor	Incidence of Tumors											
	Air and B[a]P (mg)						1500 ppm Acetaldehyde and B[a]P (mg)					
	0	3.25	6.5	13	26	52	0	3.25	6.5	13	26	52
Adenocarcinoma	0	0	0	0	0	4	0	0	0	0	0	0
Anaplastic carcinoma	0	0	0	0	0	1	0	0	0	0	0	0
Bronchioli and alveoli												
Adenoma	0	1	4	7	17	16	0	1	3	4	9	16
Squamous cell carcinoma	0	0	0	0	2	4	0	0	0	0	0	2
Squamous adenocarcinoma	0	0	0	0	0	3	0	0	0	0	1	2
Adenocarcinoma	0	0	0	0	1	1	0	0	0	0	1	2
Anaplastic carcinoma	0	0	0	0	0	2	0	0	0	0	0	0

[a]A few animals were lost through cannibalism or autolysis.

[b]$p = 0.002$, according to Fisher's Exact test.

SOURCE: Feron 1979.

TABLE 8-6

TREATMENT PROTOCOL FOR HAMSTERS EXPOSED TO EITHER AIR OR ACETALDEHYDE VAPOR

	Number and Sex of Hamsters Exposed via Inhalation to Acetaldehyde or Air		Dosage and Route of Additional Treatments to Hamsters		
Group	Air (0 ppm)	Acetaldehyde (2500-1650 ppm)	Treatment	Dosage	Route
1	18 males 18 females	18 males 18 females	None	--[a]	--
2	18 males 18 females	18 males 18 females	Saline	0.2 ml/week	Intratracheal instillation
3	30 males 30 females	30 males 30 females	B[a]P	0.35 mg/week Total 18.2 mg	Intratracheal instillation
4	30 males 30 females	30 males 30 females	B[a]P	0.70 mg/week Total 36.4 mg	Intratracheal instillation
5	30 males 30 females	30 males 30 females	DENA (0.0625%)	0.2 ml every 3 weeks	Subcutaneous injection

[a]No information was provided.

SOURCE: Feron et al. (1982).

TABLE 8-7

SITES AND INCIDENCES OF RESPIRATORY TRACT TUMORS IN HAMSTERS EXPOSED TO AIR OR ACETALDEHYDE VAPOR AND TREATED INTRATRACHEALLY WITH B[a]P OR SUBCUTANEOUSLY WITH DENA[a]

Treatment					Number of animals with tumors of the						Total Number of Respiratory Tract Tumors
Inhalation	Intratracheal Instillation	Subcutaneous Injection		Number of Animals Examined[b]	Respiratory Tract (total)	Nose	Larynx	Trachea	Bronchi	Lungs	
				Males							
Air	--[c]	--	15								
Air	0.9% NaCl[d]	--	15†	30[e]	0(0%)	0	0	0	0	0	0
Air	B[a]P(18.2 mg)[f]	--		29	4(14%)	0	0	2	1	2	5
Air	B[a]P(36.4 mg)[g]	--		30	19(63%)	0	1	8	3	13[h]	27
Air	--	DENA[i]		29	12(41%)	2	7	3	3	0	15
Acetaldehyde	--	--	15								
Acetaldehyde	0.9% NaCl[d]	--	14*	29[e]	7(24%)[j]	2	6[j]	0	0	0	8
Acetaldehyde	B[a]P(18.2 mg)[f]	--		29	12(41%)[k]	2	8[j]	3	1	1	15
Acetaldehyde	B[a]P(36.4 mg)[g]	--		27	22(81%)	1	9[j]	14	5	3[j]	32
Acetaldehyde	--	DENA[i]		30	11(37%)	3	10	2	0	0	15
				Females							
Air	--	--	14								
Air	0.9% NaCl[d]	--	14*	28[e]	0(0%)	0	0	0	0	0	0
Air	B[a]P(18.2 mg)[f]			27	3(11%)	0	1	0	1	1	3
Air	B[a]P(36.4 mg)[g]	--		24	7(29%)	0	0	3	1	5	9
Air	--	DENA[i]		27	11(41%)	0	3	8	2	0	13

TABLE 8-7 (continued)

Treatment					Number of animals with tumors of the						Total Number of Respiratory Tract Tumors
Inhalation	Intratracheal Instillation	Subcutaneous Injection		Number of Animals Examined[b]	Respiratory Tract (total)	Nose	Larynx	Trachea	Bronchi	Lungs	
Acetaldehyde	--	--	15								
Acetaldehyde	0.9% NaCl[d]	--	14†	29[e]	5(17%)	1	4	0	0	0	5
Acetaldehyde	B[a]P(18.2 mg)[f]	--		29	11(38%)	1	7[k]	4[k]	0	1	13
Acetaldehyde	B[a]P(36.4 mg)[g]	--		29	16(55%)	0	4	10	2	3	19
Acetaldehyde	--	DENA[i]		28	8(29%)	2	7	0[k]	0	0	9

[a]See Table 8-10 for types of tumors.

[b]A few animals were lost through cannibalism or autolysis.

[c]No further treatment.

[d]0.2 ml weekly for 52 weeks.

[e]Animals killed at the end of the treatment period are not included in this table.

[f]0.35 mg weekly for 52 weeks.

[g]0.70 mg 52 weekly for 52 weeks.

[h]Two animals had more than one type of pulmonary tumor.

[i]0.125 ul given subcutaneously every 3 weeks for a total of 17 injections.

[j]p _0.01, according to the Chi-square test. All statistical analyses were done by the authors.

[k]p _0.05, according to the Chi-square test. The various groups of acetaldehyde-exposed animals were compared with the corresponding groups of air-exposed controls.

SOURCE: Feron et al. 1982.

TABLE 8-8

SITES, TYPES, AND INCIDENCES OF RESPIRATORY TRACT TUMORS IN HAMSTERS EXPOSED TO AIR OR ACETALDEHYDE VAPOR AND TREATED INTRATRACHEALLY WITH B[a]P OR SUBCUTANEOUSLY WITH DENA[a]

	Incidence of Tumors							
	Inhalation of Air				Inhalation of Acetaldehyde			
Site and Type of Tumor	0.9% NaCl[b,c]	B[a]P (18.2 mg)[d]	B[a]P (36.4 mg)[c]	DENA	0.9% NaCl[b,c]	B[a]P (18.2 mg)[d]	B[a]P (36.4 mg)[c]	DENA[e]
				Males				
Larynx	(20)[f]	(28)	(29)	(28)	(23)	(26)	(25)	(30)
Polyp/papilloma	0	0	1	7	1	1	1	6
Carcinoma *in situ*	0	0	0	0	3	3	1	3
Squamous cell carcinoma	0	0	0	0	2	6[g]	5[h]	1
Trachea	(30)	(29)	(29)	(29)	(28)	(28)	(27)	(30)
Polyp/papilloma	0	2	5	3	0	2	2	2
Squamous cell carcinoma	0	0	1	0	0	1	7[h]	0
Adenocarcinoma	0	0	0	0	0	0	3	0
Anaplastic carcinoma	0	0	1	0	0	0	0	0
Sarcoma	0	0	1	0	0	0	2	0
Bronchi	(30)	(29)	(30)	(29)	(28)	(29)	(27)	(30)
Polyp/papilloma	0	1	2	3	0	1	0	0
Squamous cell carcinoma	0	0	0	0	0	0	5[h]	0
Adenocarcinoma	0	0	1	0	0	0	0	0
				Females				
Larynx	(22)	(27)	(24)	(27)	(20)	(23)	(23)	(22)
Polyp/papilloma	0	1	0	3	1	2	1	1
Carcinoma *in situ*	0	0	0	0	0	0	2	3[h]
Squamous cell carcinoma	0	0	0	0	1	5[h]	1	3[h]
Adeno-squamous carcinoma	0	0	0	0	2	0	0	0

TABLE 8-8 (continued)

Site and Type of Tumor	Incidence of Tumors							
	Inhalation of Air				Inhalation of Acetaldehyde			
	0.9% NaCl[b,c]	B[a]P (18.2 mg)[d]	B[a]P (36.4 mg)[c]	DENA	0.9% NaCl[b,c]	B[a]P (18.2 mg)[d]	B[a]P (36.4 mg)[c]	DENA[e]
Trachea	(28)	(27)	(24)	(27)	(28)	(29)	(28)	(28)
Polyp/papilloma	0	0	1	8	0	3	1	0[g]
Squamous cell carcinoma	0	0	2	0	0	1	8	0
Anaplastic carcinoma	0	0	0	0	0	0	1	0
Bronchi	(28)	(27)	(24)	(27)	(29)	(29)	(29)	(28)
Papilloma	0	1	0	2	0	0	0	0
Adenocarcinoma	0	0	1	0	0	0	1	0
Adeno-squamous carcinoma	0	0	0	0	0	0	1	0

[a]Numbers of animals examined are given in parentheses. Animals killed at the end of the treatment period are not included in this table.

[b]No further treatment.

[c]Given intratracheally (0.2 mL), weekly during 52 weeks.

[d]Given intratracheally in 52 weekly doses of 0.35 mg.

[e]Given subcutaneously in 17 doses (once every 3 weeks) of 0.125 L.

[f]Given intratracheally in 52 weekly doses of 0.70 mg.

[g]$p < 0.01$, according to the chi-square test. All statistical analyses were done by the authors.

[h]$p < 0.05$, according to the chi-square test. The various groups of acetaldehyde-exposed animals were compared with the corresponding groups of air-exposed controls.

SOURCE: Feron et al. 1982.

as well as a carcinogen to the nose and larynx with a weak initiating and a strong 'promoting' (co-carcinogenic) activity."

8.3.3 Intratracheal Instillation

Feron (1979) gave 7 groups (35 males, 35 females) of Syrian golden hamsters weekly or biweekly intratracheal instillations of saline, acetaldehyde, B[a]P, B[a]P + acetaldehyde, diethylnitrosamine (DENA), or DENA + acetaldehyde for 52 weeks. The treatment schedule and doses are presented in Table 8-9, and the incidences of respiratory tract tumors are presented in Table 8-10. Intratracheal instillation of acetaldehyde alone did not induce any respiratory tract tumors but did produce extensive, irreversible, peribronchiolar adenomatoid lesions often accompanied by inflammatory changes. These lesions were not assumed to be preneoplastic because transition of the proliferated bronchioalveolar epithelium into a neoplastic growth was not observed. Acetaldehyde neither enhanced nor inhibited the carcinogenicity of B[a]P or DENA. Both B[a]P and DENA induced a variety of benign and malignant respiratory tract tumors. Under the conditions of the study (i.e., intratracheal instillation at the concentrations used), acetaldehyde did not act as either a primary carcinogen or a promoter.

8.4 Carcinogenicity of Ethanol

An indirect source of acetaldehyde in the body results following the ingestion of ethanol in alcoholic beverages, a voluntary exposure. Ethanol is rapidly metabolized to acetaldehyde and then to acetate. IARC has found that there is sufficient evidence for the carcinogenicity of alcoholic beverages in humans (IARC, 1988). The organs for which there is clear evidence of carcinogenicity from alcoholic beverages include the oral cavity and pharynx (excluding the nasopharynx), the larynx, the esophagus, and the liver. Whether the cancer is due to chronic irritation by ethanol, the action of the metabolic product acetaldehyde, or possibly even to another chemical present in all alcoholic beverages is not clear. After ingestion of ethanol the alveolar air of humans contains levels of acetaldehyde proportional to the amount of ethanol consumed, which would provide a periodic exposure of the respiratory tract to acetaldehyde. For example, consumption of 18 milliliters of ethanol, approximately the amount in one 12 ounce can of beer, resulted in an alveolar air concentration of 0.100 μg/100 ml (1 mg/m^3 or approximately 556 ppb acetaldehyde) (Freund and O'Halloren, 1965; Freund, 1967; USEPA, 1987). (In the USEPA document the alveolar concentrations of acetaldehyde are shown as μg/100 ml. In the original paper the concentrations are mμg/100 ml, a factor of 1000 lower. Our estimates are based on the figures in the original papers.) Higher intakes led to proportionally higher concentrations of acetaldehyde in alveolar air. At the highest intake tested, 110 ml ethanol, approximately the amount of ethanol in six 12 ounce cans of beer, an alveolar air concentration of 0.53-0.56 μg/100 ml alveolar air (approximately 3 ppm) persisted for 4 to 5 hours. The upper portions of the

TABLE 8-9

TREATMENT OF HAMSTERS IN THE VARIOUS GROUPS
USED IN THE INTRATRACHEAL INSTILLATION STUDY[a]

Group Number	Type of Intratracheal Instillation[b]
1	Weekly: 0.2 ml 0.9% NaCl solution
2	Weekly: 0.2 ml 2% acetaldehyde in 0.9% NaCl solution
3	Weekly: 0.2 ml 4% acetaldehyde in 0.9% NaCl solution
4	Biweekly: 0.2 ml 0.25% B[a]P in 0.9% NaCl solution
5	Weekly: one week 0.2 ml 2% acetaldehyde in 0.9% NaCl solution, and the other week 0.1 ml 4% acetaldehyde in 0.9% NaCl solution and 0.1 ml 0.5% B[a]P in 0.9% NaCl solution
6	Biweekly: 0.2 ml 0.25% diethylnitrosamine (DENA) in 0.9% NaCl solution
7	Weekly: one week 0.2 mL 2% acetaldehyde in 0.9% NaCl solution, and the other week 0.1 ml 4% acetaldehyde in 0.9% NaCl solution and 0.1 ml 0.5% DENA in 0.9% NaCl solution

[a]Each group initially consisted of 35 males and 35 females.
[b]The intratracheal instillations were carried out during a period of 52 weeks.

SOURCE: Feron 1979.

TABLE 8-10

TYPES AND INCIDENCES OF RESPIRATORY TRACT TUMORS IN HAMSTERS GIVEN INTRATRACHEAL INSTILLATIONS OF 0.9% NaCl SOLUTION, ACETALDEHYDE, B[a]P, B[a]P + ACETALDEHYDE, DENA, OR DENA + ACETALDEHYDE

Site and Type of Tumor	Incidence of Tumors													
	0.9% NaCl		4 ul Acet-aldehyde		8 ul Acet-aldehyde		0.25% B[a]P		0.5% B[a]P+ 4 ul Acet-aldehyde		0.25% DENA		0.5% DENA+ 4 ul Acet-aldehyde	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Animals killed after 13 weeks														
Number of animals examined	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Trachea														
Papilloma	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Lungs														
Adenoma	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Animals killed after 26 weeks														
Number of animals examined	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Trachea														
Papilloma	0	0	0	0	0	0	0	0	0	0	2	1	2	2
Bronchi														
Polyp	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Animals killed after 52 weeks														
Number of animals examined	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Larynx														
Papilloma	0	0	0	0	0	0	0	0	0	0	1	1	0	3
Trachea														
Papilloma	0	0	0	0	0	0	0	0	1	0	3	3	3	3
Lungs														
Adenoma	0	0	0	0	0	0	0	0	0	0	2	2	3	3

TABLE 8-10 (continued)

Site and Type of Tumor	Incidence of Tumors													
	0.9% NaCl		4 ul Acet-aldehyde		8 ul Acet-aldehyde		0.25% B(a)P		0.5% B[a]P+ 4 ul Acet-aldehyde		0.25% DENA		0.5% DENA+ 4 ul Acet-aldehyde	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Animals that died spontaneously or were killed at the end of the experimental period or when moribund														
Number of animals examined[a]	24	25	24	25	25	23	23	25	23	23	24	25	23	24
Larynx														
Papilloma	0	0	0	0	0	0	0	0	1	1	10	2	7	7
Carcinoma	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Trachea														
Polyp	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Papilloma	0	1	0	0	0	0	6	8	6	10	23	21	22	20
Squamous cell carcinoma	0	0	0	0	0	0	3	3	7	3	0	0	0	0
Anaplastic carcinoma	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Bronchi														
Polyp	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Papilloma	0	0	0	0	0	0	0	0	1	0	0	1	1	0
Squamous cell carcinoma	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Lungs														
Adenoma	0	0	0	0	0	1	7	6	2	1	17	21	21	23
Adenocarcinoma	0	0	0	0	0	0	0	1	1	0	0	1	1	0
Squamous cell carcinoma	0	0	0	0	0	0	0	0	0	1	0	0	0	0

[a]A few animals were lost through autolysis or cannibalism.

SOURCE: Feron 1979.

respiratory tract would be exposed during exhalation. It is interesting that tumors of the larynx were observed in hamsters after acetaldehyde exposure and that tumors of the larynx are significantly increased in humans after ingestion of alcoholic beverages.

8.5 Conclusions

The only epidemiological study involving acetaldehyde exposure showed an increased incidence of total cancer among workers in an aldehyde factory in the German Democratic Republic between 1967 and 1972. However, this morbidity study had a number of limitations: concurrent exposure to other chemicals and cigarette smoke; short duration; small number of subjects; lack of information on subject selection, age, and sex distribution; and failure to age-adjust the incidence rate. Therefore, this study does not provide the evidence needed to evaluate the carcinogenicity of acetaldehyde.

Inhalation studies in rats and hamsters provide positive evidence for the carcinogenicity of acetaldehyde. The most severe nonneoplastic lesions induced by inhalation were in the nose (degeneration, hyperplasia, and metaplasia) and in the larynx (vocal cord region, predominantly hyperplasia and metaplasia). Following chronic inhalation exposure, these lesions evidently became neoplastic. Acetaldehyde induced predominantly nasal tumors in rats, mainly squamous cell carcinomas and adenocarcinomas originating in the respiratory and olfactory epithelium, respectively. In hamsters, acetaldehyde-induced tumors were found predominantly in the larynx. These effects indicate species differences in the sensitivity and response to acetaldehyde vapors.

In hamsters, inhalation of acetaldehyde potentiated the carcinogenicity of high doses of B[a]P administered by intratracheal instillation, causing a twofold increase in the number of squamous cell carcinomas of the trachea and bronchi as compared with the incidence in hamsters administered B[a]P alone. Moreover, the latency period for tumor induction decreased from 50 to 28 weeks as compared with that in hamsters exposed to air or B[a]P alone. There was no evidence that acetaldehyde exposure increased the incidence or affected the type of DENA-induced tumors in any part of the respiratory tract of hamsters.

Following intratracheal instillation, acetaldehyde did not produce respiratory tract tumors in hamsters. When given simultaneously with the respiratory carcinogens B[a]P or DENA, no potentiation of the carcinogenic effect of B[a]P or DENA in the respiratory tract of hamsters was found. In some combinations acetaldehyde did appear to exert a protective effect against some doses of other carcinogens in at least some parts of the hamster's respiratory tract, but the effects were not consistent enough to be interpretable.

In Tables 8-5, 8-8, and 8-10, acetaldehyde appears to exert a protective effect against cancer induction by known carcinogens at some anatomical sites. The strongest effect, which is statistically significant, is seen in Table 8-8 where 8 polyps/papillomas of the trachea are induced by diethylnitrosamine (DENA) in hamsters exposed to air, while none are induced by DENA in hamsters exposed to airborne acetaldehyde. Also in Table 8-10 acetaldehyde appears to protect against lung adenomas induced by benzo(a)pyrene. Yet, in the same table slightly

more adenomas are induced by DENA in the presence of acetaldehyde than in its absence. Some protective effects could be due to statistical variation while others could be real. For example, acetaldehyde is an irritant and increased mucus production caused by irritation might counteract the deleterious effect of a second chemical. However, establishment of such protective effects requires extensive experimentation, and, even if such protective effects are demonstrable, acetaldehyde alone causes respiratory tract tumors in both rats and hamsters (see above).

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC 1985). Therefore IARC classified acetaldehyde as class 2B, a possible human carcinogen. The U.S. Environmental Protection Agency (U.S. EPA), using the guidelines for Carcinogen Risk Assessment, has classified acetaldehyde as a Group B2 probable human carcinogen, based on sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (IRIS 1989, 1991) (Table 8-11). OEHHA staff concur that acetaldehyde is a potential human carcinogen. Details of the IARC and USEPA classification schemes, taken from IARC (1987) and USEPA (1986) respectively, are given in Appendix C.

TABLE 8-11

CLASSIFICATION OF ACETALDEHYDE'S CARCINOGENICITY

Organization	IARC	USEPA
Human evidence	inadequate	inadequate
Animal evidence	sufficient	sufficient
Class	2B	B2
Classification	possible	probable
Date	1985, 1987	1987

9.0 QUANTITATIVE RISK ANALYSIS

9.1. Noncarcinogenic risks

The United States Environmental Protection Agency (USEPA) has determined a Reference Concentration (RfC) for acetaldehyde of 0.009 mg/m^3 (5 ppb). The Reference Concentration of a chemical is an estimate, with an uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime of exposure. The Reference Concentration is derived from a no (NOAEL) or lowest (LOAEL) observed adverse effect level in human or animal exposure, to which uncertainty or "safety" factors are applied. For acetaldehyde a NOAEL of 150 ppm (273 mg/m^3) for degeneration of the olfactory epithelium of rats was obtained from the studies of Appleman et al. (1982) and Appleman et al. (1986). Adjustments for duration of exposure and corrections for relative areas of human and animal extrathoracic region of the respiratory tract were made resulting in a human equivalent concentration of 8.7 mg/m^3, then an uncertainty factor of 1000 was applied. This factor was the product of factors of 10 to account for the varying sensitivity to chemicals in the human population, 10 to account for subchronic (26 weeks) to chronic extrapolation, and 10 to account both for uncertainty in the interspecies extrapolation using dosimetric adjustments and for the incompleteness in the database. At 0.004 mg/m^3 (2 ppb), the annual average ambient air level of acetaldehyde estimated in part A of this document by the Air Resources Board, noncarcinogenic effects are not expected to occur (see Chapters 3, 4 and 5) since it is one-half of the RfC. However, "hot spots" of acetaldehyde exposure have not been evaluated.

9.2. Carcinogenic risks

The USEPA draft Health Assessment Document for acetaldehyde (USEPA 1987) includes a quantitative risk assessment for cancer based on animal studies and a risk assessment for acetaldehyde is listed in its Integrated Risk Information System (IRIS) database (USEPA, 1991). Office of Environmental Health Hazard Assessment (OEHHA) staff have consulted the USEPA risk assessment in the preparation of this report.

OEHHA staff use 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 at. (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).

Tumors in animals have occurred in 2 sites. There is no known site concurrence among species for carcinogens although some carcinogens do result in the same tumors in man and animals (e.g., induction of liver angiosarcomas by vinyl chloride). For acetaldehyde tumors occurred in the nasal area for

rats and in the larynx for hamsters. While it is assumed that the respiratory tract is the only organ affected by acetaldehyde, tumors in the nose in rats and in the larynx of hamsters do not directly mean that only tumors in the nose or larynx would occur in humans. In the case of formaldehyde (OEHHA, 1992), 98-99% of inhaled material is absorbed in the nasal passages in rodents, but much less is absorbed there in monkeys (Casanova et al., 1991) and also presumably in humans. By analogy much acetaldehyde should not be absorbed in the human nasal passages. In addition, humans are not obligate nose breathers. Thus, the entire human respiratory tract may be at risk for cancer induction by acetaldehyde.

9.2.1. Thresholds

A threshold dose of a toxic substance is one below which a specified outcome does not occur. While some threshold models for carcinogenesis have been proposed (based on, for example, saturation of detoxification enzymes, the existence of DNA repair mechanisms, or recurrent toxicity), none has been convincingly demonstrated.

An "epigenetic" mechanism that could result in a threshold has been invoked to explain the carcinogenic action of substances that do not directly produce genetic damage in short-term tests. At high concenntrations toxicants can kill cells. Indeed, in the case of acetaldehyde high concentrations lead to significant cell killing ("degeneration") in the respiratory epithelium (Wouterson et al., 1986) However, for acetaldehyde there is compelling evidence of genotoxicity because of binding to DNA and mutagenicity (Chapter 7). There is also experimental evidence for acetaldehyde acting as an initiator of tumorigenesis (Chapter 8). Therefore, OEHHA staff considers acetaldehyde-induced carcinogenesis as a genotoxic event and staff were unable to determine a threshold for the phenomenon.

9.2.2. Rat Nasal Carcinomas and the Multistage Model.

The data used to calculate cancer risk from the male and female rat nasal carcinomas observed in the Woutersen et al. (1986) inhalation study are given in Table 9.1 (USEPA, 1987). Three types of nasal tumors were observed: squamous cell carcinomas, adenocarcinomas, and carcinomas *in situ*. (Note that the tumors were determined after 28 months of exposure which is longer than the 24 months often used in lifetime experiments in rats.) The denominators are the same as those in Table 8-3 which are the numbers of animals examined for nasal changes. USEPA's risk assessment considered all 55 animals in the experimental groups to be at risk, whereas OEHHA staff used only the 49-53 animals of each group that were examined for nasal changes. Doses were converted to an equivalent continuous dose (USEPA 1987, 1991), because the animals were exposed for only 6 hours/day, 5 days/week. Because of the excessive morbidity (labored respiration, mouth breathing, excessive salivation, and blood around the external nostrils) encountered by Wouterson et al. with the animals exposed at the highest concentration of 3000 ppm, the concentration was eventually lowered to 1000 ppm, less than the middle concentration of 1500 ppm. Since the impact of this highly variable exposure is difficult to determine, it was not used in the running of the model.

TABLE 9-1

TUMOR INCIDENCE IN MALE AND FEMALE RATS
AFTER 28 MONTHS OF ACETALDEHYDE INHALATION

	Exposure (ppm)			Nasal Tumor
	Nominal	Measured	Continuous	Incidence
Males	0			1/49
	750	727	129.8	17/52
	1500	1438	256.8	41/53[a]
Females	0			0/50
	750	727	129.8	6/48[b]
	1500	1438	256.8	36/53

[a] The 1 metastasizing adenocarcinoma in Table 8-3 is considered to be one of the 31 total adenocarcinomas.
[b] Does not include the benign papilloma in Table 8-3.

Using the computer program GLOBAL86 (Howe et al., 1986), a linearized, time-independent multistage model was fit to the nasal carcinoma dose-response data. This multistage model may be expressed as:

$$P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + .. + q_k d^k)}$$

where P(d) is the lifetime probability of cancer for a given dose d of carcinogen, q_0 is a constant that accounts for the background incidence of cancer occurring in the absence of the carcinogen, and q_1, q_2, ... q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen to obtain the best fit of the model to the data.

The male rat nasal tumor data yielded a maximum likelihood estimate (MLE) for q_1 (the linear or slope term, which relates the probability of cancer to the first power of the dose of carcinogen administered in the equation for the multistage model) of 1.6×10^{-8} ppb^{-1}. "The multistage model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data" (USEPA 1985). In the present case, however, no higher order terms than 2, i.e., coefficients multiplied by dose raised to a power greater than 2, were obtained using the model. For the rat nasal cancer data, the equation therefore reduces to:

$$P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2)}$$

The model generated an Upper 95% Confidence Limit (UCL) on q_1 (named q_1^* and referred to as the inhalation unit risk) of 3.2×10^{-6} ppb^{-1} (Table 9.2). The female rat data (Table 9.1) yielded a somewhat lower risk with a q_1^* equal to 9.3×10^{-7} ppb^{-1} (Table 9.2). Such UCLs are calculated because they: are more stable statistically, considering the uncertainty in the risk assessment, and are health protective, i.e., statistically there is only a 5% chance that the true value of q_1 is greater than the 95% UCL.

For acetaldehyde 1 ppb = 1.8 ug/m^3. Using the latter units, the MLE for q_1 equals 8.8×10^{-9} $(ug/m^3)^{-1}$ and the 95% UCL for q_1 (q_1^*) equals 1.8×10^{-6} $(ug/m^3)^{-1}$ for the male rat data.

In its risk assessment, the USEPA combined two experiments by Wouterson et al.: the lifetime exposure experiment and an experiment in which one year of exposure was followed by 1 year of recovery. OEHHA staff, however, used only the lifetime exposure experiment. Such experiments, when available, are preferable for risk assessment since environmental risk assessments usually assume lifetime exposures to low levels of carcinogens. USEPA also used two versions of the multistage model: the standard, non-time-dependent ("quantal") version and a time-dependent, variable-dose or time-to-tumor version which is preferable when the data are available for its use. However, in the case of the Wouterson et al. data, such data as: (1) the exact time of death of each animal, (2) whether a tumor was present at the time of its death, and (3) whether a tumor was incidental to or causal of the death, were not reported. Thus USEPA made several assumptions to apply the time-to-tumor version of the model. To minimize the use of additional assumptions, OEHHA staff decided to use the standard ("quantal") version of the model. Using the assumptions the

TABLE 9-2

CARCINOGENIC POTENCY DETERMINATION BY GLOBAL86:
INHALATION UNIT RISK/PPB BASED ON RAT NASAL TUMORS

	Interspecies scaling factor		
	(1.0)[a]	Metabolic[b]	Contact[c]
males	3.2×10^{-6}	4.8×10^{-6}	2.7×10^{-5}
females	9.7×10^{-7}	1.6×10^{-6}	6.3×10^{-6}

[a] Assumes ppb equivalent between species.
[b] Assumes metabolism throughout body.
[c] Assumes metabolism in respiratory tract only.

USEPA found that the time-to-tumor version gave risks that were about 20-25% higher than those obtained using the quantal version of the model (USEPA, 1987).

9.2.3 Interspecies Scaling and Rat Nasal Carcinomas

Cancer risk assessment usually requires a means of predicting human risk from the results of an animal bioassay. Without specific information to the contrary, OEHHA assumes that a surface area scaling factor is appropriate for scaling from animals to humans. Use of a scaling factor on applied exposure provides a pragmatic way of performing the extrapolation from rodents to humans.

In its risk assessment (USEPA 1987, 1991), the USEPA assumed that units of ppm (or ppb) are risk-equivalent across species, as it had done previously with other contact carcinogens including formaldehyde and epichlorohydrin. Such an approach leads to a risk range of 9.7×10^{-7} to 3.2×10^{-6} ppb^{-1} acetaldehyde, based on female and male rat nasal carcinomas, respectively (Table 9-2).

The present work makes the basic assumption that equal concentrations of carcinogen imply equal risk across species in order to develop scaling factors in two cases. Both cases derive from the same simplified sort of metabolic model, in which the intake rate of carcinogen just equals the overall rate of metabolism of the carcinogen. This equation, a first approximation in the absence of extensive data, leads to a mathematical expression for the concentration of the carcinogen in the target tissue as the measure of the carcinogenic effect. In the first case, a systemic scaling results from assuming a quasi-uniform distribution of the carcinogen throughout the body. For the particular assumption of metabolic rate proportional to body surface area, this scaling becomes identical to the default scaling option of the California Department of Health Services guidelines for carcinogen risk assessments (CDHS, 1985). (In the second case, discussed in Section 9.2.4, a contact scaling results from assuming that the carcinogenic effect takes place only in a thin layer of tissue at the point of entry of the carcinogen.)

The simple metabolic model used to obtain scaling factors in this assessment represents the affected tissue as a single-compartment in order to estimate the concentration of carcinogen in affected tissue. Among other simplifying assumptions, especially that the chemical processes are for practical purposes homogeneous and that the actual metabolic chain of reactions can be usefully approximated by a single rate limiting step, this analysis considers concentrations to be sufficiently small that linear kinetics govern in determining the scaling.

In a compartment which consists of a given volume with chemical processes occurring at a steady state, a mass balance requires that a single input rate equals the overall rate of disappearance by metabolism in that volume, if there is no outflow:

$$I = B\,M, \qquad (1)$$

where, for that volume, I = rate of input of carcinogen in ug/hr, B = tissue concentration of carcinogen in ug/l, and M = metabolic rate per concentration ((ug/hr)/(ug/l) = 1/h).

Thus, for that volume the tissue concentration is

$$B = I / M. \tag{2}$$

According to the assumption that equal values of tissue concentration imply equal risks of cancer across species, it follows from Equation 2 that humans, designated by subscript h, will have the same risk as the rodent test species, designated by r, for

$$(I / M)_h = (I / M)_r. \tag{3}$$

(In this work the subscript following the closing parenthesis applies to the entire expression within the parentheses.) For inhalation, Equation 3 becomes

$$(a V C / M)_h = (a V C / M)_r, \tag{4}$$

where a = proportion of carcinogen absorbed, V = inhalation rate in m^3/hr, and C = atmospheric concentration in ug/m^3.

The inhalation rate across mammalian species follows the allometric relation (Weibel, 1984):

$$V_h / V_r = (W_h / W_r)^{0.75}. \tag{5}$$

where W = body mass in kg.

Using this expression in Equation 4 gives:

$$(a W^{0.75} C / M)_h = (a W^{0.75} C / M)_r. \tag{6}$$

This equation is used in both the systemic case and the contact case below. The only difference is in the calculation of M.

The systemic case assumes that the concentration and metabolism are quasi-uniformly distributed throughout the body. Let n be the exponent in the allometric relation for M_b, which represents the average metabolic rate for the whole body.

$$(M_{br} / M_{bh}) = (W_r / W_h)^n, \tag{7}$$

Dividing this equation into Equation 6 yields

$$(a W^{0.75-n} C)_h = (a W^{0.75-n} C)_r, \tag{8}$$

Solving equation (8) for C_r provides an expression to use in the risk formula for test animals in order to convert it to one for the risk for humans exposed to C_h.

$$C_r = (a_h / a_r)(W_h / W_r)^{0.75-n} C_h. \tag{9}$$

Note that n = 2/3 gives OEHHA default scaling. Allometric data related to metabolic rate show that n may be somewhat greater than 2/3. Inhalation clearance measurements for vinyl chloride appear to give n = 0.69 from mouse to human (plot of data from Buchter et al. 1977, 1978, 1980; Filser and Bolt

1979). Oxygen metabolism *in vivo* gives n = 0.75 for an even greater range of body mass (Weibel 1984). The use of 0.75 corresponds to no net scaling based on body mass.

For the case of acetaldehyde, the lack of data requires the default assumption of n = 2/3. With the further assumption that the absorption coefficients are equal because of lack of data, Equation 9 gives the following scaling factors: 1.5 for the 400 g male rat and 1.6 for the 250 g female rat, assuming 70 kg body weight for both human sexes. Using these scaling factors risk values of 1.6×10^{-6} ppb^{-1} from female rat data and 4.8×10^{-6} ppb^{-1} from male rat data are obtained (Table 9.2).

9.2.4 Rat Nasal Carcinomas and Contact Scaling

The contact case assumes the concentration of carcinogen to be distributed only in the designated volume of a thin layer in the body and nowhere else. The metabolism per unit volume is assumed to occur in that layer at the same rate as in the rest of the body. The average rate of metabolism per concentration per unit volume in the body is $M_b/(W/D)$. Thus, the overall metabolism per concentration in the layer is:

$$M_l = M_b \; D \; A \; t \; / \; W \; , \qquad (10)$$

where D = average density of the body in kg/l, A = surface area of the layer in cm^2, and t = average thickness of the layer in cm.

Inserting this expression into Equation 6 insures that the concentration in that layer is constant across species.

$$(a \; C \; W^{1.75} \; / \; M_b A \; t \; D)_h = (a \; C \; W^{1.75} \; / \; M_b A \; t \; D)_r . \qquad (11)$$

Using Equation 7 and assuming that the surface area of the lung airways has an allometric exponent of 0.75, the exponent for "metabolic size" (Gross et al. 1982), this equation becomes:

$$(a \; W^{0.75+1-0.75-n} \; C \; / \; t)_h = (a \; W^{0.75+1-0.75-n} \; C \; / \; t)_r .$$

So the equivalent rat concentration is

$$C_r = (\; a_h \; / \; a_r \;)(\; W_h \; / \; W_r \;)^{1-n} \; (\; t_r \; / \; t_h \;) \; C_h . \qquad (12)$$

Assuming for lack of better information that the value of a/t is constant across species and again using n = 2/3, Equation 12 gives the following scaling factors: 5.6 for a 400 g male rat and 6.5 for a 250 g female rat, again assuming both human sexes have 70 kg body mass. The resultant risks of 6.3×10^{-6} ppb^{-1} for female rats and 2.7×10^{-5} ppb^{-1} for male rats (Table 9-2) would be used only to predict nasal or respiratory system cancers.

The experimental data of Lam et al. (1986) on the ability of acetaldehyde to crosslink DNA to protein and of Bogdanffy et al. (1986) on differential levels of aldehyde dehydrogenase in the rat respiratory tract are consistent with the use of a contact area scaling factor. Aldehyde dehydrogenase converts active acetaldehyde to acetic acid which is much less reactive than acetaldehyde.

Thus aldehyde dehydrogenation is a detoxifying reaction. The greatly reduced presence of aldehyde dehydrogenase in rat olfactory epithelium compared to other areas (Bogdanffy et al. 1986) means that acetaldehyde can accumulate in the olfactory epithelium and be available to react with DNA and to cause genetic damage. The olfactory epithelium is the area where nasal lesions and tumors occur in rats.

Using the different assumptions indicated above, a range of risk inhalation unit values is obtained, from 9.7×10^{-7} ppb^{-1} based on female rat data without a scaling factor applied to 2.7×10^{-5} ppb^{-1} based on male rat data with a contact area correction factor applied (Table 9.2).

9.2.5. Hamster Laryngeal Carcinomas and the Multistage Model

The multistage model was also fit to the tumor data in hamsters obtained by Feron et al. (1982). These authors observed both nasal and laryngeal tumors (Table 8-4) in a single group of hamsters exposed 6 hours/day, 5 days/week to an acetaldehyde level which was initially 2500 ppm but was gradually decreased to 1650 ppm. For the 52 weeks of exposure the average level was approximately 2075 ppm; the hamsters were terminated at 81 weeks. Since the tumorigenic effect was stronger for laryngeal tumors, these were used for risk assessment. For females there were no tumors in 20 control animals and 4 laryngeal tumors in 20 treated animals. The reported exposure concentration corresponds to 370.5 continuous ppm during the exposure period of 52 weeks and 238 continuous ppm over the 81 weeks of the experiment. Under the assumption that ppm (or ppb) exposures are equivalent in man and hamster (USEPA, 1987), the female hamster data result in a q_1^* of 1.9×10^{-6} ppb^{-1}. For males there were 0 tumors in 20 controls and 6 laryngeal tumors in 23 treated hamsters. A q_1^* of 2.3×10^{-6} ppb^{-1} was obtained with these data using the multistage model. These values are very close to the ones obtained for rats under the assumption of equality of ppb exposure (Table 9.2).

9.2.6. Risk Estimate using the Gaylor-Kodell Approach

The application of the linearized multistage model requires the use of a computer program to fit the model to the data and extrapolation into the range below the lowest dose tested. An alternative approach is the technique introduced by Gaylor and Kodell (Gaylor and Kodell 1979, Williams and Burson 1985). In this method the observed responses are fit to a model, then the 95% upper confidence limit (UCL) is determined on the predicted value from the model at the lowest tested dose of chemical for which cancer risk is increased over background. This UCL is then interpolated linearly from this point to the background incidence in order to determine an upper boundary line on risk. Under the assumption of strict linearity (not just at low doses), the true risk is predicted to be at or below this line with 95% probability. For nasal carcinoma in male rats this 95% UCL on the 750 ppm exposure level (129.8 continuous ppm) was determined to be 0.406 using the multistage model. Subtracting the background incidence of 0.020 (1/49) yielded an additional risk of 0.386. Dividing this net incidence by 129,800 ppb continuous exposure yielded an inhalation unit risk of 3×10^{-6} ppb^{-1}, which agrees with the results of the multistage model.

9.2.7 Population Risk from Acetaldehyde in Ambient Air

As stated above, air modeling of acetaldehyde in California has yielded an estimated mean ambient concentration of 2 ppb (4 $\mu g/m^3$). With an estimated California population of $30x10^6$ and upper 95% confidence limits on inhalation unit risk of $0.97\text{-}27x10^{-6}$ ppb^{-1} ($0.54\text{-}15x10^{-6}$ $(\mu g/m^3)^{-1}$) derived using the multistage model (Table 9.2), the upper 95% confidence limit estimate of excess cancers over a lifetime due to exposure to acetaldehyde would be:

$$30x10^6 \times 0.97\text{-}27x10^{-6}\ ppb^{-1} \times 2\ ppb = 58\text{-}1620 \text{ excess cancers}$$

Using the approach of Gaylor and Kodell, for an ambient level of 2 ppb, the individual risk is $3 \times 10^{-6} \times 2 = 6x10^{-6}$ which yields an estimate of 180 lifetime excess cancers. The predicted numbers would occur in a background of approximately 6 to 8 million cases in this population based on recent cancer data for Los Angeles County and for all of California (World Health Organization 1982, Silverberg and Lubera 1987, Boring et al. 1991).

The range of risk values represents several sources of uncertainty, including statistical uncertainty due to the relatively small number of animals used in the bioassay. Other general sources of uncertainty include the choice of the animal-to-human scaling factors, the choice of the extrapolation model, and the large range of extrapolation (five orders of magnitude) from the adjusted acetaldehyde concentrations used in the animal experiments to current ambient levels. In addition there is the possibility in light of the absence of an epidemiological connection between exposure to acetaldehyde and cancer that the risks in rats and hamsters may not be applicable to humans, i.e., acetaldehyde is only a potential human carcinogen. While a portion of the population is exposed to concentrations of acetaldehyde greater than 2 ppb, others will be exposed to less and thus have a lower risk.

Based on the findings of carcinogenicity and the results of the risk assessment, OEHHA staff find that ambient acetaldehyde is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

9.2.8. Selection of Best Value for Risk Assessment

Using the multistage model, a range of inhalation unit risk values was obtained, from $9.7x10^{-7}$ ppb^{-1} for female rats without a scaling factor to $2.7x10^{-5}$ ppb^{-1} for male rats with a contact area correction (Table 9.2). For simplification of risk assessments a best value is often chosen from the range. In the case of acetaldehyde, a best value of $4.8x10^{-6}$ ppb^{-1} ($2.7x10^{-6}$ $(\mu g/m^3)^{-1}$) was selected. The male rat is more sensitive to tumor induction by acetaldehyde than the female rat and thus is the proper sex to select based on California procedures for cancer risk assessment. The value was obtained from the male rat data using the standard interspecies surface area correction factor. Use of the rat data set has additional health protection built in since it was obtained using tumor data obtained after 28 months of exposure to acetaldehyde which is longer than the normal exposure and observation period for most chemicals of 24 months. This best estimate predicts 288 excess lifetime cancer cases in the California population.

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APPENDIX A

RESULTS OF REPRODUCTIVE AND *IN VIVO* DEVELOPMENTAL TOXICITY STUDIES WITH ACETALDEHYDE

TABLE A-1

RESULTS OF *IN VIVO* REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES WITH ACETALDEHYDE[a]

Species/Strain	Dose	Route of Administration	Duration of Exposure	Results	Comments	Reference
Rat/CF	50, 75, 100 mg/kg	ip	GD: 10, 11, or 12 or 10-12; Sac: D21	↑Resorp; variable in litters with malformations; ↓FW; ↓CRL; ↓TUD; ↓placental wt; ↓rate skeletogenesis	Small sample size, 5-13 litters/group; no dose-response trend. Multiple days of treatment did not increase severity of effect.	Sreenathan et al. 1982
Rat/CF	50, 75, 100, 150 mg/kg	ip	GD: 8-15; Sac: D21	↑Resorp; ↑No. litters with malformations; ↓FW; ↓CRL; ↓TUD; ↓placental wt; ↓in rate of ossification; lesions in placenta	Small sample size, 7-9 dose, ↓in growth parameters all show dose-response.	Padmanabhan et al. 1983
Rat/CF	50 mg/kg	ip	GD: 8-15 Sac: D16-21	Delayed ossification; ↑in litters with malformations	Small sample size, 5-9 litters/group.	Sreenathan et al. 1984
Rat/Sprague-Dawley	100 mg/kg	ip	GD: 9-12 Sac: D12	Reduction in head length	Sample dose size not reported.	Ali and Persaud 1988

TABLE A-1 (continued)

Species/Strain	Dose	Route of Administration	Duration of Exposure	Results	Comments	Reference
Rat/Wistar	0.5 mL of 3% (v/v) solution x2 daily injections (approximately 0-53 mg/kg/inj)	ip	Throughout gestation Sac: D20	↓FW; ↑resorp; ↓litter size	Days of treatment (gestation) not specified; sample size 5-7 litters/group.	Dreosti et al. 1981
Mouse/CD-1	200 mg/kg x5 in 10 hr (total dose 1000 mg/kg)	ip	GD: 10 Sac: D18	No effect on resorptions, FW, or malformations	Small sample size, 8-14 litters/group.	Blakley and Scott 1984a
Mouse/CD-1	200 mg/kg	ip	GD: 10 Sac: 5 min-24 hr postinjection	Maximal acetaldehyde levels within 5 min; undetectable by 2 hr	Acetaldehyde does gain access to fetus.	Blakley and Scott 1984b
Mouse/LACA	2, 4, 6% (approximately 60-480 mg/kg)	ip	GD: 9 Sac: 1-24 hr post-injection	No histopathological changes seen in fetus (light microscopy)	Study limited to light microscopic examination; sample size, 3 dams/group and 3 embryos/dam.	Bannigan and Burke 1982

TABLE A-1 (continued)

Species/Strain	Dose	Route of Administration	Duration of Exposure	Results	Comments	Reference
Mouse/C57BL/6J	320 mg/kg	ip	GD: 6,7, 8, or 9--single injection; 6, 7, 8, or 9--two injections Sac: D18	Nonsignificant ↓FW; slight ↑in % fetuses with head and limb defects	Small sample size, 5-14 litters/group, data set incomplete in that control groups absent for most treatments and FW not reported for each group; makes data essentially uninterpretable.	Webster et al. 1983
Mouse/CFLP	1 or 2% (approximately 40-80 mg/kg)	iv	GD: 7-9 Sac: D10 or D19	No effect on maternal wt gain; dose-related resorp; ↓CRL; ↓FW; ↓PC; ↑No. embryos failing to turn into fetal position (2%), ↑malformations	Small sample sizes/group (7-11) occurrence of terata difficult to evaluate due to small No. litters/treatment. In fact, No. of D10 litters reported in text disagrees with No. in tables.	O'Shea and Kaufman 1979
Mouse/CFLP	0.1 mL (% solution) (approximately 80 mg/kg)	iv	GD: 6, 7, or 8; 6-8; 7-8; or 7-9 Sac: D10 or D12	Day 10 ↑resorp; ↑No. embryos failing to turn to fetal position; ↓CRL and PC; ↑No. malformed	Small sample sizes, approx. 4-9 litters/group; no D12 control groups; no consistent trends seen with ↑No. days of dosing.	O'Shea and Kaufman 1981

TABLE A-1 (continued)

Species/Strain	Dose	Route of Administration	Duration of Exposure	Results	Comments	Reference
Mouse/C57BL/6J xC_3H/He) F_1	62.5, 125, 250 mg/kg	ip	Groups of 5 to 10 male mice were dosed 5 days Sac: 5 weeks after start of treatment	No adverse effects on frequency of micronuclei, count and morphology, and testicular and seminal vesicle weights	The only study available on the toxicity of the male reproductive system, limited number of endpoints specified.	Lahdetie 1988

Abbreviations:

ip = Intraperitoneal.
iv = Intravenous.
GD = Gestation day(s) acetaldehyde was administered.
Sac = Day of pregnancy that dam was sacrificed.
D = Day.
↑ = Increase.
↓ = Decrease.
Resorp = Resorptions.
FW = Fetal weight.
CRL = Crown-rump length.
TUD = Transumbilical distance.
PC = Protein content.

SOURCE: U.S. EPA 1988.

TABLE A-2

RESULTS OF IN VITRO DEVELOPMENTAL TOXICITY STUDIES OF ACETALDEHYDE

Embryo Culture (species/strain)	Dose	Age of Embryo	Results	Comments	Reference
Mouse/C_3H	7.4, 19.7, 39.4 mg/l	Explant: D8 or 9; Examine: 28 hr later	D8 ↓somite count; CNS abnormal; ↓embryonic DNA syntheses. D9: no consistent dose trends	↑rate of development for high-dose group on D9 makes significance of data unclear	Thompson and Folb 1982
Mouse/ICR	17.6 ug/l to 1.7 g/l	Explant: D8.5 Examine: 48 hr later	↑Embryolethality; ↑No. malformed; dose-response in growth retard. (↓DNA and PC; ↓CRL, ↓head length, ↓somite number)	Effects seen at all dose levels (17.6 ug/l)	Higuchi and Matsumoto 1984
Mouse/CF-1	5 to 500 mg/100 ml	Explant: D1.5 Examine: 105 hr	No effects up to 10 mg/100 ml; higher doses lethal	Pre-implantation 2-cell stage mouse embryos highly resistant	Kalmus and Buckenmaier 1989
Rat/Sprague Dawley	5 to 100 uM	Explant: D10 Examine: 25 hr later	Embryolethality at 100 uM growth retard. (↓DNA, ↓PC, ↓CRL, ↓head length)	Effects at all dose levels No dose-response trends for growth retardation	Campbell and Fantel 1983
Rat/Albino	0.20 to 1980 mg/l	Explant: D9.5 Examine: ?	Embryolethality; growth retard. (↓No. somites, ↓PC, ↓cranio-caudal length) ↑malformations	Sample size not provided; dose-response trends present	Popov et al. 1982

TABLE A-2 (continued)

Embryo Culture (species/strain)	Dose	Age of Embryo	Results	Comments	Reference
Rat/Albino	100, 260, and 800 uM	Explant: D10 Examine: Over 48-hr period	No effect at these doses on PC, DNA, somite no., or morphology; embryolethality at 800 uM	Author suggests that differences between his data and those of Campbell and Fantel may be result of using different strains of rats	Priscott 1985

Abbreviations:

D = Day.
= Increase.
= Decrease.
CNS = Central nervous system.
PC = Protein content.
CRL = Crown-rump length.
Retard = Retardation.

APPENDIX B

MUTAGENICITY-GENOTOXICITY TESTING OF ACETALDEHYDE

TABLE B-1

MUTAGENICITY-GENOTOXICITY TESTING OF ACETALDEHYDE

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
GENE MUTATION				
Bacteria				
Salmonella typhimurium (reverse mutations)				
Plate test: Strains				
TA100	-S9	NR[b]	-	Laumbach et al. 1976
TA1535	±S9	0.44 to 110 ug/plate	-	Pool and Wiessler 1981
TA1535, TA1538	-S9	7,938 ug/plate	?[c]	Rosenkranz 1977
Preincubation method: Strains				
TA98, TA100, TA1535, TA1537	±S9	33 to 10,000 ug/plate	-	Mortelmans et al. 1986
TA104, TA102	-S9	1,000 ug/plate	-	Marnett et al. 1985

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
Escherichia coli (reverse mutation)				
Liquid incubation: Strains				
WP2*uvrA*	-S9	0.9-441 ug/ml	-	Hemminki et al. 1980
	-S9	38.8 ug/ml	+ (no dose-response relationship)	Veghelyi et al. 1978
Yeast				
Saccharomyces cerevisiae (mitochondrial mutations)	-S9	23,490 ug/ml for 30, 60, and 90 min	?[d]	Bandas 1982
Nematodes				
Caenorhabditis elegans (mutations affecting egg-laying)	-S9	783 and 7,830 ug/ml for 2 h	+ at 783 ug/ml (no dose-response relationship)	Greenwald and Horvitz 1980
Insects				
Drosophila melanogaster--Canton S (sex-linked recessive lethals)	--	22,500 ppm (injection of adult males; all germ cell stages treated)	+	Woodruff et al. 1985
		25,000 ppm (feeding)	-	

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
CHROMOSOMAL ABERRATIONS				
Plants				
Vicia faba (root-tips)		220.5 to 2,205 ug/ml for 24 h at 12 °C	+DR[e] (breaks and trans-locations)	Rieger and Michaelis 1960
Insects				
D. melanogaster--Canton S (heritable translocations)	--	22,500 ppm (injection of adult males; all germ cell stages treated)	-	Woodruff et al. 1985
Mammalian cell culture				
Rat skin fibroblasts	-S9	4.4 to 441 ug/ml for 12, 24, and 48 h	+DR (micro-nuclei)	Bird et al. 1982
		0.44 to 44.1 ug/ml for 12 and 24 h	+ (gaps, breaks, exchange-type aberrations, acentric fragments)	

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
			+?[f] (aneuploidy)	
Chinese hamster ovary (CHO) cells	-S9	15.66 to 46.98 ug/ml for 24 h	+DR (aneuploidy; chromatid or isochromatid breaks, chromatid exchanges and dicentric chromosomes; polyploidy)	Dulout and Furnus 1988
Human lymphocytes	-S9	7.83 and 15.7 ug/ml for 24 h	+ (gaps, breaks, exchange-type aberrations in Fanconi anemia cells, but was not clastogenic in normal lymphocytes at same dosages)	Obe et al. 1979
Human lymphocytes	-S9	3.97 to 47.6 ug/ml for 72 h	+DR (gaps, breaks, exchange-type aberrations)	Bhlke et al. 1983

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
Whole mammals				
Female rats/treated embryos (13th day of pregnancy)	--	7,830 ug/ml intra-amniotically	+ (gaps and breaks)	Barilyak and Kozachuk 1983
Hybrid male mice	--	0 to 500 mg/kg, single intraperitoneal (ip) injection	No effect on micronuclei frequency of early spermatids	Lahdetie 1988
SISTER CHROMATID EXCHANGE				
Mammalian cell culture				
CHO cells	-S9	3.92 and 7.83 ug/ml for 8 days	+DR	Obe and Ristow 1977
CHO cells	-S9	2 to 11.7 ug/ml for 24 h	+DR	Obe and Beek 1979
CHO cells	±S9	0.78 to 78 ug/ml--plus S9 0.78 to 39.4 ug/ml--minus S9 for 1 h	+DR (response similar +/- S9)	de Raat et al. 1983

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
Human lymphocytes	-S9	3.92 to 15.7 ug/ml for 24 h; 15.4 ug/ml for 48 h	+DR	Ristow and Obe 1978
Human lymphocytes	-S9	15.7 and 78 ug/ml for 3 h	+ (the presence of aldehyde dehydrogenase + NAD slightly reduced the response)	Obe et al. 1986
Human lymphocytes	-S9	3.97 to 7.83 ug/ml for 90 h	+DR	Jansson 1982
Human lymphocytes	-S9	3.97 to 47.6 ug/ml for 72 and 96 h	+DR	Bhlke et. al. 1983
Human whole-blood lymphocyte cultures	-S9	2.8 to 88.2 ug/ml for 48 h	+DR	Norrpa et al. 1985
Human lymphocytes	-S9	4.4 to 13.2 ug/ml for 47 and 70 h	+DR	He and Lambert 1985
		26.5 to 105.8 ug/ml for 1 h	+DR	

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
Whole Mammals				
Male CBA mice	--	0.01 and 0.02 mg/kg (ip injection)	+[g] (almost doubled background frequency at 0.02 mg/kg)	Obe et al. 1979
Male and female Chinese hamsters	--	0.01 to 0.5 mg/kg (ip injection)	+ (almost doubled background frequency at 0.5 mg/kg)	Korte and Obe 1981
OTHER ENDPOINTS INDICATIVE OF DNA DAMAGE				
Bacteria				
E. coli (*polA*$^+$/*polA*$^-$ assay)	-S9	7,830 ug/plate	weakly positive	Rosenkranz 1977

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
Mammalian cell culture (alkaline elution)				
Rat hepatocytes	-S9	1.3 to 132 ug/ml for 3 h	-	Sina et al. 1983
Human lymphocytes	-S9	441 ug/ml for 4 h	-	Lambert et al. 1985
Human bronchial epithelial cells	-S9	up to 44.1 ug/ml for 1 h	-	Saladino et al. 1985
Mouse lymphoma L5178Y/TK$^{+/-}$ cells	±S9	66 to 1936 ug/ml for 3 h	No increase in single-strand breaks	Garberg et al. 1988

TABLE B-1 (continued)

Organism	Metabolic Activation	Concentrations Tested[a]	Reported Result	Reference
(Cell transformation)				
Rat kidney cells, HRPT[4]	-S9	up to 132 ug/ml	Positive for initiation of cell transformation in the presence of tumor-promoting esters	Eker and Sanner 1986

[a]Source: Dellarco 1988.

[b]NR = Not reported.

[c]? = Although a slight increase in TA1535 revertants (16 revertants in treated versus 4 revertants in controls) was reported, the low background frequency renders the results inconclusive. Also, no dose-response relationship was demonstrated.

[d]? = marginal response that is regarded as equivocal because it occurred in the presence of high toxicity and no dose-response relationship was demonstrated.

[e]DR = Dose-related response.

[f]+? = Questionable positive because data for hyperploidy and hypoploidy were combined.

[g]+ = Positive results considered merely suggestive of an effect because only one mouse per treatment was tested and there was no sham-treated negative controls.

APPENDIX C

IARC AND USEPA CLASSIFICATION SCHEMES FOR CARCINOGENS

(*b*) *Experimental carcinogenicity data*

Data relevant to the evaluation of the carcinogenicity of the agent in animals are summarized. For each animal species and route of administration, it is stated whether an increased incidence of neoplasms was observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also indicated. Dose-response and other quantitative data may be given when available. Negative findings are also summarized.

(*c*) *Human carcinogenicity data*

Results of epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also considered.

(*d*) *Other relevant data*

Structure-activity correlations are mentioned when relevant.

Toxicological information and data on kinetics and metabolism in experimental animals are given when considered relevant. The results of tests for genetic and related effects are summarized for whole mammals, cultured mammalian cells and nonmammalian systems.

Data on other biological effects in humans of particular relevance are summarized. These may include kinetic and metabolic considerations and evidence of DNA binding, persistence of DNA lesions or genetic damage in humans exposed to the agent.

When available, comparisons of such data for humans and for animals, and particularly animals that have developed cancer, are described.

13. EVALUATION

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of the carcinogenicity of an agent. In considering all of the relevant data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

(*a*) *Degrees of evidence for carcinogenicity to humans and to experimental animals and supporting evidence*

It should be noted that these categories refer only to the strength of the evidence that these agents are carcinogenic and not to the extent of their carcinogenic activity (potency) nor to the mechanism involved. The classification of some agents may change as new information becomes available.

(i) *Human carcinogenicity data*

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of doses to which human beings are known to be exposed, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, circumstances and doses of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence for the carcinogenicity of the agent for specific organs or tissues.

(ii) *Experimental carcinogenicity data*

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms (as described on p.23) in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is *sufficient evidence* of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic.. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and doses of exposure studied.

(iii) *Supporting evidence of carcinogenicity*

The other relevant data judged to be of sufficient importance as to affect the making of the overall evaluation are indicated.

(*b*) *Overall evaluation*

Finally, the total body of evidence is taken into account; the agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1 — The agent is carcinogenic to humans.

This category is used only when there is *sufficient evidence* of carcinogenicity in humans.

Group 2

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.

Group 2A — The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of *limited evidence* of carcinogenicity in humans or of *sufficient evidence* of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B — The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is *limited evidence* in humans in the absence of *sufficient evidence* in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans or when human data are nonexistent but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3 — The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4 — The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans together with *evidence suggesting lack of carcinogenicity* in experimental animals. In some circumstances, agents for which there is *inadequate evidence* of or no data on carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

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   Number 1 (1973) 52 pages
   Number 2 (1973) 77 pages
   Number 3 (1974) 67 pages
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   Number 6 (1976) 360 pages

and well-conducted animal studies in different species.

The classifications "sufficient evidence" and "limited evidence" refer only to the weight of the experimental evidence that these agents are carcinogenic and not to the potency of their carcinogenic action.

C. Categorization of Overall Weight of Evidence for Human Carcinogenicity

The overall scheme for categorization of the weight of evidence of carcinogenicity of a chemical for humans uses a three-step process. (1) The weight of evidence in human studies or animal studies is summarized; (2) these lines of information are combined to yield a tentative assignment to a category (see Table 1); and (3) all relevant supportive information is evaluated to see if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor information from human and animal studies include structure-activity relationships; short-term test findings; results of appropriate physiological, biochemical, and toxicological observations; and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause one to adjust the overall categorization of the weight of evidence.

TABLE 1.—ILLUSTRATIVE CATEGORIZATION OF EVIDENCE BASED ON ANIMAL AND HUMAN DATA [1]

Human evidence	Animal evidence				
	Sufficient	Limited	Inadequate	No data	No Evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

[1] The above assignments are presented for illustrative purposes. There may be nuances in the classification of both animal and human data indicating that different categorizations than those given in the table should be assigned. Furthermore, these assignments are tentative and may be modified by ancillary evidence. In this regard all relevant information should be evaluated to determine if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor data from human and animal studies include structure-activity relationships, short-term test findings, results of appropriate physiological, biochemical, and toxicological observations, and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause an adjustment of the overall categorization of the weight of evidence.

The agents are categorized into five groups as follows:

Group A—Human Carcinogen

This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.

Group B—Probable Human Carcinogen

This group includes agents for which the weight of evidence of human carcinogenicity is based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups. Usually, Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies. It is reasonable, for practical purposes, to regard an agent for which there is "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under Group B2.

Group C—Possible Human Carcinogen

This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, e.g., (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background rate.

Group D—Not Classifiable as to Human Carcinogenicity

This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E—Evidence of Non-Carcinogenicity for Humans

This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

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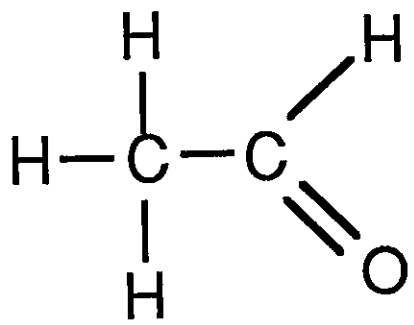
California Environmental Protection Agency

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

This document has been reviewed by the staff of the Air Resources Board and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board or the Office of Environmental Health Hazard Assessment, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

TABLE OF CONTENTS

PART C

I. Comment Letters Received on the August 1992 Preliminary Draft of the Acetaldehyde Report 1

A. Arthur D. Little, Inc. 2

B. Chevron Research and Technology Company 3

C. Motor Vehicle Manufacturers Association 6

D. The Earth Technology Corporation (TETC) 10

II. Air Resources Board Staff Responses to Summarized Comment Letters on the Preliminary Draft Part A and the Executive Summary 17

Oral Comment and ARB's Response 24
A. Takayuki Shibamoto Ph.D. 24

III. Office of Environmental Health Hazard Assessment Staff Responses to Summarized Comments on the Preliminary Draft Part B and the Executive Summary 25

PART C ADDENDUM 26

I.

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

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August 20, 1992

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

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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 Schwehr, Dean Saito (I think), Dean Simeroth + Janette Brooks.

John

Chevron

Chevron Research and Technology Company
1003 West Cutting Boulevard, Richmond, California
Mail Address: P.O. Box 4054, Richmond, CA 94804-0054

Environmental Group

September 28, 1992

OCT 1992
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TAC ID SSD

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.

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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. <u>We recommend the following information be included</u>;

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, <u>we recommend that OEHHA and the Scientific Review Panel also carefully consider</u>

<u>two specific issues associated with the quantitative risk assessment</u>.

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

OCT 1992
RECEIVED
TAC ID SSD

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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Tel. No. 313-872-4311 • Fax No. 313-872-5400

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

SEP 1992
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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)

R.S.

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

KEA:jlh
92-2811-02\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

- **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.

- **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

This document has been reviewed by the staff of the Air Resources Board and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board or the Office of Environmental Health Hazard Assessment, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

TABLE OF CONTENTS

PART C ADDENDUM

I. Comment Letters Received on the April 1993 Scientific Review Panel Version of the Acetaldehyde Report 28

A. American Automobile Manufacturers Association 29

B. American Bakers Association 31

C. Chevron Research and Technology Company 52

II. Air Resources Board Staff Responses to Summarized Comments on the SRP Version Part A and the Executive Summary 55

III. Office of Environmental Health Hazard Assessment Staff Responses to Summarized Comments on the SRP Version Part B and the Executive Summary 58

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

1993 MAY
Received
TAC ID
BRANCH

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

MAY 1993
RECEIVED
TAC ID SSD

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.

<u>Recommendation</u>: 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 (4μg/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 μg/m^3) to 39 ppb (70.2 μg/m^3). The most recent data cited by the ARB for this region (1987) reported acetaldehyde concentrations ranging from 0.9 ppb (1.6 μg/m^3) to 24.5 ppb (44.1 μg/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 μg/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 μg/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

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**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

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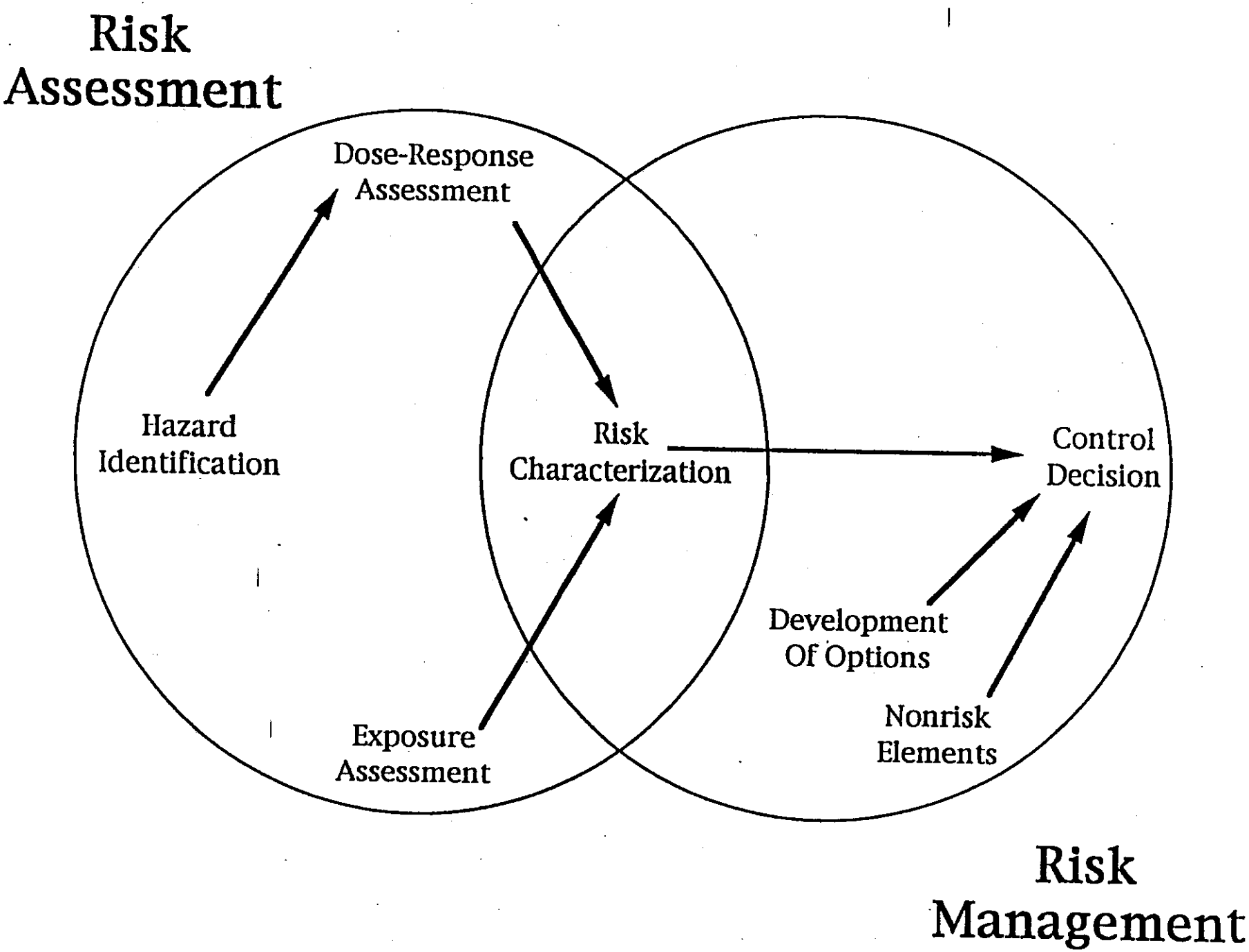
2020 L Street
Sacramento, CA 95812


Risk
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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.

OEHHA Responses to Comments by Chevron

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^*).