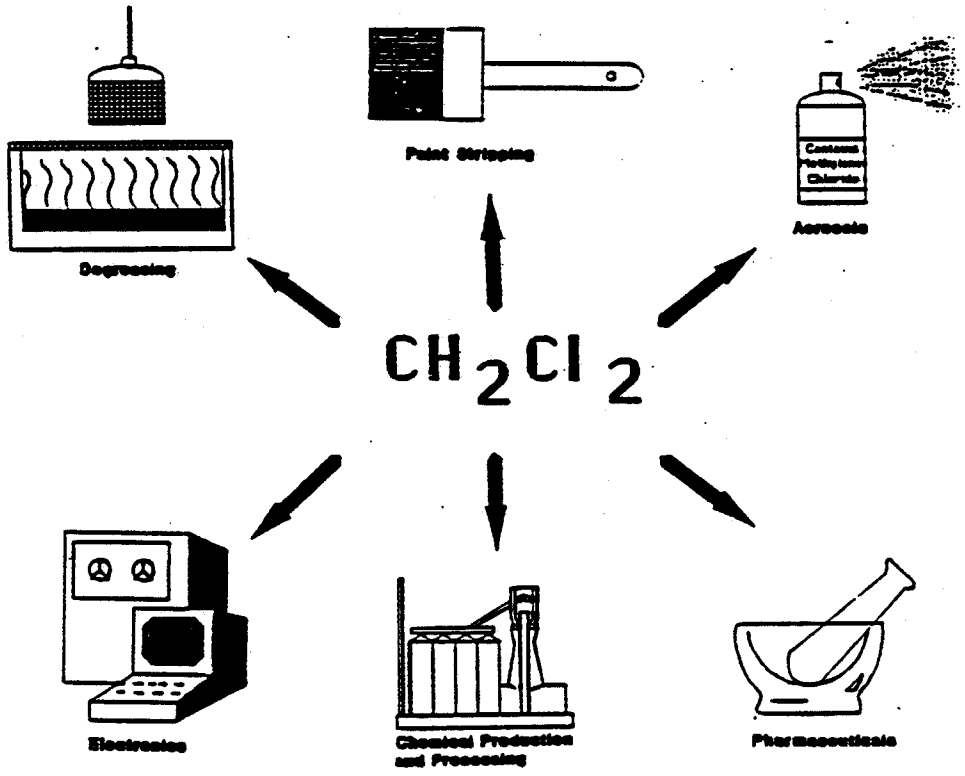
TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF METHYLENE CHLORIDE AS A TOXIC AIR CONTAMINANT

Part C Report



State of California
Air Resources Board
Stationary Source Division

May 1989

FINAL DRAFT

PART C - PUBLIC COMMENTS AND RESPONSES TO THE DRAFT PART A AND B METHYLENE CHLORIDE REPORT

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

May 1989

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A. Comments from the Halogenated Solvents Industry Alliance

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January 14, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Methylene Chloride
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

The Halogenated Solvents Industry Alliance (HSIA) offers the enclosed comments on the preliminary draft Report to the Air Resources Board on Methylene Chloride (Parts A & B).

HSIA is an association of producers, distributors, importers, and users of halogenated solvents, including methylene chloride. Our members, as well as other users of methylene chloride, have a vital interest in the accuracy and scientific validity of the Report.

Sincerely,

Paul A. Cammer

Paul A. Cammer, Ph.D.
President

Enclosure

BEFORE THE CALIFORNIA AIR
RESOURCES BOARD

Comments of the Halogenated Solvents Industry Alliance on the Preliminary Draft Report to the Air Resources Board on Methylene Chloride (Parts A & B)

Paul A. Cammer, Ph.D.
President
January 14, 1988

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INTRODUCTION AND SUMMARY

The Air Resources Board is considering whether methylene chloride should be identified as a toxic air contaminant. Such an identification requires a finding that methylene chloride "may cause or contribute to an increase in mortality or an increase in serious illness, or may pose a present or potential hazard to human health" under Section 39655 of California's Health and Safety Code.

The Halogenated Solvents Industry Alliance (HSIA) is an association of producers, distributors, and users of halogenated solvents, including methylene chloride. The comments that follow provide HSIA's views on both parts of the preliminary draft Report to the Air Resources Board on Methylene Chloride (The "draft Report"), dated November 1987. Our members, as well as other users of methylene chloride, have a vital interest in the accuracy and scientific validity of the Report.

Biological data on methylene chloride are extensive. When the bioassay results are interpreted in light of these data, described in detail below, the weight of the evidence strongly suggests that levels of methylene chloride in the California environment do not pose a human cancer risk.

First, well-conducted epidemiology studies show no evidence of an increased overall cancer risk or risk at the primary sites associated with lesions found in animal studies. This situation differs significantly from one in which only animal evidence is available and a regulatory agency has little choice other than to treat the substance as if it were a human carcinogen.

Second, methylene chloride does not appear to be acting by a direct genotoxic mechanism. In light of the overall negative results in genetic toxicity studies in higher order animals, including several important DNA-binding studies, genotoxicity would not appear to be a significant factor in inducing tumorigenic effects.

Third, the evidence for induction of lung and liver tumors in mice was obtained at toxic doses. Studies suggest that cytotoxic damage in the lungs of the mice exposed at the dose levels of the NTP study played a significant role in the enhanced lung tumor response observed. Cytotoxic effects were not observed in the rats. This difference is consistent with the known metabolic differences between lung tissue of mice, rats, and humans.

Fourth, available metabolic data indicate that substantial quantitative differences between species exist. Moreover, in vitro metabolism data are available to explain the observed sensitivity of the mouse. These data, coupled with the

high spontaneous lung and liver tumor incidence normally found in B6C3F1 mice, suggest that the mouse is a less appropriate model than the rat or hamster for predicting potential human response to this chemical.

The final version of the Report should provide the staff's reasoning in its hazard identification. It is not adequate simply to state, as the draft Report does, that (IARC) the International Agency for Research on Cancer and EPA have found the animal evidence to be sufficient and consider methylene chloride to be a probable human carcinogen. Indeed, it is incorrect to state that IARC considers methylene chloride to be a probable human carcinogen. At the same time that IARC decided to place methylene chloride in its Group 2B, it changed the terminology describing that category from "probably carcinogenic to humans" to "possibly carcinogenic to humans." This change reflects increasing awareness of the fact that classification decisions (such as IARC's) based strictly on a scoring of the bioassay evidence for carcinogenicity cannot adequately serve to characterize the overall likelihood of a substance to cause cancer in humans.

In addition, EPA's most recent assessment (the draft HAD Update) is currently being reviewed by their Science Advisory Board, which may take issue with EPA's classification of methylene chloride. Moreover, EPA is expected in the near future to reassess its Guidelines for Carcinogen Risk Assessment, in

order to take into account developments since they were proposed in 1984 and published in 1986. These include scientific advances enabling toxicological evidence to be better taken into account in the hazard identification stage and the changes in the IARC terminology.

PART A

Part A of the draft Report concerns public exposure to, and sources of, atmospheric methylene chloride in California. HSIA does not have detailed information on current ambient exposures to methylene chloride in California and cannot offer a thorough review of Part A at this time. We note that the draft Report states (page III-3) that methylene chloride use "is expected to decline due to health concerns and the possibility of governmental regulation." In summarizing methylene chloride use in Table III-1, however, estimates of current U.S. use are based on information provided by HSIA for calendar year 1983. A more realistic estimate of current U.S. use would be 497 million pounds for 1987 from an estimate by Dow Chemical Company (USA) based on current government data.

The Air Resources Board used emissions and meteorological information to estimate the ambient concentration of methylene chloride associated with operations at three different industrial facilities. The Report states that the Industrial Source Complex

Short Term (ISCST) model was used to estimate the annual average concentrations. The ISCST model is designed to estimate short-term (one to twenty-four hour) averages, not annual averages. Annual average concentrations should be estimated using a statistical summary of recorded meteorological data rather than sequential data and the long-term version of the model (ISCLT).

Hourly meteorological data should be used when short term maximum concentrations are being estimated. The hourly data allow the user to estimate short term peaks in concentrations associated with specific meteorological phenomena. If an annual average is being sought, use of a statistical summary of meteorological data is preferred as this format allows the model to consider multiple years of data (summaries are usually made from five or ten years of data) in determining the annual average concentrations.

The ISC model series includes two separate models; one for estimating short term concentrations (ISCST) and the other for use in estimating annual averages (ISCLT). ISCLT differs from ISCST on two very important points:

(1) estimated concentrations are averaged over the sector in question and "smoothed" between sectors to avoid discontinuity, and

(2) a maximum of 16 wind direction sectors is allowed rather than the 36 sectors used by the ISCST model.

The effect of both of these points is to reduce the estimated concentration in most cases. The first point recognizes the normalizing effect that the wind direction variability throughout the year would have on the annual average concentration. Secondly, since concentrations calculated by ISCST using 36 sectors (10 degrees each) can be no more than 5 degrees off the maximum centerline concentration, most calculated concentrations would be greater than if the emissions were spread over a 22.5 degree sector (the smallest allowed by ISCLT's requirement that no more than 16 sectors be considered) following the algorithm in the ISCLT model.

The Report also states that the emissions from the automobile assembly plant were modeled as an area source even though methylene chloride is actually emitted from a series of stacks. Modeling the emissions as though they emanated from an area source rather than stacks does not recognize the benefits of enhanced dispersion due to the velocity and temperature of the exhaust as it exits the stack. The ISCST model does allow the user to input an effective emissions height to account for the "plume rise" due to the momentum and/or buoyancy of the exhaust but the Report does not say if an effective emission height was calculated and used in this analysis.

The draft Report (pages II-4 and II-5) uses Gleit's method to estimate mean concentrations of methylene chloride below the level of quantification of the monitoring stations.[1] Although Gleit's method has been shown to outperform the current EPA policy of replacing monitored values below the detection limit with the detection limit, the method was designed to determine a mean for comparison with a specific value (e.g. a standard). The Air Resources Board has no specific value with which it can compare the data; rather, the Air Resources Board conducted the monitoring study to assess the potential health hazard that may be posed by existing levels of methylene chloride in the ambient air. For this purpose, a summary of the data, including the percent of data below the dection limit and a range of possible average concentrations (assuming all missing data are equal to zero for the lower limit of the range and all missing data are equal to the detection limit for the upper limit of the average) would be more informative.

The statement in the draft Report that water chlorination is a source of environmental methylene chloride seems in error. The kinetics of reaction between chlorine and organic material in water is such that only chloroform is released to any appreciable extent.[2]

The draft Report should integrate the pharmacokinetic information addressed in Part B with the exposure information in Part A. Health effects information suggests that the effects of methylene chloride at high exposure levels are unlike the effects after chronic low exposure. An analysis of the pharmacokinetics of methylene chloride provides an explanation for this difference.

Appendix A contains some detailed technical comments on Part A of the draft Report.

PART B

Part B of the draft Report concerns the health effects of methylene chloride. The Executive Summary concludes that environmental levels of methylene chloride in California are well below any known acute and noncarcinogenic chronic levels that may cause adverse health effects. This conclusion is adequately supported by the available data and by reviews by other scientific panels, including EPA's Science Advisory Board.

Because methylene chloride exposures are widespread, albeit very low, it is appropriate for the draft Report to assess the possibility of human carcinogenic effects. However, because it

concludes that methylene chloride may pose a cancer risk to humans at ambient concentrations, and presents estimates of human cancer risk derived by applying an essentially linear (multistage) model to the positive results from a single animal bioassay, the draft Report is seriously flawed. The draft Report wrongly interprets available human data, incorrectly assumes that methylene chloride is genetically active with mammalian cells, and fails to make use of available data on metabolism, pharmacokinetics, and mechanism. Most significantly, it fails to address the overall weight of the evidence as to carcinogenicity, and fails to use more biologically motivated extrapolation models. These points are addressed in turn below. If all the available data were taken into account, the draft Report would not conclude that methylene chloride is a probable human carcinogen at ambient environmental (or workplace) concentrations.

Epidemiology

The best scientific evidence addressing the potential carcinogenicity of a substance in humans is provided by studies of human populations actually exposed to the substance (i.e., epidemiology studies). Two well-conducted epidemiology studies have been completed on worker populations exposed to methylene chloride. They show no evidence of an increased overall cancer risk. The draft Report is seriously deficient in failing to

recognize that these studies provide no indication that methylene chloride has had a carcinogenic effect in workers exposed for many years on a daily basis to concentrations from 3,000 to 100,000 times higher than the three parts per billion cited in the draft Report (page i-2) as the average ambient concentration in California.

The first of these studies, of employees at an Eastman Kodak Company plant in Rochester, New York, compares mortality rates of over 1000 employees with identified methylene chloride exposure to mortality rates for an unexposed worker population, as well as to the overall mortality of upstate New York males.[3] This study indicates that workers exposed to methylene chloride for an average of 22 years actually had a decreased incidence of cancer mortality when compared to either of the comparison groups. The study demonstrates no unusual mortality patterns for such hypothesized causes as lung and liver malignancy, and concludes that there is no evidence of an increased mortality risk for lung cancer. As to mammary gland and liver tumors, the authors acknowledged that there are power limitations. With respect to lung tumors, however, they concluded that the study is sufficiently powerful that it would detect relative risks of increased lung cancer mortality of at least 1.6. Thus, the Eastman Kodak study would adequately detect any statistically meaningful increase in realtive risk caused by a carcinogen, although power limitations obviously would prevent detection of a very weak carcinogen.

Significantly, the authors compared the number of excess lung and liver cancer deaths observed in their study with the number predicted from the results of the NTP inhalation study using a mathematical extrapolation model very similar to that used in the draft Report.[4] They found that:

> [a]lthough 36.3 deaths were predicted, only 14 were observed, a highly significant difference . . . . Thus, the projections based on animal data were clearly inconsistent with human experience.

Rather than acknowledging that the Kodak study is most plausibly interpreted as indicating that exposure to methylene chloride at workplace levels does not pose an increased risk of lung cancer, the draft Report interprets it as a positive study. The draft Report states (page 7-3) that the Kodak study suggests a relationship between exposure to methylene chloride and pancreatic cancer mortality. Accordingly, it concludes (page 7-5) that risk estimates based on positive results in the animal studies are consistent with the human data. This analysis is flatly inconsistent with that of the study authors and, indeed, that of EPA, which concluded in a recent draft Update to the Health Assessment Report and Addendum for Dichloromethane (the "draft HAD Update")[5] (page 94) that

> the increase in pancreatic tumors may merely reflect the fact that a few apparent increases, even statistically significant increases, can be expected (even when no excess exists), due to chance alone. The increase in pancreatic tumors cannot be considered an unequivocal positive response and should not be interpreted as evidence that methylene chloride is a human carcinogen.

The draft Report uses the pancreatic tumor findings in a scientifically inappropriate way. An epidemiologic study that examines a large number of end points can be expected to produce false positives. In the Kodak study, the pancreas was the only site for which there was an increase in mortality above projected values. At sites where increases were hypothesized, such as lung and liver, mortality was below that expected. Moreover, deficits comparable in magnitude to the increase of pancreatic lesions were reported for two sites, colon-rectum and genito-urinary organs. It should also be noted that of the 34 deaths that have occurred in the cohort during the past two years (1985-1986), none has been due to pancreatic cancer.

A detailed discussion of this epidemiology study prepared by Eastman Kodak is contained in Appendix B.

The other epidemiology study of methylene chloride examined the health and mortality of over 1200 employees exposed to a mixture of methylene chloride, ethanol, and acetone in a fiber production plant.[6] The study showed no excess mortality from cancer in the workers exposed to methylene chloride, even though exposures had ranged up to 475 parts per million and over 300 of the workers had been followed at least 17-1/2 years after exposure. Some of the workers were exposed for over 30 years.

This study is currently being updated by Epidemiology Resources, Inc. (the New England Epidemiology Institute) to address certain weaknesses: analysis of exposure categories, reference population, number of employees lost to follow-up and length of the follow-up period.

Completion of the updated study will address the deficiencies outlined in the draft Report and will provide additional information that should be taken into account in assessing whether methylene chloride poses a cancer risk.

Genotoxicity

The draft Report correctly states that methylene chloride is weakly mutagenic in bacteria. It further states that methylene chloride has been shown to damage chromosomes in mammalian cells, and that methylene chloride should be classified as genotoxic.

Recently completed studies, however, have shown no DNA alkylation in lung and liver tissues from mice and rats exposed to high concentrations of methylene chloride. These results suggest that methylene chloride does not act directly on mammalian DNA. The genetic potential of methylene chloride is addressed extensively below.

The only consistent unequivocal positive responses across laboratories for methylene chloride genotoxicity are in genetically altered Salmonella bacteria used in the Ames assay. The positive response appears to be due to (1) the ability of the bacteria to metabolize methylene chloride to a transient reactive intermediate(s), (2) the close proximity of the unprotected DNA to the transient intermediate(s) (lack of a nuclear membrane), (3) the lack of effective DNA repair processes, and (4) the enhanced permeability of the Salmonella bacterial cell wall. These factors combine to provide an indicator of biologically reactive intermediate formation that is not predictive of effects in higher animals. The proposed reactive intermediates would not be likely to affect the protected mammalian genome due to their transient nature.[7]

As one moves up the phylogenetic tree to mammalian cells or whole animals, consistent positive responses disappear and, overall, methylene chloride appears to have little if any toxicologically relevant genotoxic activity. In yeast, methylene chloride was found to be negative in Saccharomyces cerevisiae

strain D3 and positive in strain D7.[8,9] The positive response was only observed after one hour of incubation at a test concentration (157 mM) which was lethal to 58 percent of the yeast cells. A 34 percent reduction in dose to 104 mM was devoid of significant genetic activity in this assay, thus stressing the steepness of the apparent dose-responsive curve. Interestingly, four hours of incubation with strain D7 (rather than one hour) resulted in only marginal effects. Considering all of these uncertainties (high dose, toxicity, narrow window of apparent activity, apparent lack of activity in other yeast strains), methylene chloride is not likely to be mutagenic for yeast.

Progressing to insects, two studies have been reported in Drosophila melanogaster fruit flies. Abrahamson and Valencia evaluated methylene chloride in a sex-linked recessive lethal assay either by feeding or by injection.[10] In the feeding study the flies may not have been adequately challenged because of the volatility of methylene chloride. However, injection of methylene chloride resulted in a dose-related increased mortality (up to 30 percent) indicating that this element of the study did provide an adequate challenge. Methylene chloride did not produce a mutagenic response.

In a second study, Gocke et al. exposed Drosophila to either 125 or 620 mM methylene chloride by feeding in 2 percent DMSO and 5 percent saccharose.[11] The highest dose reported was near the LD_{50}. A statistically significant increase in the

frequency of sex-linked recessive lethal mutations was reported in this study in one of three broods, after combining the two treatment groups. Neither individual dose group differed statistically from the control value.

Several factors impinge on the interpretation of the Gocke study. It is not clear whether the experiment was adequately controlled. The control value to which the treatment values were compared represented accumulated values from all of the experiments conducted (on many different compounds).. At least four different solvents (vehicles) were used from which the control values were tabulated. There is no way to tell from the data, as presented, what contribution these different solvents made to the final control values. Thus, the overall control value may have underestimated the true value which might have arisen for a particular solvent and therefore overestimated the test chemical response. Furthermore, the cumulative control values for broods 1, 2 and 3 showed enough variation (0.14-0.39 percent) that the biological significance of the brood 1 response, which was the only significant response, becomes questionable. Only by combining both treatment groups in brood 1 (125 and 620 mM) was a significant response attainable; that is, neither individual group differed statistically from the cumulative control value. Thus, this study provides only suggestive evidence for genotoxic activity of methylene chloride,

and coupled with the negative study by Abrahamson and Valencia, suggests the true biological relevance of the reported positive result to be low.

With respect to mammalian cells, methylene chloride did not induce a genotoxic response in several assay systems, including neoplastic transformation in studies in BALB/C-3T3 and C3H-10T1/2 cells, respectively.[12] While reagent grade methylene chloride gave positive transformation results in a F1076 cell line, this effect was not repeatable with purified food grade methylene chloride.[13] Methylene chloride did not induce unscheduled DNA synthesis (UDS) based on the results of Jongen et al., Andrae and Wolff, and Trueman et al.[14] The study by Trueman et al. is particularly significant since UDS was not induced either in vitro, in rat hepatocytes or in an in vivo/in vitro assay in hepatocytes from mice and rats exposed to high concentrations of methylene chloride. The "marginal positive" response reported by Thilagar et al. reflects a low but statistically significant increase in unscheduled DNA synthesis. The biological significance of such a low response is debatable. Methylene chloride has been found to be negative in CHO V79 and mouse lymphoma mammalian cell gene mutation assays.[15] Most recently, methylene chloride was evaluated and found to be negative in the mouse micronucleus test.[16]

One other system with seemingly consistent positive

responses to methylene chloride is in vitro cytogenetics.[17] At an Environmental Mutagen Society meeting in the spring of 1985, a symposium was conducted which indicated that acid, salts, and sugar can give positive in vitro chromosomal aberration results by affecting the osmolality and pH of the media (even when neutralized). In addition, cell toxicity or pharmacologic effects may be significant for the induction of chromosomal aberrations in vitro via peroxide or free radical formation. A study by Dutton and Bowden describes the concept of releasing "clastogenic factors" within the cell.[18]

The implication of these observations is that induction of chromosomal aberrations in vitro may in some cases be caused by a secondary effect on DNA through the release of intracellular factors rather than a direct chemical-DNA interaction. Thus, lowering the dose, which would preclude the events leading to the secondary effect should preclude effects on the genome. It is likely that such secondary events occurred with methylene chloride in some of the in vitro chromosomal aberration systems. Importantly, the results of Burek et al. and Gocke et al. show no induction of chromosomal effects when methylene chloride is evaluated in whole animals (in vivo cytogenetics and a micronucleus assay, respectively).[11, 19]

Finally, the potential for methylene chloride labelled with radioactive carbon to alkylate target tissue DNA has been evaluated by Schumann and coworkers.[20] Rats and hamsters were

exposed to 3,500 ppm of methylene chloride labelled with radioactive carbon for 1.5 to 3 hours and the DNA from liver and salivary tissue was isolated and purified. While radioactive carbon activity was associated with DNA in these tissues (more in the hamster, which was negative in a chronic toxicity bioassay), it appeared associated only with normal bases and nucleosides, indicating radioactive carbon incorporation by normal biosynthetic pathways (one carbon pathway pool labeling). Importantly, no alkylated bases or nucleosides were identified at low levels of detection (12 and 1 alkylation(s) per 10-6 nucleotides per fraction for nucleosides and bases, respectively). Similar in vivo experiments have now been conducted by Green and coworkers, using mouse and rat lung and liver tissue.[21] This study allowed for distinction between incorporation derived from alkylation of DNA by methylene chloride or its metabolites as opposed to incorporation via the normal C-1 metabolic pool. Again, there was no evidence for the formation of DNA adducts in either species, but the incorporation of the radioactive carbon activity via the single carbon pool was evident.

These results suggest that neither methylene chloride nor any of its metabolites act directly on mammalian DNA. This is consistent with the absence of a clear carcinogenic effect in the lungs and livers of the rats and hamsters that have been tested, and with the hypothesis, supported by experimental data, that the positive results in the mice are related to the

peculiar mechanism and metabolism of methylene chloride in that animal species.

Metabolism and Pharmacokinetics

While it is encouraging that the state recognizes the potential of physiological-pharmacokinetic (PB-PK) models for improving the accuracy of risk assessments, it is obvious that the department does not yet have a good understanding of this technique.

Many of the objections raised by DHS (which were cited by EPA in their 1985 document) as limiting the use of PB-PK have been addressed in recent studies sponsored by Dow Chemical and CEFIC and are no longer pertinent. EPA has summarized and intepreted these data in their recent draft HAD update.[5] Furthermore, significant misunderstandings of the PB-PK model are evident in DHS's statements about the role of metabolism of methylene chloride. It is not true that both pathways are equally utilized at low concentrations as stated in section 2 (page 19), and the fact that tumors increase with dose at high concentrations is completely consistent with a protective effect of the saturable MFO pathway at low doses. It is noteworthy that

the USEPA, the Canadian government, and several European governments have recently incorporated the technique into their own hazard evaluations for methylene chloride.

The draft Report fails to make use of available information on animal and human metabolism, particularly in hazard identification. A casual reader of the draft Report would not suspect that methylene chloride has been more widely studied in terms of metabolism and pharmacokinetics than virtually any other industrial chemical. The draft Report also indicates a misunderstanding of metabolism and pharmacokinetics at several points. Although the Executive Summary (page ii-2) indicates that the glutathione-S-transferase pathway is responsible for the carcinogenic response in mice, the supporting text rejects this concept. Using new studies from Dow Chemical and Imperial Chemical Industries P.L.C., the available PB-PK models show a correlation between glutathione-S-transferase activity in various animal species and tumorigenesis. Further, human glutathione-S-transferase enzyme activity now has been measured with methylene chloride as a substrate in these same laboratories. Since this is cited as one of the reasons that California did not choose the PB-PK model, these data need to be integrated and utilized in determining whether methylene chloride poses a cancer risk to humans at low concentrations. EPA has recognized in the draft HAD Update (page 29) that a PB-PK model should be used as part of any quantitative risk assessment for methylene chloride.[5]

One reason for the draft Report's inadequacy is its failure to make use of the results of current research efforts sponsored by the European Council of Chemical Manufacturer's Federation (CEFIC) and Dow Chemical Company (USA). These research programs began in late 1985, and draft and final reports have been provided to the Air Resources Board staff as they have become available.[22] The CEFIC work provided much of the data evaluated in EPA's draft HAD Update and was recently cited by members of EPA's Science Advisory Board as "indicat[ing] that methylene chloride is probably not a human carcinogen."[23] Yet these studies are not used or cited in the draft Report.

The results of the latest research strongly support earlier indications that the National Toxicology Program (NTP) mouse bioassay (discussed below) is not appropriate for evaluating the human health effects of methylene chloride, due to the peculiar metabolism of the mouse. Because of important species differences in metabolism, the mouse does not accurately predict toxic responses in rats, hamsters, or humans.

Methylene chloride is metabolized via two pathways: (1) an oxidative pathway (MFO) involving cytochrome P-450 that appears to yield carbon monoxide (CO) as well as considerable amounts of carbon dioxide (CO_2), and (2) a glutathione dependent pathway (GSH) that produces CO_2 but not CO. In vitro metabolism studies conducted to date utilizing human, mouse, rat, and

hamster liver fractions have indicated that the metabolic rate of the GSH pathway is significantly higher in the mouse than in the rat and that metabolism by this pathway was lower still in either the hamster or man.[24]

Further in vitro metabolism studies across species have been conducted using radiotracer techniques in an attempt to lower the detection limits of the earlier work. These studies detected measurable levels of glutathione-S-transferase enzyme activity (GST) that utilizes methylene chloride as a substate in mouse, rat, hamster, and human tissues. Measurements indicate that the highest level of enzyme activity is found in mouse tissue, a significantly lower level is found in rat tissue, and very low levels of activity are found in hamster and human tissue. This is consistent with the earlier findings of significant species differences in the metabolism of methylene chloride. The levels of GST found in human tissues are in substantial agreement with those estimated from allometric scaling by Anderson and coworkers.[25]

CEFIC studies completed in late 1986 determined the in vivo pharmacokinetics of methylene chloride and its major metabolites, CO and CO_2, in rats and mice both during and immediately after inhalation exposure to 500, 1,000, 2,000 and 4,000 ppm methylene chloride, the dose levels in the NTP study.[26] Saturation of the MFO pathway occurred at 500 ppm exposure. There was evidence for significant metabolism of methylene chloride in the mouse at

higher dose levels (exceeding 500 ppm) by the GSH pathway, which produces CO_2. Measurements after 4,000 ppm exposure for six hours showed almost an order of magnitude more CO_2 produced per kg body weight in the mouse than the rat, even allowing for increased MFO contribution. Overall, saturation of the MFO pathway occurred at similar levels in both species, but significantly more methylene chloride was metabolized by the GSH pathway in the mouse when assessed either from the blood levels of methylene chloride or by CO_2 formation at high dose levels. These data add to the weight of evidence indicating that, in view of its metabolic differences, the mouse is not a good model for predicting methylene chloride's effect on humans.

The extent of species differences is apparent upon application of a PB-PK model, which, by taking into account known physiological and biochemical factors, allows accurate estimation of the "internal" target tissue dose of methylene chloride or metabolic products.[25] Such models allow comparison of the "internal dose" across species (e.g., mice, rats, hamsters, man) as well as across routes of exposure (drinking water versus inhalation) and therefore allow a more informed comparative evaluation as to the relative hazard posed by exposure to methylene chloride.

A significant aspect of PB-PK modeling, in terms of hazard evaluation for humans, is its indication that the MFO pathway does not correlate with tumorigenicity. In mice,

approximately equal amounts of MFO metabolites are produced in the lung and liver at the nontumorigenic dose of 250 mg/kg and at 2,000 ppm. Very small amounts of GSH metabolites are produced at 250 mg/kg of methylene chloride in the drinking water, but significant (100-fold) lower amounts are produced at 2,000 ppm. As long as the MFO pathway is not saturated, so that there is relatively little metabolism of methylene chloride via the GSH pathway, the tumor incidence in mice does not appear to increase above background levels.

A PB-PK model also has been used to compare internal dose estimates of methylene chloride metabolites in the lung and liver of mice and humans over an exposure concentration range of 4,000 to 1 ppm methylene chloride for six hours. There is significantly less MFO metabolism in humans. Moreover, the target tissue concentration of metabolites via the biologically relevant GSH pathway was found to be significantly lower in humans at non-saturating exposure concentrations. This is in contrast to the body surface area procedure used by the Department of Health Services, which would predict that humans are most sensitive to a given concentration of methylene chloride than mice.

Thus, there are important, known differences between mice and humans with respect to the bioactivation of methylene chloride. These differences indicate that the tumorigenic

effects observed in the NTP study in B6C3F1 mice would not occur in humans exposed to ambient environmental or workplace levels of methylene chloride.

In addition to the value of the metabolic and pharmacokinetic data in predicting whether environmental or workplace concentrations of methylene chloride would pose a cancer risk to humans, a PB-PK model provides a way to incorporate these data into quantitative risk assessment. Use of a PB-PK model allows for a more realistic estimate of upper-bound risk, where such a calculation is desirable to assess the potential risk from methylene chloride if it were carcinogenic to humans. Any use of such estimates should make clear that the weight of the evidence does not support a conclusion that environmental concentrations of methylene chloride in California pose a carcinogenic risk, and that the risk, if any, could be anywhere between zero and the calculated upper-bound value. The use of upper-bound estimates is inconclusive, precisely because the risk could be zero.

It is generally agreed that, where metabolic and pharmacokinetic information is available, a low-dose extrapolation model that takes these data into account is more appropriate biologically than the linearized multistage procedure. While the draft Report (page E-4) acknowledges that use of the PB-PK model "may substantially improve the basis of risk assessment," it rejects use of the model for several

reasons, the most significant being absence of validation. None of the mathematical models used to generate risk estimates in Table 8-8 have been biologically validated, and those models incorporate a greater range of assumptions than the PB-PK model. The PB-PK model of Anderson and coworkers was validated with four sets of data from B6C3F1 mice, F344 rats and human volunteers.[25] None of these data sets were used in the derivation of model parameters, as erroneously stated in the draft Report. Consequently, rejection of the PB-PK model on these grounds seems totally unwarranted. Moreover, data from the CEFIC research program, including three reports issued in October 1987, are providing additional experimental validation in several critical areas. As indicated above, preliminary and final reports of this research are being provided to the Air Resources Board as they become available.

The draft Report indicates (page i-1 and elsewhere) that both MFO and GST pathways "theoretically" produce metabolites that may interact with DNA. There is no experimental evidence for this view. As described above, neither pathway led to observable DNA alkylation in intact animals. The draft Report also states page ii-2 that a PB-PK model is not needed because there is no evidence for "saturation" in the tumor incidence data. This statement misses the point of the need for a PB-PK model to account for the higher affinity, lower capacity MFO pathway which protects animals until it becomes saturated. In addition, this statement misinterprets the tumor incidence

record. For example, for combined adenomas or carcinomas among female mice in the NTP bioassay, 22-23 mice with tumors would be expected at the intermediate dose, based on an assumption of strict linearity, whereas 27 were found. In effect, the dose-response data form an asymptotic curve which is consistent with saturation. However, the differences are small and a better explanation for a lack of strict linearity is random statistical fluctuation. Biochemical data suggest that these levels are not saturating. Conclusions based on tumor incidence do not seem appropriate.

In its draft HAD Update, EPA used the PB-PK model to extrapolate risk across species and from high to low doses, based on the amount of metabolism of methylene chloride by the GSH pathway. In making use of the PB-PK model, EPA stated (page 29):[5]

> [I]t is clear that the model used by Andersen and Reitz may be improved by additional data and validation. Nevertheless, EPA believes that the structure of the model is sufficiently well developed at present to provide a means of considering the available knowledge of methylene chloride metabolism and pharmacokinetics, as it relates to risk assessment, in a way that is not possible

through the applied-dose method. While confidence in the results of the model are expected to increase upon further model validation, the development of preliminary estimates using the results of the model as currently developed provides insight into the effect on risk estimates of metabolism and pharmacokinetic information.

Use of the PB-PK model in the draft EPA HAD Update resulted (page 84) in a unit risk estimate of 4.7 x 10-7, as opposed to the applied-dose extrapolation in the draft Report (page i-5) of 2.6 - 3.4 x 10-6. EPA indicated (p. 85) that use of body weight rather than surface area as a scaling factor would further reduce the unit risk estimate to 3.7 x 10-8.

In its August 13, 1987 review of the draft HAD Update, EPA's Science Advisory Board indicated that it approved of EPA's use of the PB-PK model. Hence, the risk estimate contained in the draft Report maybe 10 to 100-fold higher than the estimate that EPA will be using as an upper bound on the carcinogenic potency of methylene chloride. The draft Report should be revised to incorporate the more recent scientific data.

Mechanism Data

The draft Report briefly describes postulated mechanisms of action for chemicals that are not genotoxic. It acknowledges (page 8-11) that treatment-related cytological degeneration occurred in both the male and female mice in the NTP study. It concludes (page 8-11) that methylene chloride "could induce mouse liver tumor formation simply by stimulating cell proliferation in that organ in response to cytotoxicity," but states that "there are no experimental studies using [methylene chloride] that can be used to specifically report regenerative hyperplasia resulting in tumor formation." The draft Report goes on to dismiss this plausible mechanism, based on speculation that DNA alkylation may have occurred. However, methylene chloride has not been shown to bind DNA in mammalian cells, whereas data on stimulation of S-phase in liver cells are available.[20, 21, 27]

The tumor formation observed in the NTP study is consistent with a mechanism by which methylene chloride accelerates the appearance of tumors that normally occur spontaneously later in the life of the mouse, due to toxic effects on cells in the two target organs (lung and liver) and accompanied by an accelerated cellular turnover. A 10-day inhalation toxicity study from CEFIC shows toxic effects of methylene chloride on Clara cells in the mouse lung and on the mouse liver.[28] These effects (histopathologic damage to Clara cells and statistically significant changes in liver weight) were noted at the same concentrations used in the NTP study. While it is true that increased liver size does not invariably lead to toxicity, these

observations form part of a pattern in the two target organs of the mouse. Methylene chloride caused a change in liver homeostasis, not degeneration, in a tissue prone to high spontaneous tumor incidence.

The study indicates that the appearance of lung tumors correlates with the doses at which cytotoxic effects occur in the mouse, but not other species. Studies have shown substantial acute pulmonary injury in B6C3F1 mice after only a single exposure to methylene chloride.[28] The mice suffered extensive injury to Clara cells after six-hour exposure to 4,000 or 2,000 ppm, the doses used in the NTP bioassay. Twenty-four hours after exposure, Clara cells were vacuolated and swollen, and numerous necrotic cells were present. Although some apparent accommodation was evident after two to three weeks of exposure, it seems likely that the homeostasis of the mouse lung would remain altered with continued high exposure. It seems likely that the apparent histopathological accommodation conceals an increased turnover of Clara cells in the lung and/or an increased turnover of metabolic enzymes in the Clara cell. Effects on Clara cells did not occur in Fischer 344 rats tested at the same doses.

Mouse lung differs significantly from the lung of man or other animals in the number, distribution and ultrastructural morphology of Clara cells. For example, mice have Clara cells throughout the tracheobronchial tree, whereas most human Clara cells occur in bronchioles. Clara cells in the mouse primarily

have smooth endoplasmic reticulum with associated mixed function oxidase activity. In contrast, human Clara cells have primarily rough endoplasmic reticulum, which is associated with protein synthesis. Also, the mitochondria in Clara cells of the mouse are large. These locational, ultrastructual, and metabolic differences help to explain the unusual sensitivity of the mouse.

Results from several bioassays show that the association between methylene chloride exposure and increased lung tumors is unique to mice. The Fischer 344 rats used in the NTP and Serota bioassays (discussed below) did not have a tumorigenic response in the lungs. (Indeed, the B6C3F1 mice tested in the Serota study did not show an increased incidence of lung tumors.) Similarly, hamsters in one bioassay and Sprague-Dawley rats in two bioassays did not have a statistical increase in the incidence of lung tumors. Rats and hamsters have a very low incidence of spontaneous lung tumors. There is an obvious association between the high spontaneous background incidence of lung tumors in the mouse and the observation of an increase in tumors upon exposure to high levels of methylene chloride.

There are multiple reasons to regard the doses used in the available chronic bioassays of methylene chloride as excessive. This interpretation of concurrent toxicity is consistent with a mechanism by which methylene chloride accelerates the appearance of tumors that normally occur spontaneously later in the life of

the mouse, due to toxic effects on cells in the two target organs (lung and liver) and accompanied by an accelerated cellular turnover.

NTP noted toxic effects in its chronic study as follows:

MORTALITY (NON-ACCIDENTAL DEATH)

	Control	2,000 ppm	4,000 ppm
Male	11/50	24/50	38/50
Female	24/50	22/50	40/50

CYTOLOGIC DEGENERATION OF LIVER

	Control	2,000 ppm	4,000 ppm
Male	0/50	0/50	22/50
Female	0/50	23/48	21/48

GLANDULAR STOMACH DILATION

	Control	2,000 ppm	4,000 ppm
Male	3/49	7/47	9/49
Female	1/49	2/47	10/48

KIDNEY TUBULE CASTS

	Control	2,000 ppm	4,000 ppm
Male	6/50	11/49	20/50
Female	8/49	23/48	23/47

Further, the Technical Report of the NTP bioassay (page 62) states that methylene chloride produced liver degeneration in both male and female mice.[4] Final mean body weights of high-dose male mice and high and low-dose female mice were 10 - 17% lower than chamber controls. These effects occurred late during the treatment period.

One interpretation of these observations is that tumors arose and shortened the lifetime of the tumor-bearing animals. The NTP study does not attempt direct biological observations of the cause of mortality ("attribution of death"). Mice in the treated groups could have died from either tumors (fatal tumors) or effects of methylene chloride unrelated to the occurrence of

tumors (incidental tumors). However, there are two sources of information on which an inference can be based. The first is to see if there are reasons to expect that toxicity to the whole animal that occurs independently of tumor formation is the cause of tumor formation. Alternatively, treatment with methylene chloride could be "nontoxic" except for the induction of tumors. The information in the appendix to the Technical Report supports the former interpretation. Observations independent from the bioassay suggest strongly that mortality will arise from toxicity causes unrelated to tumor formation. (Indeed, the prime candidate for a mechanism of tumor formation is recurrent organ toxicity in lung and liver, leading to selection of a previously initiated cell or earlier appearance of normally occurring tumors.)

The second source of information is statistical observations on the bioassay results. EPA carried out such an analysis in the final version of The Addendum to the Health Assessment Document for Methylene Chloride (September, 1985) and concluded that "a simple comparison demonstrates that the observed tumors may reasonably have produced this mortality." To reach this conclusion, two types of evidence were provided: (a) a table of mortality (and tumors) within time intervals in the mouse study, and (b) a comparison of risk estimates using a time-to-tumor model. In fact, neither observation is helpful, since they both assume <u>independence</u> of treatment-induced mortality from treatment-induced tumors, whereas the best hypothesis for

tumorigenesis in the mouse is that treatment-induced organ toxicity accelerates cell turnover, leading to earlier appearance of spontaneous tumors. Therefore, a more useful interpretation may be gained from observation of the mice that died earliest, since these treatment-related deaths would occur before sufficient time has elapsed for toxicity to induce tumors. For the male mice, the first five deaths occurred earlier in the treated groups.

AVERAGE WEEKS OF AGE AT DEATH

CONTROL	79
2,000 ppm	45
4,000 ppm	53

There were only small differences between the average age of death for female mice, consistent with the lower overall mortality seen with the female mice.

In the Serota study, liver histopathology was noted at the highest dose (250 mg/kg/day). A no-effect level of 185 mg/kg/day was determined. MacEwen and coworkers observed toxic effects in mice continuously exposed to 1000 ppm for 14 weeks.[29] The exposure differed somewhat from that in the NTP study, but the dose was similar to the 2,000 or 4,000 ppm used by NTP. Weinstein and Diamond observed increases in triglyceride levels, centrolobular fat accumulation, and decreased liver glycogen

levels in ICR mice exposed to 100 ppm of methylene chloride.[30] While these effects are not toxic *per se*, they support the observation of MacEwen and coworkers at the higher "environmental" exposure level. Haun and coworkers confirmed liver fat accumulation, noted the appearance of hepatocyte vacuoles, and found a decrease in the liver cytochrome P450 content of mice exposed to 100 ppm.[31] While these are not permanently toxic changes, they support the conclusion of toxicity at the higher levels.

Half-maximal saturation of the mouse's metabolic capacity for methylene chloride occurs at about 125 ppm. Bioassays conducted at levels above 125 ppm will be difficult to use in interpreting risks (and therefore weight of the evidence) for environmental exposures. At higher levels, such as the 2000 and 4000 ppm used by NTP, metabolism of methylene chloride does not resemble that occurring at low doses. Low capacity pathways become saturated, low affinity metabolic systems may produce metabolites not seen at environmental exposure levels and co-factors become depleted.

Methylene chloride induced S-phase in hepatocytes of mice *in vivo* after one or two inhalation exposures to 4000 ppm for two hours.[27] The incidence of S-phase hepatocytes increased variably, and the increases were statistically significant as compared to concurrent (air) controls. These

findings suggest rapid liver cell turnover of a small fraction of cells, while the bulk of liver cells increase in size but not number.

In sum, cell proliferation resulting from cytotoxicity is a plausible explanation for the mouse lung and liver tumors observed in the NTP study. The draft Report states (page 8-6) that "a model based on this mechanism was rejected for both sexes in this case since the observed data did not exhibit sufficient curvature to be consistent with the hypothesis of preneoplastic cell proliferation." The meaning of this statement is unclear. The curve of a data set is not necessarily inconsistent with, and cannot negate, experimental data that warrant a different approach to low-dose extrapolation. Further, as demonstrated in the metabolism section above, the number of observations in a chronic bioassay are sufficiently small that they are not amenable to precise interpretations of this kind.

Overall Weight of Evidence

While the available bioassay evidence is discussed in the draft Report (page 7-8 to 7-14, Appendix B), the draft Report fails to provide a weighing of negative and positive results, along with analysis of the other available toxicological evidence and human data, in an effort to characterize the likelihood that methylene chloride concentrations in the California environment

would pose a cancer risk to humans. As recognized by the National Academy of Sciences and the Office of Science and Technology Policy, this is an essential first step in any assessment of carcinogenic risk.[32]

The overall weight of the evidence overwhelmingly indicates that levels of methylene chloride found in the California environment are not likely to cause cancer. The bioassay results are discussed below, along with a summary of other relevant information that should be used in a weight-of-evidence evaluation.

1. The NTP Bioassay

Male and female mice in the NTP study showed an increase in lung and liver cancer which was, for the most part, statistically significant and dose-related.[4] This indicates that methylene chloride has the potential to increase the incidence of certain naturally-occurring tumors in mice. However, these tumors occurred at doses above a reasonable metabolic dose (saturated metabolism) and were accompanied by signs of overt toxicity in the lung. In addition, as discussed below, there is considerable question as to the significance of these tumors in the mouse for the assessment of cancer potential in humans.

The results of the NTP rat bioassay were quite

different from the mouse results; no increase in malignant tumors was observed. There was a statistically significant increase over the concurrent control group in benign mammary gland tumors in female rats at the two highest dose levels and in males at the highest dose level, representing an enhancement in spontaneously-occurring tumors. However, the statistical comparison disregards historical rates of benign mammary tumors in Fischer 344 rats, which average approximately 28 percent and range up to above 40 percent.[33] The response at the lower dose levels in the NTP rat study was within the mid-range of historical control data. The response at the top dose level was barely elevated above the highest incidences observed in the historical controls. The past presidents of the Society of Toxicology have determined that where incidence rates in treated groups are within historical control ranges, differences between treated and concurrent control groups may not be biologically significant.[34]

Moreover, the benign mammary gland tumors observed did not progress to malignant tumors.[35] While the technical report of the NTP bioassay indicates that there was "clear evidence of carcinogenicity" in rats as that category is defined by NTP, it emphasizes that this is based on an increased incidence of benign tumors. In April 1986, NTP changed the definition of "clear evidence of carcinogenic activity" to include an increase of benign neoplasms (assuming they are not combined with malignant neoplasms) only if "there is an indication from this

or other studies of the ability of such tumors to progress to malignancy".[36] During the review of the NTP study, it was accepted that the benign tumors observed did not progress to malignancy, and there are no other studies showing such progression.

2. Burek Study

Inhalation studies performed at Dow Chemical Company on Sprague-Dawley rats resulted in an increase in benign mammary tumors per tumor bearing rat in female (all doses) and male (high dose only) rats. Exposures were 0, 500, 1,500, and 3,500 ppm.[37] A low but statistically significant increase in sarcomas in the ventral neck region and in and around the salivary glands in male rats was observed at the high exposure and a slight elevation was observed at the 1,500 ppm dose. These results were previously reviewed by EPA's Science Advisory Board, which concluded that it would be inappropriate to use them as a basis for estimating cancer risk from methylene chloride.[38] This conclusion was based on:

- the biology of the tumors, which some Board members thought were surprising (that is, they appeared to be of connective tissue origin rather than parenchrymal cell origin) and which might be manifestations of virus

infections,

- o appearance in one sex of rat only,
- o lack of appearance in similarly-exposed hamsters,
- o an apparent lack of reproducibility in subsequent studies in rats,
- o the metabolic properties of methylene chloride, and
- o mechanistic considerations.

The overall lack of appearance of the ventral neck region tumors in the NTP bioassay would appear to support this conclusion as to the irreproducibility and lack of significance of these results.

Burek, et al. also studied the effects of methylene chloride on Syrian Golden hamsters at exposures of 0, 500, 1,500, and 3,500 ppm. There was no increase in tumors, even at the highest exposure level.

3. Nitschke Study

A second inhalation study on Sprague-Dawley rats was conducted at Dow to explore the toxicity of methylene chloride at concentrations below those that cause saturation of the metabolic processes.[39] Exposures were 0, 50, 200, and 500 ppm for two years. No increased incidence of tumors was observed, except an increase in the spontaneous incidence of benign mammary tumors in the female rats at 500 ppm. A no-observed-effect level for the rat following lifetime exposure was established at 200 ppm in this study.[40]

4. Serota Study

Other important studies of methylene chloride, sponsored by the National Coffee Association, also showed no carcinogenic response.[41] Reviewers at a Workshop sponsored by the Nutrition Foundation concluded that methylene chloride in drinking water at doses up to 250 mg/kg/day did not cause a tumorigenic response in either rats (Fischer 344) or mice (B6C3F1).[42] These studies are considered state-of-the-art, and their results must be given careful consideration in any assessment of the potential carcinogenicity of methylene chloride. The negative results cast considerable doubt on linear extrapolation from the NTP mouse data even within the same species.

5. Significance of Mouse Results

Results from several bioassays show that the association between methylene chloride exposure and increased lung tumors is unique to mice. Rats and hamsters do not exhibit a tumorigenic response in the lung. Rats and hamsters have a very low incidence of spontaneous lung tumors. There is an obvious association between the high spontaneous background incidence of lung tumors in the mouse and the observation of an increase in tumors upon exposure to high levels of methylene chloride.

The spontaneous nature of the mouse tumors and the likelihood that they signal a promotional event should be taken into account. Lung and liver tumors in B6C3F1 mice are widely recognized as having limited relevance to cancer potential in man. The risk assessment principles adopted by the Office of Science and Technology Policy recognize that evaluation of data from experimental animals that ordinarily have high incidences of certain tumors poses a number of special problems. OSTP Principle 9 states that "the interpretation of cancer incidence in some strains of rats with testicular or mammary tumors, or in some strains of mice with lung or liver tumors, must be approached carefully in the light of other biological evidence bearing on potential carcinogenicity."[43] The EPA Guidelines for Carcinogen Risk Assessment also provide for classification of mouse liver tumors as limited evidence, where certain conditions are met.[44]

EPA's Science Advisory Board has indicated that data

showing an increased incidence of mouse liver tumors alone do not meet the criterion of sufficient evidence.[45] This determination is supported by a substantial body of scientific literature.[46] A panel of distinguished scientists has urged that NTP give serious consideration to "replacement of the B6C3F1 mouse with a strain having an established lower and less variable spontaneous incidence of important tumors that are induced by chemicals."[47] The recent identification of an oncogene in B6C3F1 mouse liver tumors casts further doubt on the value of mouse liver tumors as an end-point in assessing human risk.[48] As for lung tumors, they occur spontaneously in B6C3F1 mice at an average rate of approximately 14 percent.[49]

Quantitative Evaluation

The draft Report should acknowledge, as EPA has recognized, that

> the linearized multistage procedure tends to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero. The range of risks, defined by the upper limit given by the chosen model and the lower limit which may be as

low as zero, should be explicitly stated.[50]

EPA's statement recognizes that linear estimates would give accurate projections for a few carcinogens but are not likely to give realistic estimates for most substances, which will have much lower low-dose risk.

Current methodology for quantitative risk assessment is dominated by two policy assumptions: (1) that carcinogens do not have practical thresholds; and (2) that carcinogenic risk is a linear function of dose at low doses.[51] Given these policy choices, California has chosen a mathematical model that performs well in estimating a maximum linear slope that is not inconsistent with bioassay data. The model, referred to in the draft Report as the "linearized multistage," takes incidence data obtained at all doses into account, whereas "straight-line" or "single-hit" (Poisson) models may not fit the data when more than one response point is present.[52] The linearized multistage model operates with the data from a bioassay as follows:

- A version of the multistage model is developed that mathematically resembles a true multistage model, with the number of stages constrained by the number of non-zero doses used in the bioassay.

- A maximum likelihood fit of this specific model to

the bioassay data is developed with the exponential values for each stage constrained to give only positive and increasing risks.

- All exponential values higher than the single-hit (linear) component are held fixed and the magnitude of the single-hit exponent is enlarged in the direction of increasing risk to obtain a maximum value compatible with the data in a 95% confidence limit sense. The value of the linear exponent ("q_1^*") is used for risk estimation purposes.

There are serious problems associated with use of the linearized multistage model, which has changed sufficiently from the original model of Armitage and Doll in that it no longer retains a biological rationale.[53] The stages in the linearized multistage model do not relate to discrete modifications of a cell line in the pathway to an observable tumor, and the number of stages is not related to the number of stages in the carcinogenic process. The exponents do not relate to the times between these discrete cell variants, and the overall set of exponent values do not relate to the time-to-tumor. The constraint on non-negative exponents rules out use of models in which a substance lengthens the time of one stage. However, this biological effect has been observed experimentally. In short, a linearized multistage model for a substance is not derived from

an underlying biological theory of carcinogenesis or from knowledge of relevant biological effects of the substance in question. Instead, it is a curve fitting mechanism.

Such curve-fitting exercises entail computer capabilities. Point values are produced which tend to be insensitive to changes in the shape of the dose-response curve. The confidence limit-driven slope is more sensitive to the number of animals the investigator may choose for the bioassay, which is an irrelevant variable for a model of the carcinogenic effect of a substance. This can best be visualized by applying the model to the NTP study data assuming that no effect occurred at all. If the control incidence is substituted for the actual 2,000 and 4,000 ppm values, a q_1^* value will result that does not differ drastically from the current estimate. A linearized multistage model does not readily accept pharmacokinetic or time-to-tumor data. Information on age-specific cancer incidence, background rates, including cell-turnover or cell population kinetics, and lack of mutagenicity cannot be used at all unless the model maker arbitrarily alters the parameters.

The final Report should use GST pathway target tissue dose estimates derived from the PB-PK model which then can be utilized in any risk model, including the linearized multistage model. Doses derived from the PB-PK analysis and utilized in a linear model retain the desired policy positions of linearity and no threshold, but gives a more realistic estimate for hypothetical

"what-if" risk. In addition, the PB-PK dose adjustment should be coupled with other models. The final Report might also include estimates derived from a Moolgavkar-Knudson model.[54] Moolgavkar-Knudson models describe cancer induction as a filtered Poisson process with deterministic and stochastic elements that account for the dynamics of a cell population that is intermediate between two stages, transition from normal cells and transition to malignant cells. Biologically, these two transitions are characterized as rare and irreversible in practice. Use of a Moolgavkar-Knudson model for methylene chloride offers many advantages.[55] A Moolgavkar-Knudson model can describe some of the pharmacodynamic factors involved in dose adjustment of methylene chloride between species, interrelating background rates and age-specific incidence. Many of the advantages of the Moolgavkar-Knudson model over the linearized multistage model are directly relevant to the specific properties of methylene chloride, such as (1) high background tumor rates in the rodent species used as bioassay subjects, (2) strong suggestions of action by a non-genotoxic mechanism, and (3) pharmacokinetics data that have nonlinearities. Data on liver weight changes, cell number and cells in S-phase are available for mice at tumorigenic methylene chloride doses. While use of the linearized multistage model is questionable with non-genotoxic materials, Moolgavkar-Knudson models are appropriate with either genotoxic materials or a substance like methylene chloride that appears to induce tumors at high doses through subtle, organ-specific cytotoxicity.

A Moolgavkar-Knudson model is not, however, necessarily an optimal description of methylene chloride effects. Neither absence of a threshold nor low-dose linearity necessarily applies to methylene chloride, although both assumptions are built into currently available Moolgavkar-Knudson models.

The linearized multistage model used in the draft Report incorporates dose adjustment on the basis of body surface area. Dose conversion by body weight provides a better basis for dose adjustment between species. EPA recently co-sponsored a comparison of carcinogenic potency of various substances in humans and rodents. Body weight proved far superior to body surface area for prediction of the potency value.[56] In addition, two groups of investigators have tested the ability of mice to predict results in rats, and vice-versa. Both Wilson and Crouch[57] and Gaylor and Chen[58] have found body weight superior to body surface area in predicting interspecies dose adjustment.

Reproductive and Developmental Toxicology

In addition to its shortcomings in assessing the potential carcinogenicity of methylene chloride' the draft Report does not adequately describe available data on reproductive effects. While acknowledging that methylene chloride has low teratogenic potential in rodents, the draft Report states (page i-2) that

"experimental data are inadequate to make inferences about effects on human reproduction." This is inconsistent with a determination made by EPA in 1984 to withdraw a proposed reproductive effects test rule for methylene chloride because a two-generation reproductive study in rats undertaken by HSIA "is expected to provide sufficient data to reasonably determine or predict the effects [of methylene chloride] on human reproduction". (49 Fed. Reg. 25009, June 19, 1984) A two-generation reproduction study by Nitschke and coworkers, which was submitted to EPA, showed no treatment-related reproductive effects.[59]

The conclusion that no information exists about reproductive and developmental effects is in error. First, several chronic bioassays of rodents at very high methylene chloride levels have failed to demonstrate changes in reproductive organ weights. These results have been confirmed by Bornmann and Loeser for female rats in a study of methylene chloride administered in drinking water.[60] Second, several developmental studies are available. Schwetz and coworkers directly observed development in mice and rats exposed to high methylene chloride concentrations and found no conclusive effects.[61] In the case of mice, maternal toxicity was noted at the same dose tested. Third, Nitschke and coworkers performed a two-generation inhalation reproduction study in rats exposed to methylene chloride and found no significant effects.[59] Hardin and Manson showed similar results in a one-generation design study.[62]

The draft Report concludes (page 5-3) from some of these data that methylene chloride has low teratogenic potential, but that experimental data are inadequate to make inferences about man. In fact, the data are quite extensive. It is always appropriate to question whether animal tests will be predictive of human effects. However, HSIA is aware of no medical reports suggesting a need for more exhaustive testing. The doses used in the animal studies, in relation to the approximately 10,000-fold lower ambient concentrations in California, appear to merit a more straightforward scientific conclusion that human reproductive and developmental effects are not expected.

CONCLUSIONS

The Department of Health Services, under Section 39660 of the California Health and Safety Code, is required to provide an evaluation of the health effects of substances that may be determined to be toxic air contaminants. Section 39660 requires this evaluation to assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, and to estimate levels of exposure that may cause or contribute to adverse health effects. Part B of the draft Report requires substantial revision in order to provide an adequate assessment of available biological data on methylene chloride and more realistic estimates of exposure that may cause or contribute to adverse health effects. HSIA would be pleased to assist in this process by providing additional information or amplifying these comments.

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APPENDIX A

Page III-5	Methylene chloride use has been declining at approximately 10% per year since 1984. 1987 production estimates are approximately 500 million pounds. In 1984 the market was over 600 million pounds. Aerosols and certain formulated products have shown the biggest reduction in methylene chloride use.
Page III-4 (1)	The potential for accounts receiving shipments of methylene chloride in California and then reshipping outside the state is not restricted to chemical distributors. Examples include aerosol fillers and paint stripper formulators. This volume could be more than a small fraction.
Page III-6 line 2 under Paint Removers	We question whether 7,500 tons of methylene chloride were used in paint removers in California.
Page III-8 2nd & 3rd lines from end	The percentage of methylene chloride in the total aerosol formulation depends on what the product is. Aerosol paint strippers contain 85% methylene chloride.
Page III-19 last line, 2nd to last paragraph	Voluntary labeling will begin in 1988, not 1986.
Page III-20 last few lines	Air stripping would be adequate for this volatile compound. Stream stripping would not be necessary.
Page III-9 last paragraph	Some methylene chloride is typically retained in the foam. Methylene chloride is also used as a flush for urethane foam nozzles and for cleanup purposes in polyester molding operations.

Page III-10 Degresing Operations	Few degreasers use methylene chloride. The estimates given in this paragraph appear to be for stripping and circuit board stripping.
Page III-11 Photographic Film Processing	To our knowledge, film <u>cleaning</u> is done instead with 1,1,1-trichloroethane.
Page III-11 Pesticide Mfg. 3rd line	800 tons seems high.
Page III-11 & first paragraph Page III-12	This section is confusing. Is there one facility that used 800 tons in 1983 as a solvent for process use plus 90 more tons for extraction, phase separation, purification, crystallization, and as a general transport solvent? The first page intimates there was only one facility.
Page III-12 Chemical Processing	Some of this methylene chloride could be part of the final product, which may be used (emitted) outside of California.

APPENDIX B

RESPONSE TO THE CALIFORNIA DEPARTMENT OF HEALTH SERVICES PRELIMINARY DRAFT, TECHNICAL SUPPORT DOCUMENT, PART B - HEALTH EFFECTS OF METHYLENE CHLORIDE.

Epidemiology Section
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January 1988

Introduction

This document has been prepared in response to the preliminary draft of the California Department of Health Services (DHS) entitled, "Part B: Health Effects of Methylene Chloride", dated November 1987. It addresses certain issues concerning the Eastman Kodak Company epidemiologic studies, including a comparison of animal model predictions with human findings.

Epidemiological Studies (Section 7.2)

The DHS report summarized the results of the Kodak mortality studies of two populations of workers exposed to methylene chloride: (1) a 1964 cohort of about 750 men followed through 1976[1], 1980[2], and 1984[3], and (2) a 1964-1970 cohort of approximately 1,000 men (the 751 employees originally studied as well as 262 men hired between 1965 and 1970) followed through 1984. There were two references to the second study, a presentation of preliminary findings,[4] and a description of the final results,[5] which incorporated detailed exposure history data, dose-response analyses, and comparison with animal model extrapolations.

The information, as presented, is extremely confusing. Rather than describe each of the the studies in chronological sequence, selected data (statistical results, exposure measurements, power, etc.) from the five articles were intermixed. For example, exposure estimates (p 7-5) from a preliminary analysis were shown instead of updated information from the final published report. The statement that "tobacco smoking was not considered in these analyses..." (p 7-1) may be misinterpreted as applying to all studies when, in fact, cigarette smoking was considered in the 1987 article only. Also, the follow-up rate of 99% (p 7-2) was observed only for the most recent study. As a final comment, we note that it is often unclear as to which study the observed-expected values refer.

In presenting the epidemiologic results, it would have been more appropriate to emphasize the latest study findings,[5] which provided the most complete follow-up and exposure information for an expanded cohort of

methylene chloride-exposed workers. (See Appendix A for summary.)

Risk Assessment (Section 8.5)

To evaluate the validity of animal-based risk estimates, the DHS staff used two analytic techniques: 1) a relative risk model fit to the human data, and (2) a comparison of the observed cancer mortality with predictions derived from the linearized multistage model applied to the animal data. From these analyses, they concluded "...that the quantitative extrapolation from mice to humans yields plausible estimates of cancer risk...." (p 8-15)

1. Relative Risk Model

In this approach, a 95% upper bound on risk generated from the nonsignificant human pancreatic finding was compared with a unit risk estimate derived from the female mouse lung cancer data. Specific criteria included: (1) pancreatic cancer, (2) all age groups, (3) Kodak Rochester controls, and (4) summary statistics for expected deaths and estimated dose. From the relative (multiplicative) model, the 95% upper bound on the estimated human lifetime incremental risk for 1 ppm of continuous methylene chloride exposure was estimated to be 7.90×10^{-3} (see Note below) compared with a unit risk of 3.25×10^{-2} from the mouse data.

The relatively simplistic modeling procedure used by the DHS, which was based solely on summary data, allowed only linear changes with dose while forcing the line through the origin, and thus it is not unexpected that the results would be consistent with linearized multistage model bounds. It is likely that other models utilizing more detailed dosage information would give entirely different results.

In order to examine the sensitivity of the multiplicative model, we calculated estimates of lifetime incremental risk based on variou

Note. This value is incorrect. A DHS staff member (EH) has concurred with our calculated value of 9.4×10^{-3}.

scenarios of data outcome (Table). As noted by the DHS staff, the upper bounds for Scenarios 1 (linearized multistage model applied to NTP female mouse lung adenomas and carcinomas) and 2 (multiplicative model applied to epidemiologic data for pancreatic cancer) were comparable. On the other hand, the human lower bound is negative, indicating that the data are also consistent with no excess risk. Scenario 3, in addition to using the same factors as the DHS staff, assumed that there were half as many observed pancreatic malignancy deaths in each of the three career dose categories. The results showed that the upper 95% bounds were marginally changed compared with the DHS parameters (4.2 vs. 9.4×10^{-3}), and still consistent with the animal unit risk value (3.3×10^{-3}). In Scenario 4 it was assumed that only one observed death occurred in each exposure group (a total of three deaths), which resulted in an SMR of 94. The upper 95% bound (2.1×10^{-3}) remained about the same as the animal unit risk value, albeit the maximum likelihood estimate was negative. The human lung cancer data, applied in Scenario 5, showed that even though the observed-expected ratio decreased with dose and the overall SMR was below 100, the results (1.7×10^{-3}) were still comparable to the upper bound risk derived from the mouse data.

It is thus evident that the upper bound risk generated from this model is highly insensitive to differences in both the number of observed deaths and the dose-response relationship within the cohort. Reducing the number of pancreatic cancer deaths from eight to four to three (Scenarios 2-4) did not materially affect the upper bound. Additionally, for those scenarios showing a decrease in risk with career dose and an SMR at or below unity (Scenarios 4 and 5), the upper bound remained essentially unchanged vs. the linearized multistage model.

To summarize, the draft document's risk assessment approach (1) selected the pancreatic cancer results even though they may not be related to

Scenario	Exposure Group (ppm-Years)	No. of Observed/ Expected Deaths	Parameter Estimate of b	Asymptotic Standard Error of b	Two-Tailed p Value[1]	Estimated Lifetime Incremental Risk of 1 ppm of Continuous Methylene Chloride Exposure: 95% Lower Bound	Maximum Likelihood Estimate	95% Upper Bound
Scenario 1:[2] B6F Female Mouse Data						0	2.5×10^{-9}	3.3×10^{-9}
Scenario 2: Human Pancreatic Cancer SMR = 251								
	< 350	2/0.718 = 279						
	350-749	2/1.213 = 165						
	750+	4/1.256 = 318						
	Total	8/3.187 = 251	0.583	0.358	0.10	-4.7×10^{-9}	4.7×10^{-9}	9.4×10^{-9}
Scenario 3: One Half Pancreatic Cancer Deaths SMR = 126								
	< 350	1/0.718 = 139						
	350-749	1/1.213 = 82						
	750+	2/1.256 = 159						
	Total	4/3.187 = 126	0.113	0.248	0.65	-2.4×10^{-8}	9.0×10^{-9}	4.2×10^{-8}
Scenario 4: Three Pancreatic Cancer Deaths SMR = 94								
	< 350	1/0.718 = 139						
	350-749	1/1.213 = 82						
	750+	1/1.256 = 80						
	Total	3/3.187 = 94	-0.053	0.191	0.78	-2.9×10^{-8}	-4.2×10^{-9}	2.1×10^{-8}
Scenario 5: Human Lung Cancer SMR = 85								
	< 350	4/ 3.255 = 123						
	350-749	5/ 6.121 = 82						
	750+	5/ 7.181 = 70						
	Total	14/16.557 = 85	-0.079	0.076	0.30	-7.5×10^{-8}	-2.9×10^{-9}	1.7×10^{-8}

[1] Two-tailed test of linear model parameter difference from 0.

[2] Scenario 1: B6F female mouse data, lung adenomas and carcinomas, linearized multistage model.
Scenario 2: Human pancreatic cancer, occupational controls, and summary expected deaths and dose.
Scenario 3: Same as Scenario 2, except the number of pancreatic cancer deaths is reduced by one-half in each career exposure group.
Scenario 4: Same as Scenario 2, except there is one pancreatic cancer death in each career exposure group.
Scenario [illegible] Human lung cancer, occupational controls, and summary expected deaths and dose.

[3] Standardized [illegible] Mortality Ratio.

methylene chloride exposure, (2) used a strictly linear model forced through the origin, and (3) ignored information contained in the lower bound estimate. Such a strategy virtually insures compatibility with the animal bioassay extrapolation findings. Under these circumstances, it is difficult to imagine any epidemiologic study which would provide sufficient evidence to contradict conclusions drawn from the animal studies. In our judgment the draft document should have evaluated data for all primary cancers rather than restrict the analysis to the only site for which there was a suggestive increase, which may have been due to chance.

2. Predicted Deaths from Linearized Multistage Model

For this analysis, the number of excess deaths predicted in the Kodak cohort from the application of the linearized multistage model to the female mouse lung tumor results were compared with the pancreatic cancer findings. The total of 12.5 deaths (9.3 excess plus 3.2 background) was reported to be "...quite close to the observed (eight pancreatic cancer deaths)." (p 8-14) In addition, DHS noted that the 36.3 lung/liver deaths predicted (14.5 excess plus 21.8 background) were "...within a factor of 3 of the observed 14 deaths...," (p 8-15), and thus concluded that ". .the animal-based risk assessment should be viewed as consistent with the human data." (8-14)

Contrary to the DHS statement that the numbers of observed and expected pancreatic cancers were "quite close", it should be emphasized that the probability of observing eight or fewer deaths, given expectation of 12.5, is relatively low (0.125). Similarly, although the observed and expected lung/liver cancer deaths were "within a factor of 3", it is highly unlikely (probability less than 0.0001) that 14 or fewer deaths would have been observed if the animal model predictions were correct. We, therefore, disagree with the DHS staff concerning their interpretation of the difference between the animal model predictions and the human findings.

Biologic Plausibility of Pancreatic Cancer

The DHS staff's selection of the pancreas for their animal model vs. human comparison was based on the observation that this site exhibited the "...greatest relative risk among workers occupationally exposed..." (p 8-14) As further justification, they stated that "...there is no reason to assume that the most sensitive site in animals will be the most sensitive site in humans." (p 8-13)

In assessing the risk associated with exposure to a chemical, it is essential that the issue of biologic plausibility be carefully examined. With respect to pancreatic cancer, numerous studies have been conducted that clearly demonstrate that such tumors are found in association with chemical exposures in the rat, e.g., bis(chloromethyl)ether[6], 4-hydroxyamino-quinoline-1-oxide[7], the diazoketone azaserine[8], the methylnitrosourea-containing amino acid N-(N-methyl-N-nitroso carbamoyl)-L-ornithine[9], and more recently, hypolipidemic drugs such as nafenopin[9] and clofibrate.[9] However, chronic oral[10] and inhalation[11-13] studies of methylene chloride in rats have not demonstrated the pancreas to be the site of toxic action. Similarly, chronic inhalation studies in hamsters[11,12] and mice[12,13] have not shown this chemical to be a pancreatic carcinogen. (Hamsters, in addition to rats, have been extensively used as a model for experimental pancreatic cancer induction.[9])

Since pancreatic cancer has not been observed in chronic studies with rats and mice dosed orally, or in rats, mice, and hamsters dosed by inhalation, there is no evidence that methylene chloride is a pancreatic carcinogen in animal species widely accepted as models for this disease. Assessing these results within the context of the Kodak pancreatic findings (e.g., marginally-elevated risk, no dose response, the presence of confounding variables, and the probability of a chance finding), it is unlikely that methylene chloride is a human pancreatic carcinogen.

Conclusions

We disagree with the the DHS staff's statement "...that human risk estimates based on animal studies are consistent with the results of this (Kodak) epidemiological study." (p i-3) In arriving at this conclusion, the DHS staff failed to adequately consider the overall mortality results, including total cancer and such hypothesized tumor sites as lung and liver. Instead, they restricted their analysis to the only site with an elevated SMR (pancreas) for which current evidence of an association with methylene chloride is not supported by animal model studies.

There are at least four reasons for rejecting this approach. First, it is likely that the observed-expected difference was due to chance. (This possibility has been strengthened by recent data which indicate that no new cases have occurred since the last reported follow-up in 1984.) Second, no dose-related effect was observed in the mortality study. Third, the results may have been confounded by personal (smoking, alcohol consumption, diabetes, etc.) and occupational (other chemical exposures) risk factors. And lastly, there is no apparent evidence of biologic plausibility for pancreatic cancer in man.

With reference to the DHS modeling technique, the use of an insensitive upper bound from a linear model for any cancer site with an increased relative risk is likely to demonstrate consistency with extrapolations from animal bioassay data. Finally, in interpreting the differences between animal model predictions and actual cohort mortality, it is important to recognize that the DHS staff's use of such terms as "quite close" or "within a factor of 3" is misleading since the probability of observing the cohort results (given that the predictions are valid) is small. Based on the totality of information available, we therefore conclude that the overall weight of the evidence does <u>not</u> support the allegation that methylene chloride is a human carcinogen.

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APPENDIX

SUMMARY OF HEALTH EFFECTS DATA
METHYLENE CHLORIDE MORTALITY STUDY

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Introduction

This summary report addresses the issue of the potential carcinogenic risk associated with chronic occupational exposure to methylene chloride as evaluated in a recently published epidemiologic mortality investigation of Eastman Kodak Company employees.[1]

Methodology

The population at risk in this historical cohort study included a cohort of 1,013 hourly men who were (1) employed in film coating operations (methylene chloride area) at any time between January 1964 and December 1970 and (2) had worked in this area at least one year during their Kodak careers. Employees, including retirees, were followed for a maximum of 21 years, from 1964 to 1984. Cause of death statistics were compared with mortality data for both the general population (upstate New York men, 1965-1980) and an employed population (Kodak Rochester hourly men, 1964-1984).

Standard methodological procedures were applied to calculate person-years and the expected number of deaths by major cause and cancer subcategory. The Standardized Mortality Ratio (SMR) was used to summarize the cohort's mortality experience. Based on the results of an NTP animal bioassay,[2] the hypothesized outcomes of respiratory and liver malignancy were assessed by a one-tailed test for significance at an alpha level of 5%. In contrast, nonhypothesized causes were evaluated using a two-tailed test with an alpha of 1%.

Estimates of career methylene chloride exposure were derived from extensive workplace monitoring, including > 1,200 area samples collected during the past four decades (1945-1986) and > 900 personal samples obtained since 1980. Analyses of the data by lifetime exposure (ppm-years) and latency were performed to assess dose-response relationships. Finally, to address the issue of the consistency of toxicologic and epidemiologic evidence, the number of excess lung and liver cancer deaths predicted from the NTP animal model were computed, and the results were compared with the actual number observed in the cohort.

Results

1. Cohort Description and Follow-up

The 1,013 study subjects (mean tenure: ~ 26 years) contributed more than 19,000 person-years during the 21-year observation period. There were 176 deaths (17%).

The follow-up rate was 99%. Nine persons remained untraced after a search of company and social security records and completion of a mail survey among disabled and retired employees.

2. Exposure and Latency

The mean methylene chloride concentration, adjusted for seasonal variation, was 26 ppm as an 8-hour time-weighted average. Exposures were characterized according to seven occupational categories selected on the basis of personal dosimetry results. The mean 8-hour TWA averages ranged

from < 1 ppm (polyester film worker and electroplater) to 114 ppm (group leader). Methylene chloride concentrations for other jobs were: film coater, 48 ppm; coater's assistant, 40 ppm; and cleaner, mechanic, chemical worker, 23 ppm. The maximum peak exposure estimates ranged from 500 ppm to 10,000 ppm. On average, the study population was employed in film casting operations 22 years since methylene chloride was introduced in approximately 1944.

In order to assess dose-response, the exposure data were classified into three categories of approximately the same number of employees: < 350 ppm-years, 350-749 ppm-years, and 750 or more ppm-years. The mean exposure rates were, respectively, 16, 22, and 42 ppm as 8-hour TWAs while median latencies were 17, 31, and 37 years (overall 30 years). There was approximately an 8-fold difference in career exposure levels between the highest and lowest groups (1,200 vs. 150 ppm-years).

3. Cancer Mortality

The total number of malignancy deaths (41) did not differ statistically from the number predicted based on New York State (59.3) and Kodak Rochester (52.7) death rates; the SMRs were 69 and 78, respectively. In addition, there were no significant differences between the number of observed and expected deaths for the hypothesized target organs (lung and liver). Whereas no primary hepatic neoplasms were reported, the 14 respiratory cancer deaths observed compared with expectation of 21.0 (NY State, SMR 67) and 16.6 (Kodak Rochester, SMR 84). Among non-hypothesized sites there was a suggestive excess vs. state data for pancreatic malignancy (8 observed vs. 3.2 expected) as well as comparable deficits for neoplasms of the genito-urinary organs (3 vs. 8.0) and colon-rectum (2 vs. 8.0).

4. Dose-Response

There was no evidence of a dose-response relationship with respect to ppm-years for lung and liver cancer even though, as indicated, the mean methylene chloride concentration in the highest dosage category was approximately eight times greater than that in the lowest. The chi square tests for both homogenity and trend were not statistically significant. SMRs (state rates) for lung carcinoma were, respectively, 98, 64, and 54 for the three career exposure classes. Similar results were reported for latency: < 20 years (SMR 163), 20-29 years (SMR 26), and 30 years or more (SMR 74).

5. Toxicologic vs. Epidemiologic Results

A comparison of the number of combined lung-liver cancer deaths observed in the cohort (14) with the number predicted from the animal model (36.3) demonstrated a highly significant difference ($p < 0.0001$). Furthermore, this discrepancy was apparent at even the highest career dosage level: 5 observed vs. 19.6 predicted ($p < 0.001$). Thus, the predictions from the animal bioassay were clearly inconsistent with human experience.

Discussion

1. Strengths of Study

a. Methylene Chloride Exposure

Accurate and complete characterization of exposure is an essential element for an assessment of dose-response. In the current investigation, career methylene chloride exposure estimates were derived from well-documented job history records and environmental sampling results. Factors contributing to the quality of data were:

(1) The company's industrial hygiene database included a substantial amount of both historical and current information concerning solvent levels in this department. Included were 1,220 area samples collected during the past 40 years from a wide spectrum of operating conditions, job functions, and work sites. In addition, 944 full-shift personal samples, specifically chosen to quantify exposures according to job function, were analyzed from 1980 to 1986.

(2) The personal dosimetry data, collected during usual working conditions, were considered to be representative of historical solvent levels. Although operational changes have been made during the past four decades, the technology used to manufacture film base as well the tasks associated with specific production processes have remained relatively constant.

(3) Estimates of career exposure were based on analysis of extensive occupational history information, including review of more than 4,900 individual job assignments from 1944 to 1984. The quality of the data was further enhanced by the fact that the department has traditionally adhered to a rigid organizational and job progression structure.

(4) The validity of the exposure estimates was supported by (a) mass spectrometry and/or gas chromatography analyses, (b) biologic monitoring findings, and (c) historical engineering data collected from the continuous process monitoring of solvent concentrations within the film casting machines.

b. Control Groups

The study design was strengthened by the selection of both general population and occupational referents. The primary advantages of using the New York State controls were rate stability (large population base) and geographic similarity. The choice of an industrial comparison group mitigated the bias associated with the "healthy worker effect" and assured comparability for such socio-economic and personal characteristics as pay class, education, cigarette smoking, health insurance coverage, and access to medical care.

c. Case-Finding

The study was also enhanced by the essentially complete follow-up and death certificate ascertainment.

d. Cohort Size and Follow-up

The study population of more than 1,000 men was relatively large, and the observation period (21 years) of reasonable length. In addition, the median follow-up from first exposure was 30 years.

e. Duration of Exposure

On average, cohort members worked in the methylene chloride environment 22 years; for those with the highest career exposure, the mean was 29 years.

f. Dose-Response

The relationship between methylene chloride dose and cancer mortality was assessed in terms of career exposure (ppm-years), latency (number of years elapsing between first documented exposure and last follow-up), and both indices. There was no evidence of a dose-response relationship.

g. Latency

The median latency period of 30 years was sufficient to allow expression of the postulated lung and liver cancer effects. An analysis of observed-expected differences demonstrated no consistent pattern.

h. Statistical Power

The power of a study, the probability of detecting a given increased risk if it actually exists, is important in interpreting epidemiologic findings. Power may be used to (1) detect a fixed relative risk (RR), or (2) determine the RR for a given power.

In this investigation, there was adequate power (63%, 98%, and > 99%) to detect an increased risk of respiratory carcinoma of 1.5, 2.0, and 2.5, respectively. Conversely, RRs of 1.6, 1.7, and 1.8 would be identified with 80%, 85%, and 90% power.

i. Cigarette Smoking

The principal confounding variable for lung cancer was cigarette smoking. The results of a mail questionnaire survey showed that tobacco usage patterns among surviving cohort members, including retirees, were similar to those reported for other groups of employed persons and the population at large. In addition, a review of decedents' medical records indicated that 84% were "ever smokers".

2. Limitations of Study

a. Power for Rare Forms of Cancer

With fewer than 20,000 person-years, there was clearly inadequate power to detect an excess of liver cancer. In this case, a RR of 5.7 or greater would be needed in order to achieve 80% power; however, as indicated, no liver malignancies were observed.

b. Other Exposures

Although methylene chloride has been the primary solvent in film casting operations at Kodak since approximately 1944, 1,2-dichloropropane (DCP) and 1,2-dichloroethane (DCE), both suspected animal carcinogens, were also present at similar concentrations during certain manufacturing processes from 1930 to 1966. Other potential exposures included acetone (prior to 1950), and methanol, ethanol, isopropanol, and butanol (in lesser amounts). In addition, some maintenance employees may have worked with asbestos and chromium. Since historical air sampling measurements for these materials, including the identification of potentially-exposed workers, are unavailable, it has not been possible to measure the impact of such exposures on cancer mortality.

c. Cancer Incidence Not Evaluated

Because the cohort's illness-absence experience was not studied, some malignancy sites with favorable survival rates may not have been completely assessed. On the other hand, it is likely that all lung and liver cancers were identified due to their extremely high case-fatality rates.

Conclusions

Although the study demonstrated no statistically significant observed-expected differences for total or site-specific cancers, further assessment of the pancreatic findings appears warranted.

It is important that the results of this study be incorporated in the risk-assessment process since the toxicologic findings differed from the epidemiologic experience. A possible explanation for this inconsistency may relate to the metabolic variation between the mouse and man as demonstrated in recent pharmacokinetic studies. Finally, it should be noted that one other epidemiologic investigation, an update of mortality in a South Carolina fiber manufacturing facility, may provide important evidence concerning the potential carcinogenic effects of this chemical.

Bibliography

1. Hearne FT, Grose F, Pifer JW, Friedlander BR, Raleigh RL: Methylene chloride mortality study: Dose-response characterization and animal model comparison. J Occup Med 1987;29:217-228.

2. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dichloromethane in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). National Toxicology Program. US Dept of Health and Human Services, NIH publication No. 86-2562, NTP-TR 306, 1986.

APPENDIX C

HSIA submitted extensive references to ARB concerning methylene chloride on March 27, 1986. Enclosed are the following additional references:

Transcript of EPA's Science Advisory Board (SAB) August 13, 1987 review of methylene chloride.

Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action, and Epidemiology. External Review Draft, EPA/600 18-87/030A; July, 1987.

CEFIC Statement on Research into Species Differences.

Dow Chemical Statement on Research into Species Differences.

Hearne, F. T., Grose, F., Pifer, J. W., Friedlander, B. R., and Raleigh, R. L., Methylene Chloride Mortality Study: Dose Response Characterization and Animal Model Comparison, J. Occup. Med. 29: 217-228 (1987).

Anderson, M. E., Clewell, H. J., III, Gargas, M. L., Smith, F. A., and Reitz, R. H., Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride, Tox. Appl. Pharm. 87: 185-205 (1987).

Green, T., Provan, W. M., and Gowans, N., Methylene Chloride: In Vivo Inhalation Pharmacokinetics in $B_6C_3F_1$ Mice (using stable isotopes) and F344 rats. CEFIC Report No. CTL/R/931 (1987)

Green, T., Nash, J. A., and Hill, S. J., Methylene Chloride: Glutathione-S-transferase Metabolism In Vitro in Rat, Mouse, Hamster and Human Liver Cytosol Fractions. CEFIC Report No. CTL/R/934 (1987)

Green, T., Nash, J. A., Hill, S. J., and Foster, J. R., Methylene Chloride: The Effects of Exposure To 4000 ppm On Mouse Lung Enzymes. CEFIC Report No. CTL/R/935 (1987)

B. Comments from the National Association of Photographic Manufacturers, Inc.

NATIONAL ASSOCIATION OF PHOTOGRAPHIC MANUFACTURERS, INC.

600 Mamaroneck Avenue, Harrison, New York 10528

Telephone 914 • 698-7603

January 7, 1988

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attention: Methylene Chloride
P. O. Box 2815
Sacramento, CA 95812

Re: Preliminary Draft - Report to the Air Resources Board on Methylene Chloride -- November 1987

Dear Mr. Barham:

The National Association of Photographic Manufacturers, Inc. (NAPM) is a voluntary trade association composed of companies involved in the manufacture of photographic equipment and supplies. On the supply side our members manufacture photographic film and photographic paper.

Our comments on the captioned report are directed specifically to Chapter III, Production, Uses and Emissions; Part A - Public Exposure to, and Sources of, Atmospheric Methylene Chloride in California.

In this chapter, the staff of the California Air Resources Board estimated uses of methylene chloride by the photographic industry in California, citing several sources. Included were (1) "Methylene Chloride: Initiation of Regulatory Investigation," 50 FR 42037; and (2) "Survey of Methylene Chloride Emission Sources," EPA-450/3-85-015. These EPA documents contain significant errors of fact concerning the use of methylene chloride in the photographic industry. In comments to the Environmental Protection Agency (December 16, 1985) and the Occupational Safety and Health Administration (February 19, 1987), Eastman Kodak Company, a member of NAPM, provided information to correct these factual errors. Copies of these letters (without attachments) are enclosed for your information.

Methylene chloride is used in the manufacture of photographic film. It is the principal solvent in the manufacture of cellulose triacetate photographic film base. It is also used as a solvent in the manufacture of specialized chemicals for incorporation in photographic film emulsions and for coating operations. None of these manufacturing operations are located in California.

We are not aware of any use of methylene chloride in the chemical formulations used in the processing of exposed photographic film. Photographic film is spliced into larger units for processing by most photoprocessing laboratories. All splices used in the processing of exposed photographic film, however, are mechanical tape splices. Therefore, the Draft Report is incorrect in identifying "photographic film processing" as a use category in California.

Splicing cement is used when processed film is edited during the production of motion pictures. Methylene chloride has a minor use as an ingredient in the splicing cement. Kodak informed OSHA that it processed less than 2 metric tons of methylene chloride for use in film cements for both domestic and export sale and estimated the total industry usage as less than 5 metric tons in 1984 (see enclosed letter). Using the methodology of Appendix II (11% of US population) and even assuming all domestic sales, the usage in California would be about 0.5 metric tons; therefore, the amount of methylene chloride involved in motion picture film splicing annually in California is small in relation to other emissions. It should be included as another example under "Miscellaneous Uses" (p. III-15).

The following corrections should be made in Chapter III:

Page III-2, Figure III-2 - Remove the category and data for "photo film processing" from the chart.

Page III-3, Section B - Remove "photographic film processing" from the list of uses.

Page III-5, Table III-1 - Change "Photographic Film Processing" to "Photographic Film Manufacturing" and change the estimated California use to zero (0).

Page III-7, Table III-2 - Remove "Photographic Film Proc." and associated data from this table.

Page III-11 - Remove section on "Photographic Film Processing" entirely.

Page III-15 - Under "Miscellaneous Uses," insert another example as follows: "a constituent in photographic film cement."

Appendix II, Page 1 - Remove "photographic film processing" from entry "Paint removers, aerosols, photographic film processing and miscellaneous."

Appendix II, Page IV - Add section on photographic film manufacturing as follows:

Photographic Film Manufacturing

Methylene chloride is used as a solvent in the manufacture of cellulose triacetate photographic film base. It is also used in the manufacture of specialized chemicals for photographic emulsions and for certain coating operations. Methylene chloride is not used in the above manner in California.

We appreciate the opportunity to comment and feel confident that our remarks and suggestions will be given due consideration. If there are any questions, please feel free to get in touch with me.

Sincerely,

Thomas J. Bufficy
Executive Vice President

TJD/jb
ENclosures

December 16, 1985

Document Control Officer (TS-793)
Environmental Protection Agency
Office of Toxic Substances
401 M Street, SW; Room E-209
Washington, DC 20460

Dear Sir:

Subject: Methylene Chloride: Initiation of Regulatory Investigation; 50 FR 42037; October 17, 1985; Docket No. OPTS-62045

Eastman Kodak Company is a manufacturer of imaging products, chemicals, fibers, and plastics, with major manufacturing facilities in nine states. Kodak uses methylene chloride in the manufacture of certain photographic products and has made significant capital investments in process and recyling equipment. Although Kodak does not manufacture methylene chloride, we are concerned about the potential impact on Kodak of any regulatory action on methylene chloride.

I. Introduction

Kodak is submitting these comments on the above referenced ANPR to call EPA's attention to three areas that merit consideration in EPA's evaluation of the potential risks of human exposure to methylene chloride and of regulatory measures that may be taken to ameliorate any such identified risks.

A. Kodak is concerned, based on EPA and CPSC criticisms of Kodak's epidemiologic study of methylene chloride, that EPA will discount these data, and rely exclusively on the animal toxicologic data for developing estimates of risks to humans exposed to methylene chloride. Kodak is submitting, with these comments, a detailed discussion that responds to each of the specific EPA or CPSC criticisms of the epidemiologic study. This discussion also provides additional support for Kodak's contention that the data from the epidemiologic study and follow-up reports should be incorporated into EPA's assessment of the potential risks to humans from exposure to methylene chloride.

B. Kodak is providing data to clarify, add to or correct some aspects of the information presented by EPA in the ANPR and support documents relating to the use of methylene chloride by the photographic industry and to the emissions and exposures associated with these uses.

C. Kodak is concerned that EPA is continuing to evaluate chemicals as potential substitutes for methylene chloride that may have known or relatively uncharacterized hazards of a greater magnitude than those that have been demonstrated to be associated with the use of methylene chloride. Kodak urges that EPA carefully evaluate both the identified adverse effects of the substitutes, and the significance of any data gaps relating to potential hazards of the substitutes.

II. Epidemiologic Study of Workers Exposed to Methylene Chloride

Kodak has conducted an epidemiology study on a cohort of Kodak workers who have been or are currently involved in the manufacture of cellulose triacetate film base using a solvent which incorporates methylene chloride. The initial report and first update on this study were critized by EPA as lacking sufficient latency period, cohort size, exposure data or statistical power.

Kodak recently completed a second update of this study, extending the follow-up by four years and thereby increasing the latency period and statistical power of the study. The results of this update were furnished to EPA on June 28, 1985. We are concerned that the Agency's comments in the ANPR and support documents continue to discount the use of this study and do not address the scientifically valid conclusions contained in the study. Dr. Symons, of EPA's Science Advisory Board's Environmental Health Committee, urged EPA to consider alternate conclusions that can be based on the epidemiology work. He characterized the study as "...an important piece of information that we often don't have."[3]

In the enclosed paper, Kodak Response to EPA and CPSC Comments Concerning Kodak's Epidemiologic Study of Methylene Chloride Employees, Kodak responds in detail to each of EPA's and CPSC's specific criticisms of the Kodak epidemiologic study. Kodak concludes that the size of the study cohort was adequate; the latency period in the study was sufficient to allow the hypothesized effects to be expressed; the exposure levels were sufficiently well characterized for epidemiologic risk assessment purposes; and the statistical power of the study was adequate to detect excess deaths from certain hypothesized causes at low to moderate levels of relative risk. Kodak is also presenting in the enclosed paper a brief discussion of an analysis comparing the results actually observed in the epidemiologic study with the results predicted from models extrapolating from the animal bioassay data.

Significant conclusions from the epidemiologic study (and updates) include:

1. There is "no evidence of an increased mortality risk for lung cancer" resulting from worker exposures to methylene chloride; and

2. The study cohort showed an approximate 30% deficit in both total mortality and total cancer deaths compared to the general population, and showed no significant differences in total mortality or total cancer deaths when compared to an industrial control group.

Kodak urges EPA to reconsider its evaluation of the Kodak epidemiologic study, and to incorporate the significant data and conclusions from this study into its risk assessment of methylene chloride.

III. Uses of Methylene Chloride in the Photographic Industry

A. Photographic Manufacturing

The ANPR contains several factual errors relating to the use of methylene chloride in the photographic industry. The major use by Kodak of methylene chloride is in the manufacture of certain photographic products.

Methylene chloride is used by Kodak in the manufacture of clear plastic sheet and some photographic products, not in the processing of photographic films and papers. The principal use for methylene chloride by Kodak is as a solvent in the manufacture of cellulose triacetate plastic film base. We believe that certain non-U.S. manufacturers of photographic products also use methylene chloride in the production of film base. Other uses in the manufacture of photographic products include use as a solvent for applying surface coatings to photographic film base and lithographic plates. It is also used as a solvent in the production of certain chemicals used in the manufacture of photographic films and papers.

The major Kodak manufacturing processes are designed to recycle substantially all of the methylene chloride used in the processes. Typically, the recovery rate for methylene chloride exceeds 90%. Projecting total industry use and emissions based on the use experience with methylene chloride by Eastman Kodak Company, we estimate that total ambient emissions of methylene chloride from use in manufacture of photographic products would be about 5,000 metric tons per year.

Methylene chloride ambient emissions and exposures in the photographic manufacturing industry occur at two Kodak sites, and, perhaps, at a limited number of additional sites in the industry. Potential population exposure, therefore, is not nationwide and must be substantially less than 227 million people. Potential exposure during use of methylene chloride by Kodak involves less than 1,500 workers.

We suggest EPA add a second job category of "production worker" under "photographic applications" in Table 1 to reflect the workers involved in the manufacture of film base and other photographic products. We also suggest Table 2 be changed by adding a source category of "photographic manufacturing" with two known sites and annual emissions of 5000 metric tons.

B. Other Uses of Methylene Chloride in the Photographic Industry

Section II of the ANPR contains the statement that "other major uses of methylene chloride include use in ... photographic film processing ... ." (50 FR 42038). Table 2 lists "photo processing" as a source category, with emissions of 8,100 metric tons (MT/yr) and general population exposure of 227 million people. (50 FR 42045) The ANPR is based on the support document, which lists use of methylene chloride in film splicing cements and assumes total consumption and emission of 8,100 metric tons (Mg) in 1983[1]. The ANPR and the support document do not contain any explanation of the derivation of the general population exposure estimate of 227 million people. As discussed in the following sections, methylene chloride is not used in photo processing operations and the quantity of methylene chloride used in and emitted during film splicing is less than 5 metric tons, which is considerably lower than the estimates given by EPA in the ANPR.

1. Photo processing

Kodak does not include methylene chloride as an ingredient in any photochemicals used in the processing of photographic films or papers. Moreover, we are not aware of any photoprocessing chemicals of other companies that utilize methylene chloride. The statement in the ANPR that photographic film processing is a major use of methylene chloride is wrong and should be deleted. Table 2 in the ANPR should be amended to delete "photo processing" as a major source category for methylene chloride.

As indicated in Table 1 (50 FR 42045), liquid film cement comtaining methylene chloride is used in splicing certain photographic films. EPA states this use involves less than 1400 workers who are exposed at a maximum 8-hour TWA exposure level of 3 milligrams per cubic meter. It should be noted that this is the lowest exposure level for any entry indicated in Table 1. However, the data in Table 2, "Methylene Chloride Ambient Releases and Exposures" relating to potential emissions from the use of methylene chloride in photographic processing are not correct. (50 FR 42045).

In 1984, Kodak processed less than 2 metric tons of methylene chloride for incorporation in film cement products for both domestic and export sale in containers of one gallon or less. These Kodak products are used only for splicing motion picture films, which is done in about 500 U. S. motion picture laboratories.[2] While other companies also sell motion picture film cements, we estimate the total quantity (inclusive of Kodak's use) will be less than 5 metric tons of methylene chloride.

Only an extremely small amount of this total of methylene chloride is used in the cement involved in any one splice, resulting in an exposure level that EPA estimated to be 3 milligrams per cubic meter. Moreover, no methylene chloride is used in the processing of photographic films or papers. The emissions from this source, therefore, cannot conceivably result in the exposure of the entire national population (227 million) to methylene chloride as indicated in this Table.

Table 2 in the ANPR should be corrected as follows:

a. The identity of the source category should be amended to "photographic film splicing;"

b. The quantity of emissions from this source should be amended from 8,100 metric tons per year to 5 metric tons;

c. The population estimate should be revised to reflect the limited number of sites and the small quantity of methylene chloride used in film splicing operations.

In summary, Tables 1 and 2 should be revised as follows to reflect accurate data on the use of methylene chloride by Kodak in the photographic industry:

Table 1

Industry Category	Job Category	Estimated No. of Workers
Photographic Applications	Splicer	1376
	Production Worker	1500

Table 2

Source Category	No. of Sites	Emissions (MT/yr)
Photographic Film Splicing	500	5
Photographic Manufacture	2	5,000
Photoprocessing (delete)	(delete)	(delete)

IV. Comments on Potential Substitutes for Methylene Chloride

A. Potential Substitutes for Methylene Chloride in Photographic Manufacture

Each photographic film product is designed to provide a combination of photographic and physical properties required for proper customer use of the photographic films and for customer satisfaction with product quality. Selection of the appropriate film base material is important in order to achieve the desired product properties. There are no suitable substitutes for the cellulose triacetate film base which is manufactured by Kodak using methylene chloride. Moreover, photographic products available from non U.S. manufacturers also utilize cellulose triacetate film base manufactured, we believe, with methylene chloride.

Kodak has explored the use of alternate solvents in manufacturing cellulose triacetate film base. No adequate substitutes have been found because of the solubility characteristics of cellulose triacetate or the known or potential toxicity and physical hazards of other solvents, such as flammability.

B. Comments on Potential Substitutes Suggested in the ANPR

The use of several of the materials suggested in the ANPR (50 FR 42042) as possible substitutes for methylene chloride has been reduced or discontinued because of known or potential toxicity and physical hazards. For example, the Recommended Maximum Contaminant Level (RMCL) established by EPA under the Safe Drinking Water Act for trichloroethylene and carbon tetrachloride is zero (50 FR 46380). This RMCL was established on the basis of suspected carcinogenicity. We are not aware of any report that demonstrates the proposed substitutes have been as carefully evaluated by human epidemiological studies during industrial use as has been methylene chloride. EPA should not continue consideration of use of these substances as alternatives for methylene chloride.

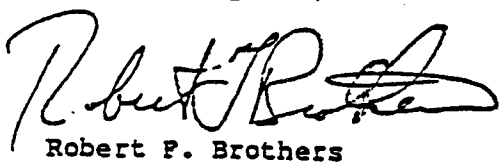
V. Conclusion

Kodak urges EPA to give careful consideration to the epidemiological data that have been developed on methylene chloride, and strongly suggests that EPA incorporate these data into its assessment of the risks of methylene chloride exposures to humans. Kodak requests that EPA correct

its data on the uses of, and exposures to, methylene chloride in the photographic industry, as described in these comments, and that EPA incorporate the new information on exposures associated with photographic manufacturing into its data base. Furthermore, Kodak suggests that EPA give particular consideration to the known or potential hazards associated with the suggested substitutes for methylene chloride.

Kodak is continuing to study the use of methylene chloride, the data on occupational exposure, and the epidemiological studies of Kodak workers exposed to methylene chloride. Kodak expects to share any further conclusions or new information developed during these studies with EPA. Kodak is available to discuss these comments with the Agency at any time.

Very truly yours,



Robert P. Brothers
Director, Regulatory Affairs

RFB:nls
1909e
Enclosure

cc: Dr. P. A. Cammer,
Halogenated Solvents Industry Alliance

Mr. T. J. Dufficy
National Association of Photographic Manufacturers

References

1. Source Assessment of Methylene Chloride Emissions; August 1985; DCN No. 231-020-19-06-02.

2. 1984-1985, Wolfman Report on the Photographic and Imaging Industry in the United States, Pg. 92, ABC Leisure Magazines, Inc.

3. Dr. Michael Symons, Transcript, Pg. 76, June 7, 1984, Science Advisory Board Environmental Health Committee

February 19, 1987

Docket Office
Occupational Safety and Health Administration
Docket No. H-71; Room N-3670
U.S. Department Of Labor
200 Constitution Ave. N.W.
Washington, D.C. 20201

Dear Sirs:

Subject: Occupational Exposure to Methylene Chloride: 51 FR 42257; November 24, 1986

Eastman Kodak Company (Kodak) is a manufacturer of photographic products with major manufacturing facilities in nine states. As a multi-state employer, we share the interest of the public, Congress and OSHA in a safe workplace.

Kodak uses methylene chloride in the manufacture of certain photographic products and has made significant capital investments in process and recycling equipment. In addition, Kodak has conducted epidemiology studies on employees with job assignments in areas where this solvent is used. We have reviewed the referenced Advanced Notice of Proposed Rulemaking and submit the following comments and information on Sections A, B, D, F, I, and M.

A. Health Effects:

Kodak has conducted an epidemiologic mortality study on a cohort of Kodak workers who have been or are currently involved in the manufacture of cellulose triacetate film base using a solvent containing methylene chloride. Specifically the study addresses the potential health risks, including the risk of carcinogenicity, associated with chronic occupational exposure to this chemical.

The initial study report based on a 1964 cohort, was published in 1978 followed by an update in 1981. (OSHA Exs. 4-027 & 4-030) A second update was conducted through 1984, extending the follow-up period by four years, thereby increasing the latency period and statistical power of the study. The update was submitted to OSHA and other government agencies in 1985. (OSHA Ex. 7-044)

Kodak continued work on the epidemiology study and presented preliminary findings at the Winter Toxicology Forum in February 1986. The study cohort was expanded to include workers employed in film coating operations during 1964-70. A dose response assessment using an index of career exposure was also performed. An initial analysis of these findings was provided to OSHA, EPA, FDA and CPSC in meetings with representatives of these agencies during 1986. (OSHA Ex. 7-040)

A report of the expanded epidemiology study has been completed and is attached as Appendix 1. This report is scheduled for publication in 1987, although minor editorial changes may be made prior to publication. Appendix 2 is a summary of the report, prepared by its authors, and a discussion of its relevance to assessment of potential human health risks.

Significant conclusions from the epidemiology report include:

> This epidemiologic investigation of more than 1000 employees chronically exposed to methylene chloride demonstrated no unusual mortality patterns for such hypothesized causes as lung and liver malignancy and ischemic heart disease. There was, in addition, no evidence of a dose-response relationship with respect to career exposure and latency. (Appendix 1, p. 35)

OSHA has cited an evaluation conducted by CAG/EPA in 1985 of the Kodak reports published in 1978 and 81. After reviewing that evaluation, OSHA stated "based on current published data, the essentially negative Friedlander studies do not appear to have the power to rule out an overall cancer risk or the lung cancer risk that is predicted from the NTP mice study." ((51 FR 42262)

The CAG/EPA assessment was based on the study report published in 1978 of a cohort of 252 long-term workers. The most recent Kodak study reports on an expanded cohort of 1,013 workers, as well as covering a longer latency period and including more extensive exposure data (see Appendix 1). Appendix 2 includes a discussion of risk assessment and power calculations based on the most recent data and states:

> We therefore conclude from the 1986 study results that the power to identify total cancer and respiratory malignancy, predicted from the animal bioassay, was substantially greater (0.48 - 0.63) than the lower estimate reported by CAG (0.07 and 0.09, respectively, for total malignancy and lung cancer deaths).

Kodak urges OSHA to evaluate the most recent epidemiology information, submitted with these comments, and to incorporate the significant data and conclusions from this human epidemiology study as OSHA develops its own assessment of occupational exposures and risks.

B. Permissible Exposure Levels

The Kodak Health and Environment Laboratories review available health effects data on chemicals of interest to Kodak. The Laboratories reviewed the American Conference of Government and Industrial Hygienists (ACGIH) decision to reduce its recommended threshold limit value (TLV) from 500 ppm to 100 ppm. The laboratories concurred and established an exposure guideline of 100 ppm for Kodak operations.

In 1986, the ACGIH proposed to further lower the TLV for methylene chloride from 100 ppm to 50 ppm. However, the most recent update and expansion of the Kodak epidemiology study of workers involved in manufacturing operations using methylene chloride demonstrated no unusual mortality patterns for hypothesized causes of death and no evidence of a dose-response relationship with respect to career exposure and latency. (see Appendices 1 and 2) New information, including the latest epidemiologic findings, confirms Kodak's conclusion that continued use of this solvent at current occupational exposure levels in Kodak's operations does not present a significant risk of serious human health effects.

D. Substitution Availability:

The major use by Kodak of methylene chloride is in the manufacture of certain photographic products. Principally this involves use as a solvent in the manufacture of cellulose triacetate plastic film base. Each photographic film product is designed to provide a combination of photographic and physical properties required for proper customer use of the film and for customer satisfaction with product quality. For certain products, cellulose triacetate exhibits a unique combination of the necessary characteristics, which are described in Appendix 3. For the reasons discussed in Appendix 3, we are not aware of any satisfactory replacement film base material, for those products now using cellulose triacetate, that can achieve the desired product properties and meet customer needs.

Kodak has reviewed potential substitutes for methylene chloride as a solvent in the manufacture of cellulose triacetate film base. Appendix 3 also contains a discussion of the necessary solubility characteristics of any potential solvent and demonstrates that most potential solvents do not possess the necessary characteristics to be effective substitutes. Appendix 4 contains a review of the physical and health hazards of four possible alternative solvents. In addition to the undesirable characteristics cited in Appendix 4, these chemicals have not been as carefully evaluated for possible human health effects, particularly by epidemiological studies during industrial use in Kodak's operations, as has been methylene chloride. Based on this information, Kodak has concluded methylene chloride is necessary as a solvent for cellulose triacetate film support production because no other potential coating solvent is known to be as safe as methylene chloride.

In addition to the potential physical and health hazards associated with substitutes, replacement of methylene chloride would be a major change in the manufacturing process for production of cellulose triacetate film base. Each photographic product must pass a battery of quality assurance tests designed to measure the photographic quality and stability of the product. These tests are rigorous, costly and time-consuming and must be satisfactorily completed before a product is introduced into the marketplace. Changing from methylene chloride as the base-making solvent would require photographic revalidation of all of the products that would be coated on the base material made by the new process. This would require at a minimum several years to complete and would involve significant expenses in addition to any capital investments required by substitution.

Based on our review of the solvent characteristics, physical properties and health hazards of possible substitutes, Kodak has concluded that there are no solvents currently available that would be acceptable as alternatives to the continued use of methylene chloride in the manufacture of cellulose triacetate film base.

F. Workers exposure and monitoring:

OSHA has cited the report prepared for EPA by Pedco Environmental, Inc. as its "primary source of occupational exposure data." (51 FR 42260) This report contains factual errors relating to the use of methylene chloride in the photographic industry. These errors were pointed out to EPA in our comments dated December 16, 1985. (OSHA Reference 4-096)

The Pedco report contained no information on the major use by Kodak in the manufacture of certain photographic products. Principally, this involves use as a solvent in the manufacture of cellulose triacetate plastic film base. Extensive data on job categories, exposure and monitoring methods associated with this use can be found in the attached epidemiology report. (see Appendix 1)

Other uses in the manufacture of photographic products include use as a solvent for applying surface coatings to photographic film base and lithographic plates. The chemical is also used as a solvent in the production of certain chemicals used in the manufacture of photographic films and papers.

The only job category cited in the Pedco report for photographic applications is splicer. Liquid film cement containing methylene chloride is used in splicing certain photographic films. In 1984, Kodak processed less than 2 metric tons of methylene chloride for incorporation in film cement products for both domestic and export sale in containers of one gallon or less. These products are used only for splicing motion picture films, which is done in about 500 motion picture laboratories. Only an extremely small amount of methylene chloride is used in the cement involved in any one splice, resulting in an exposure level that EPA estimated to be 3 milligrams per cubic meter.

I. Control measures and benefits:

Kodak has reviewed its manufacturing operations and considered the costs of implementing engineering controls to reduce current occupational exposure levels. A capital investment program of as much as $100 million would probably be required to meet the ACGIH proposed reduction. Achievement of significantly lower exposure levels would require a substantially larger financial investment, including development of new manufacturing technology and the design and construction of new manufacturing facilities. No identifiable benefit would result in an occupational setting for which the latest epidemiology study "demonstrated no unusual mortality patterns" and "no evidence of a dose-response relationship with respect to career exposure and latency." (see Appendix 1, p. 35)

M. Financial and Economic Profile:

Cellulose triacetate film base is a photographic support material manufactured by Kodak and used for many Kodak motion picture, graphic arts, and amateur roll and movie film products. Kodak is currently the only domestic manufacturer of cellulose triacetate film base. This base material is manufactured by other companies at sites outside the U. S. and is used as the support material for competitive photographic products. Unreasonable regulatory requirements that apply only to domestic manufacture of this film base may adversely affect the U. S. trade balance in view of the availability of competitive film products on the same base material provided by non-domestic manufacturers.

Docket Office —6
February 19, 1987

Conclusion

Kodak urges OSHA to give careful consideration to the new data included in the attached epidemiology report and to incorporate it into its assessment of occupational exposures and the risk of human health effects. Furthermore, OSHA should give particular consideration to the known physical and health hazards associated with any potential substitutes for methylene chloride as well as to the infeasibility of substitution for technical reasons. Finally, OSHA must carefully review the potential economic impact of imposing excessive regulatory requirements on the domestic photographic industry in view of the new epidemiologic findings based on this industry.

We appreciate the opportunity to provide this information to OSHA. We will submit a copy of the paper on the epidemiology study when it has been published.

Very truly yours,

Robert F. Brothers
Director, Regulatory Affairs

RFB:nls
Enclosures

C. Comments from the Allied Corporation

Allied Corporation
Department of Toxicology
P.O. Box 1021R
Morristown, New Jersey 07960

December 16, 1987

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn.: Methylene Chloride
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Barham:

On November 23, 1987, Peter D. Venturini, Chief of the Stationary Source Division of the State of California Air Resources Board announced that the preliminary draft report on methylene chloride was available for review and comment.

We appreciate the opportunity to comment on the preliminary draft report which includes: Part A - Public Exposure to, and Sources, of Atmospheric Methylene Chloride in California, and, Part B - Health Effects of Methylene Chloride.

In Part B - Health effects of Methylene Chloride, we are in basic agreement with your conclusion that "the environmental concentrations in California of 3 ppb are well below any known acute and non-carcinogenic chronic levels that may cause adverse health effects". However, we would extend this further to include the contention that no carcinogenic effects or cancer-related mortality would be expected to occur at current ambient levels. At the present time, compelling scientific evidence to refute this latter contention simply does not exist. Liver tumors associated with oral exposure of laboratory animals to methylene chloride or other agents (e.g., carbon tetrachloride) are always preceded by clinically observable hepatic damage which is considered to be a preprequisite to tumor formation. In the preliminary draft of the technical support document Part B - Health Effects of Methylene Chloride, a calculated no observable adverse effect level (NOAEL) for adverse health effects, other than cancer, for humans is suggested to be 5 ppm, based on the assumption of equivalency of toxicity by the oral and inhalation exposure routes for methylene chloride. We would agree this is a reasonable and scientifically-sound assumption.

In the 1982 National Coffee Association drinking water study in rats, in which the lowest oral dose used was 5 mg/kg/day (equivalent to the suggested human NOAEL of 5 ppm), zero hepatocellular carcinomas were observed. This result is clearly indicative of a NOAEL for a carcinogenic effect. At the high dose of 250 mg/kg/day, only one male and two female rats were observed with hepatocellular carcinomas. Furthermore, rats exposed to 250 mg/kg/day for 78 weeks and then allowed

to recover, did not develop hepatocellular carcinomas. This implies some type of repair mechanism being operative during the recovery phase following liver insult from methylene chloride exposure. This same repair mechanism appears to be overwhelmed during high-dose exposure in the absence of a recovery period. At low dose where there is no observable hepatotoxicity, there should be no cause for concern for carcinogenicity. If one accepts the validity of this statement and the supporting animal data, then the concept of mathematical modeling used for low-dose extrapolation of human carcinogenic risk clearly does not apply in the case of methylene chloride. Other carcinogenicity studies, outlined in Part B, also suffer from either exceedingly high dose exposures which lose relevance when viewed in the context of current ambient levels and cancer incidence, or tend to lose statistical significance when data are compared to concurrent or historical control data. In addition to liver tumors, other types of tumors observed from animal experimentation were not seen in human epidemiological studies. Moreover, from the epidemiological study [Friedlander, et al. (1986) and Hearne et al. (1987)] of Eastman Kodak employees, no statistically significant differences were found between observed and expected deaths for respiratory and hepatic cancers which were hypothesized by the authors based upon results from animal studies. The possibility of causation of pancreatic cancer in humans by exposure to methylene chloride (8 observed versus 3.2 expected) is at best only suggestive. Apparent disagreement exists on the statistical significance of this finding which is definitely not consistent with tumor profiles obtained through laboratory animal studies. One would not expect adverse non-carcinogenic or carcinogenic health effects to occur at current California ambient air levels of methylene chloride which are 3 to 4 orders of magnitude less than the 5 ppm NOAEL suggested for humans.

Allied-Signal Inc. endorses the Halogenated Solvents Industry Alliance (HSIA) belief that methylene chloride does not cause adverse health effects when used according to current industrial hygiene guidelines or labeled instructions and firmly believes that methylene chloride should not be identified as a toxic air contaminant.

We thank you for the opportunity to provide comment on the preliminary draft report on methylene chloride.

Sincerely yours,

Roger W. Reinhold

RWR:rb

Roger W. Reinhold, Ph.D., D.A.B.T.
Manager, Department of Toxicology

Allied Corporation
Department of Toxicology
P.O. Box 1021R
Morristown, New Jersey 07960

December 17, 1987

Dr. Paul A. Cammer
Executive Director
Halogenated Solvents Industry Alliance
2315 M Street, N.W., Third Floor
Washington, D.C. 20037

Dear Paul,

It was nice talking with you last week relative to methylene chloride. Thank you for your time and thoughts.

Per your request, enclosed is a copy of a rather hastily prepared (though hopefully well-thought out) response to the California Air Resources Board's request for review and comment on the preliminary draft report on methylene chloride.

Thank you, once again, for allowing us to emphasize HSIA's belief that methylene chloride does not merit identification as a toxic air contaminant.

Sincerely yours,

Roger W. Reinhold

RWR:rb
Enc.

Roger W. Reinhold, Ph.D., D.A.B.T.
Manager, Department of Toxicology

cc: G. Loewengart
G.M. Rusch
File

D. Comments from Bendix Environmental Research, Inc.

ENDIX
ENVIRONMENTAL RESEARCH, INC.
FOX PLAZA, SUITE 902 • 1390 MARKET STREET • SAN FRANCISCO, CA 94102 • TELEPHONE (415) 861-8484

30 November 1987

Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
ATTN: methylene chloride
P.O. Box 2815
Sacramento, CA 95812

RE: Preliminary Draft Report to the Air Resources Board on Methylene Chloride, Part A

Dear Mr. Barham:

I would like to call your attention to a growing use of methylene chloride to degrease sampling tubes used for soil and sediment samples at contaminated or potentially contaminated sites. Although undoubtedly a small use in the spectrum of total use of methylene chloride, I am concerned that this methodology is being recommended by the Environmental Protection Agency. I feel that, in view of the questions about the safety of methylene chloride, it is unwise to encourage new uses for this substance. Geotechnical field personnel are not commonly trained in the handling of carcinogens and there is a potential for substantial exposure to geotechnical personnel and of improper disposal of the used methylene chloride. I believe that regulatory agencies should encourage the use of safer solvents in procedures designed to evaluate and abate existing environmental problems.

Sincerely,

Selina Bendix, Ph.D.
President

SB:bdw

E. Comments from Roger Atkinson and Arthur Winer, University of California, Riverside

UNIVERSITY OF CALIFORNIA, RIVERSIDE

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STATEWIDE AIR POLLUTION RESEARCH CENTER-6 RIVERSIDE, CALIFORNIA 92521-0425

December 22, 1987

Dr. Robert Barham
Toxic Air Contaminant Identification Branch
Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Barham:

Thank you for your letter of November 23, 1987, enclosing the preliminary draft methylene chloride identification report for our comments. As you requested, our comments deal only with the section concerning the atmospheric fate of methylene chloride.

Since it is clear that CH_2Cl_2 reacts relatively slowly with the OH radical, it will undergo long range transport and dispersion. Hence the use of a regionally or globally averaged OH radical concentration is required to calculate the atmospheric lifetime of CH_2Cl_2 due to this reaction. Despite the uncertainities in the ambient atmospheric OH radical concentrations, the annually and diurnally averaged OH radical concentration is, based upon the measured lifetimes of various tracers and computer modeling studies, approximately 5×10^5 molecule cm^{-3}. For tropospheric temperatures of 265-298 K this leads to a calculated lifetime of CH_2Cl_2 of 150-250 days.

As stated on page IV-5, the initial reaction with the OH radical does form the $CHCl_2$ radical (reaction 2). The subsequent reactions of this radical are as follows. The $CHCl_2$ radical will rapidly react with O_2 to form a peroxy radical.

$$CHCl_2 + O_2 = OOCHCl_2$$

This peroxy radical will then react with NO (if present), HO_2 radicals or other peroxy (RO_2) radicals

$$OOCHCl_2 + NO = OCHCl_2 + NO_2$$

$$OOCHCl_2 + HO_2 = HOOCHCl_2 + O_2 \quad \text{(forming dichloromethylhydroperoxide)}$$

$$OOCHCl_2 + RO_2 = OCHCl_2 + \text{other products}$$

These reactions have not been experimentally studied; rather they are expected to occur based on our knowledge of the atmospheric reactions of other simple alkyl peroxy and haloalkyl peroxy radicals (see, for example,

DeMore et al., 1985, and D. L. Baulch, R. A. Cox, R. F. Hampson, Jr., J. A. Kerr, J. Troe and R. T. Watson, J. Phys. Chem. ref. Data, 13, 1259-1380, 1984). The $CHCl_2O$ radical is known (H. Niki, P. D. Maker, C. M. Savage and L. P. Breitenbach, Int. J. Chem. Kinet., 12, 1001-1012, 1981) to eliminate a chlorine atom to form formyl chloride

$$OCHCl_2 = HC(O)Cl + Cl$$

The Cl atom will react with whichever organics are present (in the cleaner troposphere this will be mainly with methane) to yield HCl.

The above paragraph should replace the last 4 lines of page IV-5 and all of page IV-6.

The following additional points may be helpful in revising the present draft:

- It would be helpful to the reader to reference the five groups cited at the bottom of page IV-2, in which case the sentence stating the years in which they published their data could be eliminated.
- In the first paragraph on page IV-3, it is not clear what the phrase "included to illustrate the variation among the different studies" refers to. Also in this paragraph it should be "authors'" and not "author's".
- At the bottom of page IV-3 you may want to state explicitly for the uninitiated reader that OH radicals are only present during daylight.
- In the last sentence of the first paragraph on page IV-5, it is not clear which OH radical concentration "this" refers to.

We hope that this will be of help to you; if you have any further questions regarding this draft report, please feel free to contact us.

Yours sincerely,

Roger Atkinson
Research Chemist

Arthur M. Winer
Research Chemist

II. Air Resources Board Responses to Part A - Related Comments

AIR RESOURCES BOARD STAFF RESPONSES TO PUBLIC COMMENTS

ON THE DRAFT PART A REPORT ON METHYLENE CHLORIDE

1) The Halogenated Solvents Industry Alliance, January 14, 1988.

a) Comment: In summarizing methylene chloride use in Table III-1, estimates of current U.S. use are based on information provided by HSIA for calendar year 1983. A more realistic estimate of current U.S. use would be 497 million pounds (248,500 tons) for 1987 from an estimate by Dow Chemical (USA) based on current governmental data.

Response: As stated in Table III-1, the U.S. use estimate for methylene chloride is 241,000 tons for 1983. Staff acknowledge that this estimate does not represent current U.S. methylene chloride use. Data for 1983 were used because 1983 was the most recent year where methylene chloride consumption by use category was available. However, in response to your comment, the U.S. use estimate listed in Table III-1 has been footnoted to indicate the U.S. use estimate for 1987 as estimated by Dow Chemical.

b) Comment: The report states that the Industrial Source Complex Short Term (ISCST) model was used to estimate annual average concentrations. The ISCST model is designed to estimate short-term (one to 24 hour) averages, not annual averages. Annual average concentrations should be estimated using a statistical summary of recorded meteorological data rather than sequential data and the long-term version of the model (ISCLT).

Response: This comment concerns the belief that ISCLT is more appropriate than ISCST for estimating annual average concentrations. However, we believe this to be untrue. ISCLT uses sector averaging which can lead to under-predictions of peak concentrations. Also, ISCLT uses average mixing heights and ambient temperatures. Again, the use of average values leads to under-prediction of peak concentrations. For these reasons, we do not recommend the use of ISCLT.

The South Coast Air Quality Management District has selected the ISCST model for use in new source review for carcinogenic air contaminants (see SCAQMD proposed Rules 223 and 1401). In addition, the "Air Toxics Assessment Manual" (1987) prepared by the Interagency Working Group has omitted the ISCLT model from the list of models recommended for use in toxic modeling studies. In this document, the ISCST model is recommended for all averaging times. The Agencies participating in the review and release of this document include the Environmental Protection Agency, California Air Resources Board, South Coast AQMD, San Diego APCD, Bay Area AQMD, and Engineering-Science, Inc.

c) Comment: Hourly meteorological data should be used when short-term maximums are being estimated.

Response: See response to comment (b).

d) Comment: For estimating an annual average, use of a statistical summary of meteorological data is preferred to hourly meteorological data as this format allows the model to consider multiple years of data (summaries are usually made from five to ten years of data) in determining the annual average concentrations.

Response: See response to comment (b).

e) Comment: ISCLT differs from ISCST on two very important points:

1) estimated concentrations are averaged over the sector in question and "smoothed" between sectors to avoid discontinuity.

2) a maximum of 16 wind direction sectors is allowed rather than the 36 sectors used by the ISCST model.

The effect of both of these points is to reduce the estimated concentration in most cases.

Response: See response to comment (b).

f) Comment: The report states that the emissions from an automobile assembly plant were modeled as an area source even though methylene chloride was emitted from a series of stacks. Modeling the emissions as though they emanated from an area source rather than stacks does not recognize enhanced dispersion due to the velocity and temperature of the exhaust as it exits the stack.

Response: The stacks at the Automobile assembly plant were modeled as an area source with an effective release height of approximately 289 feet, which accounts for both the buoyancy and momentum of the exhaust under neutral atmospheric conditions.

g) Comment: The report does not say if an effective emission height was calculated and used in the analysis.

Response: The report has been revised to state that the effective emission release height is approximately 289 feet.

h) Comment: The draft report (pages II-4 and II-5) uses Gleit's method to estimate mean concentrations of methylene chloride below the level of quantitation of the monitoring stations. The method was designed to determine a mean for comparison with a specific value (e.g. a standard). The Air Resources Board has no specific value with which to compare the data.

Response: The use of Gleit's statistical method for estimating the "expected value" for data below the detection limit does not involve comparison with any specific value. The statistical method used in our estimates has been compared with other commonly used estimators and was found to outperform all available techniques.

i) Comment: A summary of the data including the percent of data below detection and a possible range of average concentrations (assuming all missing data are equal to zero for the lower limit of the range and all missing data are

equal to the detection limit for the upper limit of the average) would be more informative.

Response: Table II-1 currently reports the number of samples for each station and percent of values below detection.

The use of zero and the detection limit do not give an actual lower and upper limit of annual mean concentrations. The limited sample size and uncertainties encountered in sample collection and analysis outweigh the uncertainty caused by the use of Gleit's statistical methods for estimating values for censored data. The estimates reported by ARB use both a 20% uncertainty in sampling and analysis and two standard errors to estimate the expected range of the mean concentrations.

j) Comment: The statement in the draft report that water chlorination is a source of environmental methylene chloride seems in error. The kinetics of reaction between chlorine and organic material in water is such that only chloroform is released to any appreciable extent.

Response: We agree that the kinetics of reaction between chlorine and organic material in water is not likely to favor the formation of appreciable amounts of methylene chloride. However, limited data suggests that a minor source of methylene chloride emissions may result from the chlorination of water.

k) Comment: The draft report should integrate the pharmacokinetic information addressed in Part B with the exposure information in Part A.

Response: The Overview, which will be released with the final draft of the methylene chloride report, integrates the information in the risk assessment (Part B report) with the information presented in the exposure assessment (Part A Report).

l) Comment: Health effects information suggests that the effects of methylene chloride at high exposure levels are unlike the effects after chronic low exposure.

Response: All comments concerning the health effects of methylene chloride will be responded to by the Department of Health Services.

m) Comment: Page III-5 - Methylene chloride use has been declining at approximately 10 percent per year since 1984. 1987 production estimates are approximately 500 million pounds. In 1984 the market was over 600 million pounds. Aerosols and certain formulated products have shown the biggest reduction in methylene chloride use.

Response: Refer to our response to comment (a).

n) Comment: Page III-6, line 2 - We question whether 7,500 tons of methylene chloride were used in paint removers in California.

Response: The basis for estimating emissions of methylene chloride from paint removers in California is provided in the report. If you have information which indicates that this estimate is not accurate, we would be interested in reviewing it.

o) Comment: Page III-8, 2nd and 3rd lines - The percentage of methylene chloride in the total aerosol formulation depends on what the product is. Aerosol paint strippers contain 85% methylene chloride.

Response: The report was revised to clarify that the amount of methylene chloride in product formulations depends upon what the product is.

p) Comment: Page III-19, last line of second paragraph - Voluntary labeling will begin in 1988, not 1986.

Response: In 1986, some manufacturers of consumer products containing methylene chloride voluntarily labeled their products with additional health warnings and use recommendations. However, enforcement of these labeling requirements becomes effective for products whose labels are printed after March 14, 1988 and after September 14, 1988 for products that are packaged.

q) Comment: Page III-20, last few lines - Air stripping would be adequate for this volatile compound. Steam stripping would not be necessary.

Response: Should methylene chloride be identified as a toxic air contaminant, appropriate levels of control for methylene chloride emissions sources will be evaluated in the subsequent risk management phase.

r) Comment: Page III-9, last paragraph - Some methylene chloride is typically retained in the foam. Methylene chloride is also used as a flush for urethane foam nozzles and for cleanup purposes in polyester molding operations.

Response: We acknowledge that a small fraction of the methylene chloride used in the manufacture of urethane foam may be retained in the foam after curing. Staff also acknowledge that there may be other uses for methylene chloride in the foam manufacturing industry that are not discussed in the report. However, if methylene chloride is identified as a toxic air contaminant, its uses by the foam manufacturing industry will be evaluated in greater detail during the subsequent risk management phase.

s) Comment: Page III-10 - Few degreasers use methylene chloride. The estimates given in this paragraph appear to be for stripping and circuit board stripping.

Response: The EPA estimated methylene chloride emissions from degreasing operations in a variety of industries, primarily within five distinct Standard Industrial Classifications (SICs). Based on information provided by HSIA, the EPA estimated U.S. emissions of methylene chloride from degreasing operations at 23,700 tons in 1983 (U.S. EPA, 1985). In addition, ARB's emissions data system identifies a number of sources in California that use substantial amounts of methylene chloride for degreasing.

t) Comment: Page III-11 - to our knowledge, film cleaning is done instead with 1,1,1-trichloroethane.

Response: Based on comments from the National Association of Photographic Manufacturers, Inc., the discussion on photographic film processing has been deleted from the text.

u) Comment: Page III-11, 3rd line - 800 tons seems to high.

Response: This use estimate is based on information provided by the EPA for one pesticide manufacturing facility in California for 1983 (see Table III-1). This estimate is only for process use and does not include any methylene chloride consumed as an ingredient in pesticide formulations.

v) Comment: Page III-11 and 1st paragraph of III-12 - This section is confusing. Is there one facility that used 800 tons in 1983 as a solvent for process use plus 90 more tons for extraction, phase separation, purification, crystallization, and as a general transport solvent? The first paragraph indicates that there is one facility.

Response: The text has been revised to clarify that the source which used 800 tons of methylene chloride is the same source that is estimated to have emitted 90 tons.

2) The National Association of Photographic Manufacturers, Inc., January 7, 1988

The NAPM states that the draft report is incorrect in identifying "photographic film processing" as a use category. The NAPM's comments were accompanied with well documented letters describing the uses and emissions of methylene chloride by the photographic industry. The NAPM concluded their comments by recommending the following changes to the report.

a) Comment: Page III-2, Figure III-2 - Remove the category and data for "photo film processing" from the chart.

Response: The category photographic film processing has been removed from Figure III-2 and replaced with photographic film manufacturing.

b) Comment: Page III-3, Section B - Remove "photographic film processing" from the list of uses.

Response: The category photographic film processing has been removed from the list.

c) Comment: Page III-5, Table III-1 - Change "photographic film processing" to "photographic film manufacturing" and change the estimated California use to zero (0).

Response: The report has been revised to reflect your comments.

d) Comment: Page III-7, Table III-2 - Remove "photographic film processing" and associated data from this table.

Response: The report has been revised to reflect your comments.

e) Comment: Page III-11 - Remove section on "photographic film processing" entirely.

Response: The report has been revised to reflect your comment.

f) Comment: Page III-15 - Under "Miscellaneous Uses," insert another example as follows: "a constituent in photographic film cement."

Response: The use of methylene chloride as a constituent in film cement is now listed under miscellaneous uses.

g) Comment: Appendix II, Page 1 - Remove "photographic film processing" from entry "paint removers, aerosols, photographic film processing and miscellaneous."

Response: The report was revised to reflect your comment.

h) Comment: Appendix II, Page IV - Add section on photographic film manufacturing as follows:

Photographic Film Manufacturing

Methylene chloride is used as a solvent in the manufacture of cellulose triacetate photographic film base. It is also used in the manufacture of specialized chemicals for photographic emulsions and for certain coating operations. Methylene chloride is not used in the above manner in California.

Response: The purpose of Appendix II is to describe the methods used to estimate California methylene chloride use. Since methylene chloride is not used for this category in California, Appendix II was not revised to reflect your comment.

3) Bendix Environmental Research, Inc., November 30, 1987

The comments concerned the use of methylene chloride to degrease sampling tubes used for soil and sediment samples at contaminated or potentially contaminated sites.

a) Comment: "I believe that regulatory agencies should encourage the use of safer solvents in procedures designed to evaluate and abate existing environmental problems."

Response: If methylene chloride is identified as a toxic air contaminant, the subsequent risk management phase will evaluate its uses in more detail. Part of the evaluation will be to consider strategies intended to reduce exposure, one of which is to encourage the use substitute compounds.

4) University of California, Riverside, December 22, 1987

a) Comment: Despite the uncertainties in the ambient atmospheric OH concentrations, the annually and diurnally averaged OH radical concentration is, based upon the measured lifetimes of various tracers and computer modeling studies, approximately 5×10^5 molecules cm^{-3}.

Response: The report relies on a range of average OH radical concentrations (5×10^5 to 1×10^6 molecules cm^{-3}) which includes the concentration that you recommend.

b) Comment: As stated on Page IV-5, the initial reaction with OH radical does form the $CHCl_2$ radical (reaction 2). The subsequent reactions of this radical are as follows. The $CHCl_2$ radical will rapidly react with O_2 to form a peroxy radical.

$$CHCl_2 + O_2 = OOCHCl_2$$

This peroxy radical will then react with NO (if present), HO_2 radicals or other peroxy (RO_2) radicals.

$$OOCHCl_2 + NO = OCHCl_2 + NO_2$$

$$OOCHCl_2 + HO_2 = HOOCHCl_2 + O_2$$
(forming dichloromethylhydroperoxide)

$$OOCHCl_2 + RO_2 = OCHCl_2 + \text{other products}$$

These reactions have not been experimentally studied; rather they are expected to occur based on our knowledge of the atmospheric reactions of other simple alkyl peroxy and haloalkyl peroxy radials. The $CHCl_2O$ radical is known to eliminate a chlorine atom to form formyl chloride:

$$OCHCl_2 = HC(O)Cl + Cl$$

The Cl atom will react with whichever organics are present (in the cleaner troposphere this will be mainly with methane) to yield HCl.

The above paragraph should replace the last four lines of page IV-5 and all of page IV-6.

Response: The report was revised to reflect your comments with your letter cited as the source.

c) Comment: It would be helpful to the reader to reference the five groups cited at the bottom of page IV-2, in which case the sentence stating the years in which they published their data could be eliminated.

Response: The report was revised to reflect your comment.

d) Comment: In the first paragraph on page IV-3, it is not clear what the phrase "included to illustrate the variation among the different studies" refers to. Also, in this paragraph it should be "authors'" not "author's".

Response: The sentence has been deleted and the typographical error corrected.

e) Comment: At the bottom of page IV-3, you may want to state explicitly for the uninitiated reader the OH radicals are only present during daylight.

Response: The report has been revised to state this fact.

f) Comment: In the last sentence of the first paragraph on page IV-5, it is not clear which OH radical concentration "this" refers to.

Response: The range of OH radical concentration being discussed in the paragraph was used to estimate a range of atmospheric lifetime estimates. Therefore, the word "this" was replaced with "these".

III – Department of Health Services Responses to Part B – Related Comments

DEPARTMENT OF HEALTH SERVICES
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE PRELIMINARY DRAFT REPORT TO THE AIR RESOURCES BOARD
ON METHYLENE CHLORIDE:
PART B -- HEALTH EFFECTS OF METHYLENE CHLORIDE

TOPIC: Genotoxicity

Comment: Methylene chloride does not appear to act by a direct genotoxic mechanism. In light of the overall negative results in genetic toxicity studies in higher order animals, including several important DNA-binding studies, genotoxicity would not appear to be a significant factor in inducing tumorigenic effects. (Halogenated Solvents Industry Alliance [HSIA]).

Response: Methylene chloride is consistently positive, in a dose-related manner, in Salmonella strains TA1535, TA98, and TA100, in both the presence and absence of metabolic activation systems. In the case of methylene chloride, the chemical tests positive in the Ames assay and has been shown to produce tumors in two species. As indicated on page 6-2 of the health effects document, methylene chloride has also exhibited mutagenic activity in E. coli. Three of the arguments listed by HSIA (page 14) against applying the Ames test results to higher animals are generic for testing any chemical in a bacterial system. However, since tests in Salmonella and E. coli have been shown to be useful in evaluating mutagenicity of chemicals and in indicating possible mechanisms of carcinogenicity, the generic criticisms of bacterial test systems (e.g., bacterial cells are different from mammalian cells) will not be addressed in this response. The one HSIA comment on bacterial test systems specific to methylene chloride is

that the bacteria may "metabolize methylene chloride to a transient reactive intermediate(s)." However, HSIA comments also indicate that methylene chloride's metabolism to an active intermediate in animals may be a determining factor of its tumorigenicity and HSIA's pharmacokinetic model is based on this assumption. Thus, the fact that bacteria may metabolize methylene chloride to a reactive intermediate is a reason to regard the bacterial mutagenicity data as relevant. There is no convincing evidence that bacteria produce a reactive intermediate that is not produced in animals. Furthermore, a reactive intermediate, solely responsible for the positive response in Salmonella and E. coli., has not been identified.

The results in yeast and Drosophilla, as discussed in the DHS report (page 6-3), are listed as equivocal. However, the most recent review by IARC (IARC Monographs, 1987, Supplement 7:194-195) states: "...It induced sex-linked recessive lethal mutations in Drosophila. It was mutagenic to plants and induced mutation, mitotic recombination and gene conversion in Saccharomyces cerevisiae under conditions in which endogenous levels of cytochrome P450 were enhanced..." Thus, although the genotoxic results in yeast and Drosophilla are not strong, they do not support the HSIA argument that positive genetic toxicity test results were confined to bacteria.

As indicated in the DHS report, methylene chloride has induced transformation of virus-infected Fischer rat cells and has produced equivocal indications of cell transformation in Syrian hamster embryo cells. The compound has induced chromosomal aberrations in rodent cells in vitro and has induced positive results of sister chromatid exchange in Chinese hamster ovary cells. Thus, as concluded in the DHS report, methylene

chloride appears to exhibit clastogenic activity. These results refute the assertion that genetic toxicity studies in higher order animals are negative overall.

Reactive intermediates, which may be genotoxic, appear to be formed in mammalian cells during methylene chloride metabolism. Mechanism studies of Clara cell toxicity indicate that metabolism of methylene chloride in the mouse lung by P450 results in P450 damage (supplemental information submitted by HSIA, Green et al., Report No. CTL/R/935). This implies that the Clara cell P450 is metabolizing methylene chloride to a reactive intermediate. Also, in support of its physiologically-based pharmacokinetic models, HSIA explicitly accepts the assumption that methylene chloride may produce tumors by production of a reactive intermediate via the glutathione-S-transferase route. Consequently, mammalian cells may metabolize methylene chloride to a reactive intermediate via both the P450 route and the glutathione-S-transferase route. Since reactive intermediates are formed in mammalian cells, methylene chloride is potentially genotoxic to mammalian cells.

In conclusion, the comment hypothesizes that methylene chloride is not genotoxic and that the positive results in bacteria do not reflect the negative genetic toxicity results in higher order animals. However, the consistent positive results in Salmonella, along with the positive and borderline results in higher order test systems, cannot be ignored. A negative or equivocal response in another genotoxic test system may simply reflect the test's evaluation of a different mechanism of genotoxic action. Two potential genotoxic mechanisms of carcinogenesis, that is, mutagenesis

and clastogenesis, have been discussed in the DHS health effects document (page 8-8 to 8-12). Furthermore, reactive intermediates may be formed via two metabolic routes in mammalian cells. Currently, there is no direct evidence to provide support for only one of the hypothesized mechanisms of methylene chloride carcinogenicity. Because the data indicate that methylene chloride is weakly genotoxic, and because reactive intermediates have been identified, DHS staff do not agree that methylene chloride produces its tumorigenic effects by a nongenotoxic mechanism.

TOPIC: Teratogenicity

Comment: The draft report incorrectly concludes that experimental data are inadequate to make inferences about the teratogenic potential of methylene chloride in man. No medical reports suggest a need for more exhaustive testing. The available data merit a more straightforward conclusion than that human reproductive and developmental effects are not expected at ambient concentrations of methylene chloride in California (HSIA).

Response: As indicated in the conclusion of Section 5 of the DHS report: "Experiments performed to date have been limited in that either they employed only one dose level, utilized relatively few test animals, or demonstrated signs of maternal toxicity possibly as a result of carboxyhemoglobin formation." Additionally, rats were used in all studies except one, which tested mice at one dose level that was maternally toxic. For these reasons, DHS staff conclude that methylene chloride has not been sufficiently tested for developmental toxicity. Positive human medical reports linking methylene chloride to reproductive or birth defects in

humans are not necessary to indicate a need for further testing. Considering the large volume of methylene chloride used in industry and by consumers, more information is needed on the potential developmental toxicity of methylene chloride. However, the assessment by DHS staff is that no birth defects or other reproductive effects are expected at ambient levels of methylene chloride.

TOPIC: Carcinogenicity

Comment: The International Agency for Research on Cancer (IARC) considers methylene chloride to be "possibly carcinogenic to humans," rather than a probable human carcinogen. Classifications based strictly on scoring bioassay evidence of carcinogenicity cannot adequately characterize the overall likelihood of a substance to cause cancer in humans. The draft report does not adequately elucidate the staff reasoning regarding hazard identification (HSIA).

Response: Generally, DHS follows the procedures for carcinogen identification that are utilized by IARC and have been described in numerous IARC monographs. A specific discussion on DHS's reasoning regarding hazard identification is presented in the report "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale," published by the Health and Welfare Agency in 1985. Since methylene chloride exhibits sufficient evidence of carcinogenicity in animals (Group 2), IARC could have classified it as a probable (2A) or possible (2B) human carcinogen. The distinction reflects the quantity and quality of human epidemiologic data available for consideration. There is no clear reason to regard the line

between these two groups as signaling action/no action or concern/no concern. Methylene chloride was classified by IARC as a "possible" human carcinogen as a result of inadequate epidemiologic data indicating carcinogenicity. As described in the DHS report, two epidemiologic studies are available. Although the results reported were negative, the studies had limited power to detect excess risk.

Comment: The weight of evidence suggests that levels of methylene chloride in the California environment do not pose a human cancer risk (HSIA). No carcinogenic effects would be expected to occur at current ambient levels and there is no compelling scientific evidence to refute this conclusion (Allied Corporation [Allied]).

Response: DHS staff do not agree that the weight of evidence indicates that ambient levels of methylene chloride do not pose a human cancer risk. Methylene chloride exhibits genotoxic potential and has been shown to be an animal carcinogen in two species. There is no "proof" that it is carcinogenic at ambient levels because an experiment to test this hypothesis cannot be conducted. High doses are used in animal studies to ensure a sensitive test, given a relatively small number of animals. DHS staff conducted a quantitative risk assessment using the best available data and standard methods of extrapolation to estimate the risk at ambient levels. After reviewing the health effects literature for methylene chloride, including the evidence referred to by HSIA and Allied, DHS staff conclude that methylene chloride is a potential human carcinogen and that a threshold for its carcinogenicity has not been established. Thus, DHS staff conclude

that methylene chloride poses a carcinogenic risk to humans at ambient levels.

Comment: Lung and liver tumors in mice were observed only at toxic doses. Cytotoxic damage in mouse lung may have played a significant role in the enhanced lung tumor response observed in the National Toxicology Program (NTP) study. Cytotoxic effects were not observed in rats, a finding consistent with known metabolic differences between lung tissue of mice, rats, and humans. This may indicate that levels of methylene chloride in the California environment do not pose a human cancer risk (HSIA). Clinically observable hepatic damage is considered to be a prerequisite to liver tumor formation (Allied). The 1982 National Coffee Association drinking water study in rats indicated that 5 ppm is a no observable adverse effect level for a carcinogenic effect (Allied). Even at higher doses, a repair mechanism may operate to prevent liver tumors following insult from methylene chloride (Allied).

Response: The relationship between cytotoxic damage and enhanced lung or hepatic tumor production is unclear. The NTP inhalation study in mice did not report any increase in nonneoplastic changes in the lungs. There was no increase in epithelial hyperplasia, inflammation, or edema. However, the NTP study did report that "alveolar/bronchiolar adenomas, alveolar bronchiolar carcinomas, and alveolar/bronchiolar adenomas or carcinomas (combined) in male and female mice occurred with significant positive trends..." Thus, an association between cytologic damage in the lung and tumor production is not evident in the NTP study. However, HSIA states (page 30) that an unpublished 10-day inhalation study (Reference 28 in HSIA

comments) showed histopathologic damage to Clara cells. While this report might suggest cytotoxicity in mice at the NTP exposure level, it is by no means conclusive. Note that while there is some evidence that the Clara cell is the origin of some chemically induced bronchial tumors (e.g., Kaufmann et al., 1979. Lab Invest 40:708), there is also immunocytochemical evidence suggesting that the vast majority of naturally occurring and experimentally induced pulmonary neoplasms of mice are alveolar Type II cell adenomas and carcinomas (Ward et al., 1985. Am J Pathol 118:493). Furthermore, cell proliferation could be occurring simultaneously with genotoxicity, and still exhibit a linear response at low concentrations.

HSIA also indicates that in the 10-day mouse inhalation study mentioned above there were statistically significant changes in liver weight. Increased liver size does not invariably lead to toxicity, as stated on page 30 of the HSIA comments. Thus, the 10-day study described by HSIA is not considered conclusive evidence that hepatic cytotoxicity preceded tumor formation in the mouse NTP inhalation study. The NTP inhalation study with mice does indicate "cytologic degeneration" was observed in three of the four dose groups. However, an increase in hepatic tumors was observed in all four groups (male and female, low and high doses). Other hepatic tissue changes such as congestion, inflammation, or necrosis were not observed in any of the dose groups. Clinical signs of hepatoxicity (such as SGOT or SGPT changes) were not reported in the NTP study. Thus, clinically observable hepatic damage was not observed in the treated animals.

Thus, the preliminary information presented by HSIA may suggest the possibility of hepatic cytotoxicity at the doses used in the NTP mouse

study, but the relationship of cytotoxicity to tumorigenicity has not been established in this case. The NTP mouse inhalation study does not in itself lend strong support to the hypothesis that methylene chloride cytotoxicity results in tumorigenicity. Furthermore, cytotoxicity was not observed in the NTP rat inhalation study even though rats exhibited a dose-related increase in mammary gland tumors in both sexes. Methylene chloride may cause tumors by mechanisms other than cytotoxicity, even at high doses. Thus, the available data do not indicate that any single mechanism is operating exclusive of other hypothesized mechanisms.

Comment: The final report might include estimates from a Moolgavkar-Knudson model for methylene chloride, which would offer many advantages (HSIA).

Response: As indicated in the report, DHS staff fit several low-dose risk assessment models to the data, including the multistage, time-dependent multistage, probit, logit, Weibull, gamma multihit, and two-stage models. DHS also applied a physiologically-based pharmacokinetic model to the data. The Moolgavkar-Knudson model allows utilization of mechanistic information of carcinogenesis. Risk estimates from this type of model are provided on pages 8-9 and 8-23 of the DHS report.

Comment: The draft report fails to make use of available data on metabolism, pharmacokinetics and mechanism, including those discussed in a recent update to the U.S. Environmental Protection Agency (US EPA) hazard assessment document (HSIA).

Response: Estimates of risk using pharmacokinetic models were calculated by DHS staff and are presented in the DHS report, particularly in Appendix E. DHS staff conducted an extensive examination of data on metabolism, pharmacokinetics and mechanism, which included discussions with US EPAstaff and representatives from industry. The DHS report does not mention the US EPA document specifically because the US EPA document is a review draft labeled "Do not cite or quote." In the DHS report, Section 2 considers metabolism and pharmacokinetics. Sections 6 and 8.4 discuss the mechanism of carcinogenic action. DHS staff applied a physiologically-based pharmacokinetic model to estimate low-dose risks. The model suggested lower human risks than predicted by the other methods. However, as indicated in the Executive Summary "...DHS staff concluded that the relative absence of detailed information on human metabolism of [methylene chloride], the failure of the NTP bioassay to demonstrate saturation of the carcinogenic effect, and other factors indicate that application of a pharmacokinetic approach to risk assessment is premature." This physiologically-based pharmacokinetic model has not been validated by independent experimental data. The model has not been shown to predict any toxicologic effect with greater precision than direct use of the exposure concentration. Current validation of the physiologically-based pharmacokinetic model rests on theoretical considerations. DHS staff is willing to use this model approach when: 1) additional human and animal parameters have been measured, 2) when it is independently validated experimentally, and 3) when the approach, for the compound under consideration, is shown to exhibit a better correlation with response than the applied dose. Consequently, DHS staff considered the factors indicated by the comment.

Comment: Interspecies differences in metabolism may be substantial. Available data explain the observed sensitivity of the mouse. B6C3F1 mice normally exhibit high spontaneous lung and liver tumor rates. This suggests that the mouse is a less appropriate model than the rat or hamster for predicting human response to methylene chloride, and may indicate that levels of methylene chloride in the California environment do not pose a human cancer risk (HSIA).

Response: This argument does not distinguish between published results, unpublished results and inference. DHS staff agrees that interspecies differences in enzymatic rates exist. Nevertheless, the connection between a specific metabolic intermediate and carcinogenicity has not been shown. The available data mentioned in the comment are unpublished results submitted by HSIA. Several key problems with these data are: 1) the human metabolism of methylene chloride by glutathione-S-transferase was reported to be zero in one of the reports. Another unpublished report indicates that the human metabolism is in the range of the rat and hamster. Knowledge of the interindividual variability among humans of this enzyme activity is very incomplete. The current pool of subjects tested is very small. 2) the available data do not have the power to associate only the glutathione (GSH) pathway with tumors. Other pathways may have a greater effect proportionately at low doses. As indicated above, the Clara cell has been shown in mice to produce reactive intermediates in the lung via the P450 pathway. Since these reactive intermediates have the ability to alkylate protein they may also alkylate DNA. This assumption would be consistent with tumor production exhibited in the mouse lung.

Comment: The draft report's presentation of epidemiological studies is confusing. This is due in part to intermixing data from five articles, rather than presenting them in chronological order (Eastman Kodak Company [Kodak]).

Response: The final draft to the Scientific Review Panel will be revised to make the presentation less confusing and to clarify statements that may be misinterpreted by those unfamiliar with the studies.

Comment: The findings from the latest epidemiological studies should have been emphasized, because these studies provided the most complete follow-up and exposure information (Kodak).

Response: DHS staff felt that the latest findings were emphasized in the document, but it is hoped that in the revised version this will be more readily apparent.

Comment: Epidemiological studies show no evidence of an increased cancer risk for all sites or for the primary sites associated with lesions found in animal studies. The finding among Eastman Kodak employees of 8 observed cases of pancreatic cancer versus 3.2 expected does not imply a causal association with methylene chloride; it may have been due to chance (Allied, Kodak). No dose-related effect was observed in the mortality study; the results may have been confounded by smoking, alcohol consumption, diabetes, other chemical exposures, and other risk factors (Kodak). This may indicate that levels of methylene chloride in the California environment do not pose

a human cancer risk. The report should give greater weight to the negative findings at the high exposure levels in the studies of workers (HSIA).

Response: DHS staff does not believe that the epidemiological studies are definitive, due to their limited power. As indicated on pages 7-2, 7-3, 7-4, and 7-7 of the draft report, the available epidemiological data do not indicate a significantly increased cancer rate from methylene chloride exposure, where the test was done with an α-level (two-sided) of 0.01. The actual p-value associated with the observed pancreatic cancer deaths is 0.017 using New York State Controls, and 0.014 using Kodak controls. To conclude that a compound is likely to be carcinogenic in humans does not require positive human evidence; strong animal evidence may be sufficient. To rule out carcinogenicity on the basis of human data, for any compound, would require multiple, negative, well-designed studies. Such negative studies would need to have historical exposure information (i.e., industrial hygiene samples) for all relevant job sites, and individual employee records relating work periods to job sites. These studies would also need to have sufficient power, a long follow-up period, and substantial data on confounding. In light of the clear carcinogenicity of methylene chloride in two animal species, additional negative epidemiologic data would be required to separate the animal and human responses. For these reasons, DHS staff do not give great weight to the negative findings in the epidemiological studies as is suggested by the comment.

Comment: There is no apparent evidence of biologic plausibility for pancreatic cancer in man (Kodak). Pancreatic cancer has been found in association with certain chemical exposures in the rat and hamster, (e.g.,

bis(chloromethyl)ether, 4-hydroxyamino-quinoline-1-oxide, the diazoketone azaserine, the methylnitrosourea-containing amino acid N-(N-methyl-N-nitroso carbamoyl)-L-ornithine, nafenopin and clofibrate) but following exposure to methylene chloride it was not observed in rats dosed orally or in rats or hamsters dosed by inhalation (Kodak). It is unlikely that methylene chloride is a human pancreatic carcinogen (Kodak).

Response: A substantial amount of information on the potential carcinogenicity of these six compounds in animals is not available, but the IARC monographs contained the following information. Methylnitrosourea produced tumors in the pancreas of rats under certain protocols, but it produced pancreatic tumors consistently in guinea pigs. In contrast, methylnitrosourea did not produce pancreatic tumors in mice, hamsters, pigs, dogs, rabbits, or gerbils; in these species other tumors were produced following methylnitrosourea exposure. These other tumors include those in the central and peripheral nervous tissue, stomach, esophagus, respiratory tract, intestine, lymphoreticular tissues, skin and kidney. The tumor site(s) for methylnitrosourea depends on the species tested and the route of exposure. The production of pancreatic tumors in rats or guinea pigs following exposure to methylnitrosourea did not predict the presence of pancreatic tumors in the other species tested. Nafenopin produced pancreatic and hepatocellular carcinomas in the rat but produced only hepatocellular carcinomas in mice. Thus, the production of pancreatic tumors in rats was not predictive of pancreatic tumors in mice. Clofibrate has been tested only in rats and produced pancreatic carcinomas (3/36), hepatocellular carcinomas (14/36), and numerous types of tumors in various other tissues. Thus, these studies indicate that the production of a

specific tumor type cannot necessarily be extrapolated across species. This lack of concordance for specific tumor sites is not restricted to pancreatic tumors, but is characteristic of many chemically induced tumor types. In addition, although pancreatic tumors have been produced by some chemicals in some studies with rats and hamsters, these two species have not been shown to be specifically sensitive to the development of pancreatic cancer. A negative result in the pancreas from any specific chemical would therefore not provide assurance that the chemical would not produce pancreatic cancer in humans.

With this information, one can focus on whether pancreatic tumors in man are inconsistent with tumors produced by methylene chloride in animals. Methylene chloride produces tumors at different sites across species. As a result of methylene chloride inhalation, rats have developed salivary gland tumors, mammary tumors and liver tumors, while mice have experienced increased incidences of liver tumors and lung tumors. Thus, although pancreatic tumors were not produced in rats or mice by inhalation, the specific tumor types that might occur in man following methylene chloride exposure cannot be accurately predicted. The Kodak comment states that pancreatic cancer in rats has not been asociated with oral or inhalation exposure to methylene chloride. The studies cited were the NTP inhalation studies and several industry-sponsored studies. However, a draft NTP gavage study reports that 19 of 50 male rats given 500 mg/kg-day methylene chloride developed pancreatic adenomas (Draft NTP Technical Report on the Carcinogenesis Bioassay of Dichloromethane in F344/N Rats and B6C3F1 mice, 1982). For male rats given 1000 mg/kg-day, 15 of 47 developed pancreatic tumors. In contrast, 2 of 96 control male animals developed pancreatic

tumors. Thus, methylene chloride produces tumors in several tissues and there is some suggestive evidence that methylene chloride can induce pancreatic tumors in rats.

In summary, strong concordance does not exist between tumor sites in animals and in man. Compounds that produce tumors in the liver, lung or other sites in one species may produce pancreatic tumors in another species. Some limited evidence indicates that methylene chloride may produce pancreatic tumors in the rat. Evidence for the biological plausibility for methylene chloride's production of pancreatic tumors in man is available in the literature. Consequently, although methylene chloride has not been causally associated with pancreatic cancer in humans, the suggestive human evidence is not inconsistent with the location of tumors produced by methylene chloride in experimental animals.

Comment: To evaluate the validity of the risk estimates from animal data, the staff of DHS derived risk estimates from epidemiological data. To do so, the staff used a modeling procedure that allowed only linear changes with dose and forced the (linear) response function through the origin. The upper bound risk estimate generated from the model used in the draft report is highly insensitive to differences in the number of observed deaths and the dose-response relationship within the cohort. It should therefore have been expected that the resulting estimates would be consistent with those derived from animal data and the linearized multistage model (Kodak). Using mortality findings from a tumor site of questionable significance and ignoring information contained in the lower bound estimates contributed to the lack of contradiction between the estimates derived from the animal and

epidemiological studies. Thus, the human and animal data are not consistent with one another (Kodak).

Response: DHS staff did not ignore the information in the human lower bound estimates; the human lower bound estimates are consistent with no excess cancer risk. The purpose of examining the upper bound estimates was to determine if the human finding was consistent with the carcinogenic potency of methylene chloride estimated in animals. The lack of sensitivity of the multiplicative model does not diminish the consistency between animal and human data. It may simply indicate the lack of power of the epidemiological study to clearly distinguish a negative human result from risks predicted by a positive animal result.

A second approach taken by DHS staff to assess the consistency of the animal-based risk assessment with the results of epidemiologic studies was not mentioned in the comment. This approach has been used to evaluate other compounds, and in two cases, ethylene dibromide and cadmium, detected a discrepancy of over ten-fold. This approach is sensitive enough to detect major discrepancies between the observed epidemiologic data and predictions based on extrapolation from animal bioassay. As stated in the draft document (pages 8-14), this approach showed predictions to fall within a factor of two of the observed. Thus, two approaches indicated that the human epidemiologic data was consistent with that predicted from the animal bioassays.

Comment: The probability of observing eight or fewer pancreatic cancer deaths, given an animal-based expectation of 12.5, is relatively low

(0.125). Similarly, although the observed-versus-expected lung and liver cancer deaths were within a factor of 3, the human findings at these sites are highly unlikely, given the animal model predictions (probability less than 0.0001) (Kodak).

Response: A probability of 0.125 associated with the observed data, under a null hypothesis of 12.5 or greater, is not particularly low and does not seem to be a basis to reject the hypothesis. Although the animal-based model predicts higher lung and liver cancer rates than observed in humans, DHS staff believes that considering the enormous uncertainties in extrapolating from high to low doses and from animals to man, a factor of three should be viewed as consistent.

Comment: The draft report should have evaluated data for all primary cancers rather than only those from the site (pancreas) for which there was a suggestive increase (Kodak).

Response: In the DHS staff analysis, the most sensitive animal site was compared to the human site exhibiting the greatest response in the epidemiologic study. The suggestion by Kodak that the analysis should now be redone looking at all cancers in humans and all cancers in animals would not resolve the issue. Use of all primary cancer sites is a poor way to evaluate a specific carcinogen, since individual chemical compounds tend to affect certain sites more than others. In light of the high background cancer rates in humans and other animals, combining chemically-induced and background sites would substantially dilute the sensitivity of the analysis.

IV. Air Resources Board
Letters to Comment Originators

STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
CRAMENTO, CA 95812

April 11, 1988

Paul A. Cammer, President
Halogenated Solvents Industry Alliance
1225 19th Street, N.W., Suite 300
Washington, D.C. 20036

Dear Mr. Cammer:

Thank you for your comments on Parts A and B of the Preliminary Draft Report on Methylene Chloride. My staff has prepared responses concerning comments on the Part A report while the California Department of Health Services is responding to comments on Part B. Both sets of responses will be incorporated into Part C of the final draft report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 323-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

cc: George Alexeeff
Department of Health Services

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

April 11, 1988

Thomas J. Dufficy
National Association of Photographic Manufacturers, Inc.
600 Mamaroneck Ave.
Harrison, New York 10528

Dear Mr. Dufficy:

Thank you for your comments on Part A of the Preliminary Draft Report on Methylene Chloride. My staff has prepared responses to your comments which will be incorporated into Part C of the final draft report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 323-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

April 11, 1988

Roger W. Reinhold, Manager
Department of Toxicology
Allied Corporation
P.O. Box 1021 R
Morristown, New Jersey 07960

Dear Mr. Reinhold:

Thank you for your comments on Part B of the Preliminary Draft Report on Methylene Chloride. Your comments have been forwarded to the California Department of Health Services. Their staff is preparing responses which will be incorporated into Part C of the Final Draft Report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 323-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

cc: George Alexeeff
Department of Health Services

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

April 11, 1988

Selina Bendix, President
Bendix Environmental Research, Inc.
Fox Plaza, Suite 902
1390 Market St.
San Francisco, CA 94102

Dear Ms. Bendix:

Thank you for your comments on Part A of the Preliminary Draft Report on Methylene Chloride. My staff has prepared responses to your comments which will be incorporated into Part C of the final draft report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 232-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

STATE OF CALIFORNIA
AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
S MENTO, CA 95812

GEORGE DEUKMEJIAN, Governor

April 11, 1988

Dr. Roger Atkinson
University of California, Riverside
Statewide Air Pollution Research Center
Riverside, CA 92521

Dear Dr. Atkinson:

Thank you for your comments on Part A of the Preliminary Draft Report on Methylene Chloride. My staff has prepared responses to your comments which will be incorporated into Part C of the final draft report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 323-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

April 11, 1988

Dr. Arthur Winer
University of California, Riverside
Statewide Air Pollution Research Center
Riverside, CA 92521

Dear Dr. Winer:

Thank you for your comments on Part A of the Preliminary Draft Report on Methylene Chloride. My staff has prepared responses to your comments which will be incorporated into Part C of the final draft report, which is expected to be released to the public within a month.

If you have any questions concerning the report, please contact Richard Corey of my staff at (916) 323-8511.

Sincerely,

Joan E. Denton

Joan Denton, Ph.D., Manager
Substance Evaluation Section
Stationary Source Division

PART C ADDENDUM

PUBLIC COMMENTS AND RESPONSES TO THE FINAL DRAFT METHYLENE CHLORIDE REPORT

Prepared by the staff of the Air Resources Board

March 1989

(Part C Addendum reflects the comments received from the public during May 3, 1988 to may 24, 1988 public review period for the Final Draft Report. The responses of the air Resources Board staff to those comments are contained in Part C Addendum)

ADDENDUM TO PART C - CONTENTS

I. Comments Received from the Public

A. The Halogenated Solvents Industry Alliance

Heron, Burchette, Ruckert & Rothwell

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1025 Thomas Jefferson Street, N.W.
Washington, D.C. 20007

(202) 337-7700
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(602) 248-0036
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One City Centre
770 L Street, Suite 1150
Sacramento, CA 95814
(916) 446-1428
FAX (916) 446-6003

1400 MBank Tower
221 West Sixth Street
Austin, TX 78701
(512) 499-0606
FAX (512) 499-8729

May 24, 1988

BY COURIER

Mr. Robert Barham
Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
P.O. Box 2815
Sacramento, California 95812

Re: Methylene Chloride

Dear Mr. Barham:

Enclosed are the comments of the Halogenated Solvents Industry Alliance (HSIA) on the final draft report on methylene chloride. In light of the significant scientific and science policy questions raised by the recommendations and the health effects assessment in the draft report, HSIA requests an opportunity to appear before the Scientific Review Panel when it addresses methylene chloride. HSIA representatives will be in touch with you concerning this request.

Sincerely,

Caffey Norman

W. Caffey Norman, III

Enclosure

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

March 9, 1988

SAB-EHC-88-013

OFFICE OF
THE ADMINISTRATOR

Hon. Lee M. Thomas
Administrator
U.S. Environmental Protection
Agency
401 M Street SW
Washington, D.C. 20460

Dear Mr. Thomas:

On August 13-14 1987 the Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee met in Washington, D.C. to review two documents prepared by EPA's Office of Research and Development that assess health effects associated with dichloromethane (methylene chloride). These documents included:

- a June 1987 Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments, and
- a July 1987 Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology.

The Subcommittee's evaluation of these documents is presented in two parts: 1) a discussion of scientific issues related to pharmacokinetics and metabolism, and 2) review of specific issues pertinent to the addendum. The Subcommittee focused less attention on the former document because much of its scientific content overlapped with the Addendum.

The Subcommittee concludes that the Addendum was one of the best documents it has reviewed in terms of its clarity, coverage of the data and analysis of scientific issues. This document clearly demonstrates the potential utility of pharmacokinetic data in risk assessment. EPA should continue to use this approach in future risk assessments, whenever scientifically possible.

For reasons discussed in the attached report, the Subcommittee concludes that the level of uncertainty is greater and the hazard posed by dichloromethane may be less than that expressed by the categories of EPA's cancer risk assessment guidelines.

The Subcommittee appreciates the opportunity to conduct this scientific review. In behalf of the Subcommittee we request that the Agency formally respond to the scientific advice provided in its attached report.

Sincerely,

Norton Nelson, Chair
Executive Committee

Richard A. Griesemer, Chair
Environmental Health Committee

John Doull, Chair
Halogenated Organics Subcommittee

Halogenated Organics Subcommittee
Review of the June 1987 Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments: and July 1987 Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology

Pharmacokinetics and Metabolism

The application of a physiologically based pharmacokinetics (PBPK) model presented in the document is generally well conceptualized and organized. This application represents a novel approach that can sharpen EPA's ability to refine human risk estimates in the future. The Subcommittee commends EPA for incorporating such information into the weight of evidence determination of the carcinogenic potential of dichloromethane. Adoption of the Reitz-Anderson model, with certain modifications, is a positive step forward for the Agency's risk assessment process. The critical analysis of the constraints of the model are thoroughly discussed and scientifically balanced. EPA, for example, is justified in adjusting the estimates of Reitz-Anderson for breathing rates traditionally used in EPA models. The rationale for using surface area factor adjustment, and contrary arguments, are clearly described.

The PBPK model has appeared in the published peer reviewed literature. The novel applications of the latest data concerning the model that were presented at the meeting are new and received enthusiastic support from the Subcommittee, which also recommends publication of this approach. The Subcommittee recognizes that validation will be required for this and other compounds before using this approach generally for human risk calculations.

One possible problem is that the metabolic conversion of dichloromethane by different animal species by either the cytochrome P-450 oxidase system (mixed function oxidase or MFO) or the glutathione-S-transferase system (GST) was not supported by data indicating that measurements in each species were conducted at conditions optimal for pH, ionic strength or temperature for that substrate in that tissue for each specific species. Unless such conditions are utilized, interspecies quantitative data may be meaningless, and the basis for the use of this approach in human risk estimation could be flawed.

Comparative in vitro studies with rat, mouse, hamster and human cytosol showed that the dichloromethane-GST conjugation rates in humans were at least 50 times lower than in mice. The Subcommittee points out that: 1) mice have the highest activity and liver tumor induction that correlates with GSH-metabolite production above saturation of the MFO system; 2) hamsters have much lower activity and no liver tumors; and 3) humans have even lower activity indicating very low, if any, liver tumor inducing potential for dichloromethane. There was a good correlation between the relative rates of dichloromethane-GSH conjugation and susceptibility of liver tumors. The conclusion that, at low exposure levels, the carcinogenic hazard to humans

from dichloromethane appears very low needs to be clearly stated in the document.

The document could be simplified by eliminating the Chapter 7 discussion of a "rationale" for surface area scaling and replacing it with the statement on page 107 that, "The fact that there is no clear basis for choosing the use of surface area correction or not...is a weakness of the current state-of-the-art of quantitative risk assessment."

Discussion of Specific Scientific Issues Related to the Addendum

1. In considering an overall weight of evidence approach to risk assessment, other factors, such as the nature of the animal tumor response, mechanistic data (such as binding of the chemical to DNA), genotoxic activity and epidemiological data should also be discussed.

2. In evaluating the tumor data, the Subcommittee urges caution in extrapolating the existing animal bioassay to humans. Although dichloromethane induced both lung and liver tumors in the mouse models, these observations occurred only at high doses which likely influenced the compound's overall metabolism. Other bioassays in other species, or at lower doses in mice, induced negative results. The fact that the Reitz-Anderson model is able to predict these responses suggests that an interspecies correction factor based on surface area may not be necessary for extrapolating the tumor data to humans. This is particularly true when hamster and rat data (GSH transferase) are considered using the PBPK analysis. The observation of benign mammary tumors and salivary gland tumors in rats should not be used as strong evidence for human carcinogenic potential given the uncertain significance of these lesions. The benign mammary tumors have very low potential for predicting malignancy even in the rat, and salivary gland tumors were reported in only one of the studies.

3. EPA should discuss the findings of several investigators (Shumann et. al., Dow Chemical; Green et. al., ICI, U.K.) that indicate that dichloromethane or its metabolites do not exhibit any potential to alkylate liver or lung DNA following in vivo exposure. Such findings raise the clear possibility that dichloromethane may have produced its carcinogenic responses in mice by non-genotoxic mechanisms, and may include an important contribution of cytotoxicity in the overall tumorigenic process. Such data become particularly relevant as carcinogenicity was observed only at extremely high exposures and was absent at lower, potentially noncytotoxic doses.

4. Critical uncertainties remain regarding the relationship between dose to target tissues and tumor incidence, since little information on the mechanism of action is available for dichloromethane. The Subcommittee accepts EPA's use of a surface area scaling factor for delivered dose as appropriate for calculating an upper bound estimate, but it views this usage as more conservative than the usual "default" assumption from the Agency cancer guidelines, scaling administered dose by surface area from animals to humans. Further research may indicate that, at least for some substances, scaling delivered dose on the basis of body weight is more appropriate than scaling by surface area.

5. The degree of nonlinearity in the dose reponse relationship for delivered dose is an important source of uncertainty. As noted on page 110 of the Addendum, EPA uses the linearized multi-stage model to calculate an upper bound estimate. The true dose response curve may fall off more rapidly than a linear relationship at low doses. Biological information supporting a nonlinear or threshold type of dose response relationship is potentially important for risk management decision making because it becomes less likely that the default plausible upper bound linear estimate will be an accurate estimate of human risk, especially at low exposure levels in the ambient environment.

6. The Subcommittee was presented with a brief report on the current status of the Kodak epidemiological study of dichloromethane. A slight excess of pancreatic cancer deaths has been separately reported. However, the study is based only on death certificate data and has not included a histopathologic review of biopsies or surgical specimens from such patients. The incidence of pancreatic cancers tended to cluster, and only with further surveillance of the population can a more definitive statement be made on human health risk. The clinical diagnosis of pancreatic cancer is difficult and may be easily confused with other abdominal malignancies. Thus, without pathologic confirmation, the Subcommittee cannot necessarily conclude that an excess of pancreatic cancer deaths has occurred. However, neither can it be concluded that dichloromethane is safe for humans at the occupational exposure levels seen in the study. The Agency should determine the criteria of the Kodak epidemiological study necessary to substituting the animal derived risk estimate with a human derived risk estimate. Finally, the Subcommittee recommends the continuation of this important study.

7. Although there is an impressive weight of evidence implicating metabolites of dichloromethane in tumors, the possibility should not be discounted that the actual tumor inducing agent is the parent compound(s). In order to present a more balanced document, this possibility should be discussed at greater length, perhaps in Chapter 8.

8. Both the scaling factor and the shape of the dose response relationship are important areas for further work in order to aid development of risk assessment methods that incorporate available scientific data and judgement on biological mechanisms. As better information is developed on pharmacokinetics, pharmacodynamics and mechanisms for chemical carcinogenesis, it should be possible to further reduce uncertainties in human risk estimates.

9. For all of the above reasons, therefore, the Subcommittee concludes that the level of uncertainty is greater and that the hazard for dichloromethane may be less than that expressed by the Agency's classification system in its cancer risk assessment guidelines.

More detailed discussion of these and other issues by individual Subcommittee members has been forwarded to the Office of Research and Development.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Roster for August 13-14, 1987 Review of the Draft
Assessment Documents for Dichloromethane

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BEFORE THE CALIFORNIA AIR RESOURCES BOARD

PROPOSED IDENTIFICATION OF METHYLENE CHLORIDE AS A TOXIC AIR CONTAMINANT

Comments of the
Halogenated Solvents Industry Alliance
1225 19th Street, N.W.
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President

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May 24, 1988

PROPOSED IDENTIFICATION OF METHYLENE CHLORIDE AS A TOXIC AIR CONTAMINANT

By letter dated April 28, 1988, the final draft Report to the Air Resources Board on Methylene Chloride (the draft Report), prepared by the staffs of the Air Resources Board (the Board) and the Department of Health Services (DHS), was made available for review and comment before submission to the Scientific Review Panel (the Panel). The draft Report consists of Parts A (use and exposure), B (health effects), and C (public comments on Parts A and B and the DHS staff response), and also contains an overview and recommendation that methylene chloride be identified as a toxic air contaminant under Cal. Health and Safety Code § 39660.

The Halogenated Solvents Industry Alliance (HSIA) commented extensively in January 1988 on the preliminary draft report on methylene chloride, released in late November 1987. HSIA's 60-page comment focused primarily on Part B (health effects). Accordingly, we were very surprised and disappointed to find that Part B has not been revised at all by DHS staff, and is the same document (November 1987 draft) that was sent out during the first comment period. HSIA expended significant effort and resources to respond within 45 days to the DHS staff assessment. No purpose would be served by repeating the earlier HSIA comments, which are reprinted in Part C of the draft Report.

The letter soliciting comment on the final draft Report states that any revisions to the DHS staff health effects assessment (Part B) will be incorporated into the Report after the comment period and before review by the Panel. This highly unusual procedure for peer reviewing a health effects assessment would seem to be inconsistent with Health and Safety Code § 39660, which requires that "the report, together with the scientific data on which the report is based, shall . . . be made available to the public and shall be formally reviewed by the scientific review panel" (emphasis added). The law does not provide for one draft of the report to be made available for public review and a later, different version to be reviewed by the Panel. We submit that the Board could not sustain a decision to identify methylene chloride as a toxic air contaminant based on a health effects assessment that the public was not allowed to review prior to Panel consideration.

HSIA's expression of concern is not an effort to rely on a technicality to delay or subvert the statutory process for identifying toxic air contaminants. The staff recommendation to the Board is premised on a risk assessment that rejects the use of scientific information that has been acknowledged by academic and government scientists alike as a milestone in efforts to predict more accurately the health risk, if any,

from atmospheric concentrations of pollutants.[1] Indeed, the DHS staff assessment will not be helpful to the Board in addressing a critical regulatory issue -- whether there is a threshold exposure level below which no significant adverse health effects can realistically be anticipated. See Health and Safety Code § 39662(c).

None of the key points in the January 1988 HSIA comments has been adequately addressed by DHS staff. The DHS response is confusing in several respects, e.g., its use of the International Agency for Research on Carcinogens (IARC) classification of methylene chloride as a "possible," but not a "probable," human carcinogen to support identification of methylene chloride as a toxic air contaminant. The DHS response fails to note as well that EPA's Science Advisory Board, an independent peer review panel established by federal statute, has formally stated that "the level of uncertainty is greater and the hazard posed by dichloromethane [methylene chloride] may be less than that expressed by the categories of EPA's cancer risk assessment guidelines."[2]

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[1] DHS staff is required by law to consider all available scientific data on health effects, including potency, mode of action, and other relevant biological factors. Health and Safety Code § 39660(b),(c).

[2] Letter to Lee M. Thomas, EPA Administrator, from Drs. Nelson, Griesemer, and Doull, EPA Science Advisory Board (Mar. 9, 1988) (attached).

Rather than repeating our January 1988 comments, two key issues will be discussed below to show the importance of a thorough review by the Panel.[3] On both points, the DHS staff health effects assessment is inconsistent with (i) EPA's evaluation of methylene chloride, culminating an 8-year effort involving independent scientific peer review on a number of separate occasions; (ii) the recommendations made by EPA's Science Advisory Board; and/or (iii) the overwhelming weight of current scientific consensus.

A. Available Human Evidence Indicates No Increased Cancer Risk from Methylene Chloride

The DHS health effects assessment transforms a state-of-the-art epidemiology study, showing no indication of increased overall cancer risk, into evidence for the staff's position that methylene chloride causes cancer in humans. Since the study has been reported in the scientific literature as showing no evidence of increased overall cancer risk,[4] and

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3 The DHS staff response, contained in Part C of the draft Report, rejects virtually every public comment on its health effects assessment. HSIA disagrees with DHS staff on each of these points and reserves the right to raise before the Panel each of the points that warrant a determination by the Panel that the DHS health effects assessment is seriously deficient.

4 Hearne, et al., Methylene Chloride Mortality Study: Dose-Response Characterization and Animal Model Comparison, J. Occ. Med. 29:217-228 (1987).

accepted as a negative study by EPA, an unusual interpretation of the results was necessary in order for DHS staff to consider the study to be consistent with "human risk estimates based on animal studies." The only way the results could be so interpreted would be to ignore the overall mortality results (i.e., total cancer and hypothesized tumor sites such as lung and liver), and to restrict the analysis to the only site (pancreas) showing an increased number of cancer deaths (8 observed vs. 3.2 expected). This is the approach taken in the DHS health effects assessment.

Without repeating the criticisms of the DHS staff interpretation that have been submitted by Eastman Kodak Company, we note that there were several sites (colon-rectum, genito-urinary) where a result of the same magnitude was seen, but in the opposite direction (2 observed vs. 7 expected, 3 observed vs. 8 expected, respectively). Observed-expected differences of this type are likely, due to chance alone. Perhaps in recognition of the weakness of its interpretation, the DHS staff response (p. 15-16) dredges up animal bioassay results and relies on these results as "[e]vidence for the biological plausibility for methylene chloride's production of pancreatic tumors in man." The source for this purported evidence is a draft NTP technical report.[6] Based on "significant discrepancies in experimental data," however, NTP

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[6] Draft NTP Technical Report on the Carcinogenesis Bioassay of Dichloromethane (Methylene Chloride) (T.R. No. 254) (Sept. 22, 1982).

announced the cancellation of this report in 1983.[5] We submit that a strange interpretation of human evidence, supported by admittedly flawed animal data, has no place in a scientific risk assessment.

B. Failure to Use Available Pharmacokinetic Data Is Inconsistent with Current Scientific Practice

The DHS staff health effects assessment recognizes that extensive scientific data on the metabolism, pharmacokinetics, and mechanism of methylene chloride are currently available, but declines to make use of this information either in its assessment of whether atmospheric concentrations of methylene chloride are likely to pose a cancer risk to humans or in its estimate of the magnitude of the theoretical cancer risk. The failure to incorporate this information, after a request from a Panel member that "future documents include a

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[5] 48 Fed. Reg. 35508 (Aug. 4, 1983). The deficiencies in the study on which the DHS staff response relies triggered a Congressional investigation of the NTP bioassay program and its quality-assurance procedures, and the termination of the contractor that had performed the defective study and some fifty others. See Hearings before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, 98th Cong., 1st Sess. (Nov. 7, 1983), Serial No. 98-97; General Accounting Office, Report to the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, National Toxicology Program: Efforts to Improve Oversight of Contractors Testing Chemicals (June 25, 1985).

section on pharmacokinetics,"[6] has not been adequately explained.

In its response to public comments, DHS staff asserts that its refusal to make use of these relevant data is appropriate because the data are unpublished and EPA's risk assessment, which does make use of these data, is in draft form. Extensive research on the metabolism and pharmacokinetics of methylene chloride has, however, been published in the open scientific literature and provided to DHS.[7] Published articles include Andersen et al., Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride, Tox. Appl. Pharm. 87:185-205 (1987); Reitz et al., Development of Multispecies, Multiroute Pharmacokinetic Models for Methylene Chloride and 1,1,1-Trichloroethane (Methyl Chloroform), in Pharmacokinetics and Risk Assessment 391-409 (National Academy Press 1987); and Green et al., Macromolecular Interactions of Inhaled Methylene Chloride in Rats and Mice, Tox. Appl. Pharm. 93:1:10 (1988). Numerous other articles are mentioned in our January 1988 comments.

The Addendum to the EPA Health Assessment Document on Methylene Chloride is, as the DHS response correctly states, a

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[6] Meeting Summary, Scientific Review Panel on Toxic Air Contaminants (July 7, 1987), at 3.

[7] HSIA sponsored a seminar on this research for the benefit of DHS staff on June 4, 1986, at the DHS offices in Berkeley.

review draft. It has, however, now been formally approved by EPA's Science Advisory Board, which stated:

> The Subcommittee [Halogenated Organics] concludes that the Addendum was one of the best documents it has reviewed in terms of its clarity, coverage of the data and analysis of scientific issues. This document clearly demonstrates the potential utility of pharmacokinetic data in risk assessment. EPA should continue to use this approach in future risk assessments, whenever scientifically possible.[8]

Moreover, as indicated in the January 1988 HSIA comments, it has been clear since well before release of the DHS draft Report in November 1987 that there is strong scientific support for the use of metabolic and pharmacokinetic information on methylene chloride in risk assessment.[9]

In reviewing an earlier draft Addendum to the EPA Health Assessment Document on Methylene Chloride, Dr. John Doull had stated:

> [W]e criticize modeling because we say that it ignores the relevant biology. Here we have, if anyplace, we have relevant biology, and gee whiz, if we can't make it work with methylene chloride, we're in deep trouble.[10]

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[8] Letter to Lee M. Thomas, EPA Administrator, from Drs. Nelson, Griesemer, and Doull, EPA Science Advisory Board (March 19, 1988).

[9] See, e.g., New Data Indicate Methylene Chloride Not Carcinogenic, Some SAB Members Say, Chem. Reg. Rep. (BNA) 11:862 (Aug. 14, 1987).

[10] Transcript, Science Advisory Board Review of Draft Addendum to the Health Assessment Document for Methylene Chloride (May 23, 1985), at 86.

In response to similar statements from scientists and regulators, a major research program was undertaken in late 1985 by the European Council of Chemical Manufacturer's Federation (CEFIC) and by Dow Chemical U.S.A. in an attempt to investigate the strikingly different responses seen in various long-term bioassays of methylene chloride. This research program has cost several million dollars and taken over two years of effort. The results have been published as rapidly as possible, and use of the information in risk assessment has been recommended by a National Academy of Sciences Workshop, praised by the FDA official responsible for methylene chloride risk assessment as an "interesting and useful . . . approach," and recognized by a broad scientific consensus as an important step forward.[11] In light of the widespread review of this scientific research, the willingness of EPA to make use of the data, and the fact that HSIA and CEFIC have made every effort to ensure that DHS staff receive all relevant information as soon as it is available, the failure to make use of the data in the DHS health effects assessment seems inexplicable.[12]

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[11] See, e.g., Pharmacokinetics Seen Reducing Risk Assessment Uncertainties, Food Chemical News at 8-10 (Mar. 14, 1988) (report of Toxicology Forum meeting); Physiologically-Based Pharmacokinetic Risk Assessment Model Hailed, Food Chemical News at 29-31 (Feb. 24, 1986) (same).

[12] We note also that DHS staff apparently had no reservations about using data in a draft NTP report to support its position on pancreatic tumors, discussed above, even though the report was formally withdrawn after peer review. In light of this, it is difficult to understand an unwillingness to use the analysis in a draft EPA report that has been approved after peer review and will shortly be published.

Conclusion

The foregoing discussion addresses only two of the most serious shortcomings in the DHS health effects assessment. In addition, the Board and the Panel should give careful consideration to the regulatory and science policy consequences of approving a health effects evaluation that disregards available data and calculates risk estimates at significant variance from estimates that have been scientifically peer reviewed and will form the basis for federal regulatory evaluations of methylene chloride. Continued reliance on an archaic approach to risk assessment will set DHS staff apart from the scientific community and could hinder the Board's ability to make rational regulatory decisions. The Panel should conclude that the draft health effects assessment is "seriously deficient" for purposes of Health and Safety Code § 39661(c).

Attachment

II. Air Resources Board Responses to Comments

1) The Halogenated Solvents Industry Alliance

a) Comment: The letter soliciting comment on the final draft report states that any revisions to the DHS staff health effects assessment (Part B) will be incorporated into the report after the comment period and before review by the Panel. This highly unusual procedure for peer reviewing a health effects assessment would seem to be inconsistent with Health and Safety Code Section 39660, which requires that "the report, together with the scientific data on which the report is based, shall ... be made available to the public and shall be formally reviewed by the Scientific Review Panel" (emphasis added). The law does not provide for one draft of the report to be made available for public review and a later, different version to be reviewed by the Panel. We submit that the Board could not sustain a decision to identify methylene chloride as a toxic air contaminant based on a health effects assessment that the public was not allowed to review prior to Panel consideration.

Response: See section IV for ARB's July 1, 1988 letter to HSIA regarding their comments.

III. Department of Health Services Responses to Comments

DEPARTMENT OF HEALTH SERVICES
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE DRAFT REPORT TO THE AIR RESOURCES BOARD
ON METHYLENE CHLORIDE:

SECOND COMMENT PERIOD

General Comment

Comment: Several comments were made by the Halogenated Solvents Industry Alliance (HSIA) with regard to the procedures in submitting the draft report for public comment. These procedural questions are under the jurisdiction of the Air Resources Board. However, one of HSIA's comments expressed concerns that Part B had not been revised after the first public review, which requires a response from Department of Health Services' (DHS) staff.

Response: As indicated in the previous DHS staff responses to comments, the presentation of the epidemiologic studies would be revised to provide better clarity as requested by Kodak. Only minor changes (such as the numerical error noted in the Kodak comment) were to be made in response to the first comment period. Since no substantial changes were to be made in response to the first public review period, a revised draft was not submitted.

TOPIC: Risk Assessment

Comment: The DHS response during the first comment period reported that a draft National Toxicology Program (NTP, 1982) study found pancreatic tumors in rats and that this was evidence for the biological plausibility of pancreatic tumor induction in humans by methylene chloride. The report in which these findings were published was subsequently canceled by its sponsoring agency (the National Toxicology Program), based on discrepancies in experimental data. In light of this, it is difficult to understand the unwillingness of DHS to use information in draft U.S. Environmental Protection Agency (EPA) reports (the June 1987 Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments, and the July 1987 Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology). The NTP report was withdrawn after it was peer reviewed, and the EPA reports have been approved by peer reviewers. (HSIA)

Response: The draft results of the NTP gavage study are not central to DHS' conclusions regarding biological plausibility. Methylene chloride has been shown to be carcinogenic in two animal species at several sites. These tumors include salivary gland sarcomas in rats (Burek et al. 1984), mammary gland tumors in rats (Burek et al. 1984, NTP 1986), combined liver tumors in rats (Serota et al. 1986a), hepatocellular adenomas and carcinomas in mice (Serota et al. 1986b, NTP 1986), and alveolar/bronchiolar adenomas and carcinomas in mice (NTP 1986). DHS staff concluded that the induction of pancreatic tumors by methylene chloride in humans is biologically plausible based on the lack site specificity in rodents. The Kodak comment (page 13) in the first public response period indicated that since rodents tumors had never been found in the pancreas resulting from methylene chloride exposure, there was no biological plausibility for pancreatic tumor induction. The

DHS staff comment merely pointed out that such a position is very weak due to the lack of site concordance and since a draft NTP study had indicated the pancreas as a potential tumor site. However, the fact that the NTP report has been withdrawn underscores the weakness in using any draft report (including the 1987 EPA reports, "Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments," and "Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology") to support a scientific argument. This would appear to be particularly important when the document has the words "Do not cite or quote" imprinted on it, as do the above-mentioned EPA documents; furthermore EPA staff had specifically asked DHS staff not to cite the reports since they were not final. However, subsequent to the first comment period EPA staff indicated that since much of the information in the document had been presented at scientific meetings and is present in a Consumer Product Safety Commission report (Cohn 1987), the document could be cited as a draft. DHS staff have evaluated the information in the EPA draft reports on its own merits. As a result, DHS staff have incorporated much of the EPA draft analysis into the current document. Consequently, a risk estimate based on the EPA draft report is included in the DHS document and reference is made to the EPA documents to acknowledge their source.

Comment: The DHS health effects assessment transformed an epidemiology study showing no indication of increased overall cancer risk "into evidence for the staff's position that methylene chloride causes cancer in humans." The DHS analysis is based on an observed excess of pancreatic cancer. Note, however, that there were several sites (colon-rectum, genito-urinary) where a result of the same magnitude was seen, but in the opposite direction. Observed-expected differences of this type can occur by chance alone. On this point, the DHS staff health effects assessment is inconsistent with EPA's evaluation of methylene chloride and the overwhelming current scientific consensus. (HSIA)

Response: The DHS health effects assessment document concurs with the EPA in concluding that human data for carcinogenicity are inadequate. The Hearne et al. (1987) study reported an excess in pancreatic malignancy deaths and this result is reported in the DHS health effects assessment document. As discussed in the health efffects document, and in the following comment, DHS staff used the reported excess of pancreatic cancer in its comparison of risk estimates from animal and human exposure. Such comparisons can be made even when there is no excess cancer risk observed by taking into account the statistical power of the epidemiological study.

Comment: The DHS health effects assessment employs an unusual interpretation of an epidemiological study in order to find it to be consistent with human risk estimates based on animal data. The interpretation is unusual in that it ignores the overall mortality results and restricts the analysis to the only site (pancreas) showing an increased number of cancer deaths. (HSIA)

Response: Hearne et al. (1987) and DHS staff both conducted comparisons of human and animal risk estimates. The differences in the procedures for comparing human and animal risks are spelled out in the DHS health effects document on methylene chloride. In the DHS staff analysis, the most sensitive animal site was compared to the human site exhibiting the greatest

response in the epidemiologic study. Use of all primary cancer sites to evaluate a specific carcinogen will dilute any effect that might observed, since individual chemical compounds affect certain sites more than others. Furthermore, in light of the high background rates of some cancers in humans and other animals, combining chemically induced and background sites would substantially decrease the sensitivity of the analysis. A similar type of analysis was conducted by EPA and Consumer Products Safety Commission (EPA 1987a) where they concluded (page 102): "Even if the pancreatic cancer deaths are discounted, the 95% upper-limit estimates based on lung tumors from the epidemiologic analysis ... are comparable to the upper-limit estimates derived from the mouse metabolized dose data."

Comment: The DHS staff declines to make use of extensive data on the metabolism, pharmacokinetics, and mechanism of methylene chloride that are currently available and has been provided to DHS staff. As a result, the DHS staff health effects assessment is inconsistent with EPA's draft evaluation of methylene chloride which makes use of the published and unpublished data provided to them. HSIA sponsored a seminar on this research for the benefit of DHS staff. The European Council of Chemical Manufacturers Federation (CEFIC) has undertaken an intense, costly investigation of the striking differences among the results of various long-term bioassays of methylene chloride. Use of information from this investigation has been recommended by a National Academy of Sciences Workshop and recognized by a broad scientific consensus as an important step forward. This scientific research has been widely reviewed, the EPA is willing to make use of the data, and HSIA and CEFIC have made every effort to ensure that DHS staff receive all relevant information as soon as it is available. In light of the above, the failure to make use of the data in the DHS health effects assessment seems inexplicable. Furthermore, a Scientific Review Panel member has requested that future documents include a section on pharmacokinetics. (HSIA)

Response: As indicated in the health effects document and in the response to a similar question in the first comment period (page 9), risk estimates based on pharmacokinetic data were calculated in the document. However, the DHS staff did not incorporate the information into the final risk assessment due to the numerous assumptions required and the extensive use of unpublished data in the model. Since the first comment period, much of the data has been published or extensively reviewed by independent scientific groups and DHS staff have reassessed the use of the model. After critical review of the pharmacokinetic information submitted by HSIA, DHS staff concluded that application of pharmacokinetics to calculate the internal dose of the sustance represented a plausible scientific approach for evaluating the cancer risks of methylene chloride. As discussed extensively in the document, DHS staff still have many reservations regarding the use of the Andersen et al. (1987) model, particularly since the pharmacokinetic adjustment may add uncertainty to the final potency values due to the additional assumptions necessary to estimate the dose. These assumptions include the following: the identification of the methylene chloride-glutathione conjugate as the sole metabolite responsible for carcinogenicity in laboratory animals and humans; the relative tissue distribution of glutathione and metabolic activities in laboratory animals versus humans; the relative tissue susceptibility to carcinogenic methylene chloride metabolites; the use of in vitro constants and acute metabolic values for

the prediction of chronic responses; and the use of estimates of physiologic parameters, partition coefficients, and metabolic constants that may not accurately reflect the actual human values. Substantial additional research is needed to externally validate the pharmacokinetic model and to determine the extent of human variability in the pharmacokinetics and pharmacodynamics of methylene chloride and its metabolites. However, DHS staff believe that pharmacokinetic modeling represents a scientifically plausible approach to evaluating the internal dose. Consequently, pharmacokinetic information submitted by HSIA was used in the final risk assessment range presented by DHS staff in Part B.

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IV. Air Resources Board Letters to Comment Originators

TE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor
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D··· ENTO, CA 95812

July 1, 1988

W. Caffey Norman, III
Heron, Burchette, Ruckert & Rothwell
Suite 700
1025 Thomas Jefferson Street, N.W.
Washington, D.C. 20007

Dear Mr. Norman:

Thank you for providing HSIA's comments on the final draft report on methylene chloride. HSIA's comments on Part B have been forwarded to the Department of Health Services (DHS). DHS staff are preparing responses which will be incorporated as an addendum to Part C of the report submitted to the Scientific Review Panel (SRP).

In addition to commenting on Part B, HSIA requested the opportunity to appear before the SRP when it reviews Parts A and B of the methylene chloride report. We have discussed your request with Dr. James Kendrick, Chair of the Scientific Review Panel. Dr. Kendrick supports the SRP's long-standing policy of not accepting written or oral testimony at SRP meetings. The SRP decided that by requiring public comment and agency responses in advance of the submission of the report to the SRP, the SRP's review would be both comprehensive and timely. The ARB Legal Office has advised the SRP that its process meets the statutory requirements set forth in Health and Safety Code Section 39661. The SRP receives the information submitted by the public, as all comments received regarding the substance under review and the report are included in Part C. Additionally, the report which is reviewed by the SRP is available to the public.

Before making a recommendation as to whether methylene chloride should be identified as a TAC, the SRP will carefully consider all comments that have been received. They will also evaluate the adequacy of ARB and DHS responses to comments as well as revisions to the report. The Panel may request further clarification if it believes this is necessary. There will also be an opportunity to testify before the Board when it considers the Panel's findings.

If you have any questions regarding this letter, please call me at (916) 322-7072.

Sincerely,

Robert D. Barham, Chief
Toxic Air Contaminant
Identification Branch

cc: Dr. Kendrick, Chairman
Scientific Review Panel
David Nawi
Bill Lockett
Peter Venturini