



California Air Resources Board

Proposed Identification of
TRICHLOROETHYLENE
as a Toxic Air Contaminant

Part C
Public Comments and ARB/DHS Staff Responses

State of California
Air Resources Board
Stationary Source Division

AUGUST 1990

**PART C - PUBLIC COMMENTS AND RESPONSES TO THE PRELIMINARY DRAFT
PART A AND B TRICHLOROETHYLENE REPORT**

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

March 1990

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I.

Comment Letters Received on the Preliminary Draft Version
of Trichloroethylene Parts A and B

HSIA HALOGENATED SOLVENTS INDUSTRY ALLIANCE

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September 8, 1989

Mr. Robert D. Barham
Chief
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Re: Trichloroethylene

Dear Mr. Barham:

Thank you for the opportunity to review the draft Technical Support Documents for the Proposed Identification of Trichloroethylene as a Toxic Air Contaminant. HSIA represents users, distributors, and producers of various chlorinated solvents, including trichloroethylene.

HSIA's comments to the Air Resources Board (ARB) address Part B of the draft report which reviews the Health Effects of Trichloroethylene. Our comments are enclosed with this letter, as well as copies of referenced documents which have not already been cited in the draft report.

Please do not hesitate to call me if the staff of the ARB or the Department of Health Services wish to discuss HSIA's comments on Part B of the draft report.

Sincerely,



Paul A. Cammer, Ph.D.
President

Enclosures

**BEFORE THE AIR RESOURCES BOARD
OF THE
STATE OF CALIFORNIA**

**Comments of the
Halogenated Solvents Industry Alliance
on the
Draft Technical Support Document:
Proposed Identification of Trichloroethylene
as a Toxic Air Contaminant
(Part B: Health Effects of Trichloroethylene)
July 1989**

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September 8, 1989

**Paul A. Cammer, Ph.D.
President**

BEFORE THE
CALIFORNIA AIR RESOURCES BOARD

COMMENTS OF THE
HALOGENATED SOLVENTS INDUSTRY ALLIANCE
ON THE
DRAFT TECHNICAL SUPPORT DOCUMENT:
PROPOSED IDENTIFICATION OF TRICHLOROETHYLENE
AS A TOXIC AIR CONTAMINANT
(Part B: Health Effects of Trichloroethylene)

Executive Summary

The Halogenated Solvents Industry Alliance (HSIA) offers these comments to the Air Resources Board (ARB) on Part B (Health Effects of Trichloroethylene) of the Draft Technical Support Document for the Proposed Identification of Trichloroethylene as a Toxic Air Contaminant. Our comments include a summary of the pertinent literature on the carcinogenic potential of trichloroethylene in animals and humans, a discussion of the importance of species differences in metabolism of this chemical, and a recommendation to develop a more plausible estimate of potential risk by better reflecting pharmacokinetic information.

HSIA is an association of users, distributors, and producers of chlorinated solvents, including trichloroethylene. Our members, as well as other users of trichloroethylene, have a vital interest in the accuracy and scientific validity of the Technical Support Documents which serve as the basis for the proposal to identify trichloroethylene as a toxic air contaminant. Decisions made by the ARB on the basis of the

Technical Support Documents will have a significant effect on actions taken by local air districts in California to regulate trichloroethylene. As a consequence of those actions, a large number of industrial and commercial users of trichloroethylene will be affected, as will the public that benefits from the applications of the chemical.

The overall weight of the scientific evidence for trichloroethylene suggests that it is unlikely to pose a carcinogenic risk to humans at ambient environmental or occupational exposure levels. The health effects of trichloroethylene have been studied extensively. The most significant finding to surface from the many long-term animal studies of trichloroethylene is that it produces liver cancer in mice, but not in rats and humans. The proximal carcinogen is trichloroacetic acid, a metabolite of trichloroethylene, which induces proliferation of peroxisomes in liver cells. Humans produce less trichloroacetic acid than mice and rats, and do not exhibit the critical biological response of peroxisome proliferation which is responsible for the formation of liver tumors in rodents. These documented species differences in response to trichloroethylene exposure between mice and rats, and between rodents and humans, provide strong support for the conclusion that the chemical does not pose a carcinogenic risk to humans.

Adding support to this conclusion are the findings of epidemiologic studies in workers exposed to trichloroethylene. None of these studies indicates elevated levels of cancer mortality in exposed populations. In the most important study, a cohort of over 2600 workers was examined at a manufacturing plant that used trichloroethylene as a degreasing agent, and no increased risk of cancer was found when compared to a comparable group of unexposed workers.

HSIA recommends that the draft report reflect more clearly the significant qualitative differences in metabolism of trichloroethylene between mice and rats, and between rodents and humans, and the preponderance of strong negative evidence for - carcinogenicity in human studies. Based on the weight of the scientific evidence, and the expert opinions of the International Agency for Research on Cancer (IARC) and the Science Advisory Board (SAB) of the U.S. Environmental Protection Agency (EPA), the data do not support the conclusion that the chemical poses a cancer risk to humans. If the ARB must perform a quantitative risk assessment for trichloroethylene, HSIA recommends that risk estimates reported in the draft document better reflect pharmacokinetic information. Such an approach will reduce the uncertainties inherent in the risk assessment process and will result in a more plausible estimate of risk to humans, as recommended by the ARB.

Carcinogenic Potential of Trichloroethylene

I. Experimental Animal Data

The animal carcinogenicity studies reviewed in the draft report are summarized below.

A. Mouse Studies

1. NCL, 1976

This gavage study showed an increased incidence of liver tumors in male and female B6C3F1 mice. The Science Advisory Board (SAB) of the U.S. Environmental Protection Agency (EPA) and other groups have offered a number of criticisms of the study, including the use of massive doses in large amounts of corn oil and improper housing of the test animals (SAB, 1984).

Interpretation of the study is confounded by the presence of stabilizers, including epichlorohydrin, a rodent carcinogen, in the test material. In addition, a large variation in response occurred between male B6C3F1 mice from two suppliers. It is appropriate, therefore, to eliminate these responses from consideration.

2. NTP, 1982

This gavage study also showed an increased incidence of liver tumors in B6C3F1 mice. Although the test material was purified, the same gavage dosing technique was used as in the 1976 study, resulting in bolus administration of the dose which seriously alters the absorption, pharmacokinetics, and metabolism of the test material relative to human exposure conditions.

3. Henschler et al., 1980

NMRI mice were exposed to purified trichloroethylene by inhalation. No increase in cancer was reported in male mice. An increase in the incidence of lymphomas was observed in females, but the authors did not ascribe this effect to trichloroethylene exposure.

4. Henschler et al., 1984

This corn oil gavage study showed no significant increases in tumors in either sex of Swiss mice gavaged with purified trichloroethylene. The authors concluded that "there is no indication of a tumorigenic potential of pure, amine based-stabilized TRI [trichloroethylene]" and "this study does not support the suggestion that trichloroethylene itself is carcinogenic under realistic exposure conditions."

5. Fukuda et al., 1983

ICR mice were treated by inhalation with trichloroethylene. No increased incidence of tumors was observed in the males. Female mice had an increased incidence of lung tumors at the two highest doses. If adenomas and carcinomas are combined, no increase in tumors was observed. Instead, there was a high incidence of benign adenomas in untreated controls, some of which appeared to convert to adenocarcinomas after exposure to trichloroethylene.

6. Maltoni et al., 1986

This inhalation study showed an increased incidence of lung tumors in male Swiss mice and female B6C3F1 mice. Only benign

adenomas were found, not carcinomas. Hepatomas were also observed in male Swiss mice and both sexes of B6C3F1 mice. These results have not been peer-reviewed.

7. Van Duuren et al., 1979

This series of studies in female Swiss mice involved administration of trichloroethylene by topical, subcutaneous, and gavage routes and included initiation-promotion studies. No carcinogenic response was reported.

8. Herren-Freund et al., 1986

No statistically significant increase in tumors was found in male B6C3F1 mice exposed to trichloroethylene by drinking water in this study. Treatment by a trichloroethylene metabolite increased the incidence of liver carcinomas.

B. Rat Studies

1. NCI, 1976

This gavage study showed no increased incidence of cancer in Osborne-Mendel rats.

2. NTP, 1982

This gavage study in Fischer 344 rats was considered inadequate to evaluate the presence or absence of a carcinogenic response.

3. NTP, 1988

These gavage studies in four strains of rats were considered inadequate to evaluate the presence or absence of a carcinogenic response.

4. Henschler et al., 1980

This inhalation study showed no increased incidence of cancer in Wistar rats.

5. Fukuda et al., 1983

This inhalation study showed no increased incidence of cancer in female Sprague-Dawley rats.

6. Maltoni et al., 1986

These studies in Sprague-Dawley rats, both by gavage and inhalation, reportedly showed an increased trend or incidence of leukemias, renal adenocarcinomas, and Leydig cell tumors in males. No increased incidence of cancer was observed in the females. The response rate for renal tumors was low. These results have not been peer-reviewed. Additionally, the incidence of "leukemias" is within the range of values for control groups reported in other Maltoni studies.

C. Other Studies

1. Henschler et al., 1980

This inhalation study showed no increased incidence of cancer in Syrian hamsters.

2. Bell et al., 1978

An audit of an inhalation study conducted by Industrial Biotest Laboratories, Inc., in Charles River rats and B6C3F1 mice concluded that it was inadequate to evaluate the presence or absence of a carcinogenic response.

II. Interpretation of Animal Bioassay Data

Analysis of the animal bioassay data on trichloroethylene is difficult because of the existence of conflicting results. Three inhalation studies show such conflicting results in four different strains of mice. An increase in lung tumors was reported in male Swiss mice and female B6C3F1 mice, and in female ICR mice. No increase in lung tumors was reported in either sex of NMRI mice, male B6C3F1 mice, female Swiss mice, or male ICR mice. The mechanism by which lung tumors have been produced is not understood, nor is the reason for the conflicting results in various strains apparent. In these circumstances, pending a determination of the biological significance of the varying mouse lung results, the positive studies should be considered limited, not sufficient, evidence of carcinogenicity in animals.

Kimbrough et al. (1985) offered the following critique of the study by Fukuda et al. (1983):

The incidence of total lung tumors -- that is, adenomas and adenocarcinomas -- was not significantly increased if controls were compared to exposed mice. In addition, the incidence at the higher dose was about the same as that at the lower dose.

The authors also noted that a number of putative carcinogenic substances were present in the reagent grade of trichloroethylene that was used in the Fukuda study.

The Maltoni studies have not been published in the peer-reviewed scientific literature. In 1988, the EPA Science Advisory Board made the following statement:

Unpublished experimental data should either be subjected to quality assurance checks and external peer review or used in only a limited way, if at all, as a basis of quantitative risk assessment. The report of studies by Maltoni using trichloroethylene are incomplete and, thus, of questionable value.

Marginal, nonstatistically significant increases in certain renal cell tumors were observed in two rat studies; the other rat studies were negative. Maltoni et al. (1986) found a small increase in the incidence of renal tubular adenocarcinomas in male Sprague-Dawley rats exposed to 600 ppm trichloroethylene by inhalation for 104 weeks. This effect was also observed by the National Toxicology Program (NTP, 1982) in Fischer 344 male rats following gavage administration of trichloroethylene at 1000 mg/kg/day for 103 weeks. In a separate set of studies conducted by NTP (1988), however, trichloroethylene administered at the same dosing regimen to four different strains of male and female rats (ACI, August, Osborne-Mendel, and Marshall) did not show strain or sex selectivity, and resulted in small but statistically nonsignificant increases in renal cell adenocarcinomas. Importantly, trichloroethylene caused tubular cell cytomegaly in 82-100 percent of dosed animals. Thus, it is reasonable to assume that the chemical was nephrotoxic to rats at the high dose levels used in this set of studies.

The 1988 NTP studies in multiple rat strains should not be given weight as supporting evidence of the carcinogenic potential of trichloroethylene. NTP itself concluded that these studies

are inadequate to show either the presence or absence of carcinogenic activity "because of chemical induced toxicity, reduced survival and deficiencies in the conduct of these studies."

In light of the expert assessments of the Fukuda and Maltoni studies, DHS should revise the conclusion of the draft report that these results "provide unambiguous support for the U.S. EPA classification of 'sufficient' evidence of carcinogenicity in animals because they showed statistically significant increases in malignant pulmonary tumors and liver tumors in treated mice" (page 4-58). As described more fully below, the bioassay data were not considered sufficient by the International Agency for Research on Cancer (IARC) even to support designation of trichloroethylene as "possibly carcinogenic to humans." The IARC review considered all the relevant evidence. The draft report should place greater emphasis on the study by Henschler et al. (1984), in which the authors concluded that evidence does not support the suggestion that trichloroethylene itself is carcinogenic under realistic exposure conditions, and that a nongenotoxic mechanism may account for observed mouse liver tumors.

III. Species Differences

There is little meaningful discussion in the draft report about the significant differences in the biologic responses to trichloroethylene exposure among species. In evaluating whether

it is biologically plausible that a test chemical shown to produce liver tumors in mice would be likely to produce such a response in humans, it is important to integrate both mechanistic considerations and known species differences in the pharmacokinetics and metabolism of the agent.

The major documented pathway for trichloroethylene metabolism, as the draft report correctly states, involves the formation of chloral, followed by conversion to trichloroethanol (reduction) or trichloroacetic acid (oxidation). Trichloroacetic acid is the major metabolite of trichloroethylene in mice, rats, and man. These metabolic products have been demonstrated to occur in intact animals in the appropriate kinetic sequence.

The preponderant evidence from pharmacokinetic, whole animal bioassay, and cell culture experiments is that trichloroacetic acid appears to be the proximal carcinogen in rodent liver by virtue of its ability to cause the proliferation of peroxisomes. Trichloroacetic acid has been shown to cause peroxisome proliferation in mouse liver cells and to induce liver tumors in mice when given alone. The level of peroxisome proliferation in rodents corresponds closely to the level of trichloroacetic acid production. Following exposure to trichloroethylene, blood levels of trichloroacetic acid are 7-fold greater in mice than in rats (Green and Prout, 1985). Monster (1979) has shown that rats, in turn, metabolize trichloroethylene at a 20-fold greater rate than humans.

In cell culture experiments, Elcombe (1985) has shown that mouse hepatocytes produce 30-fold more trichloroacetic acid than rat hepatocytes, which in turn produce 3-fold more trichloroacetic acid than human hepatocytes. Significantly, Elcombe (1985) has shown that peroxisome proliferation does not occur in human liver cells following in vitro exposure to trichloroacetic acid. In light of his findings, Elcombe made the following conclusion:

It is postulated that the species difference in hepatocarcinogenicity of TRI [trichloroethylene]. . . is due to species differences in peroxisome proliferation which in turn is a result of differences in the rate of formation of TCA from TRI. On this basis it is proposed that TRI presents no significant human hepatocarcinogenic hazard since (1) human hepatocytes produced TCA at a rate even lower than that of the rat, and (2) TCA was not a peroxisome proliferator in human hepatocytes.

While scientific evidence does not permit a definitive statement of the role of peroxisome proliferation in liver carcinogenesis, these data strongly suggest the absence of such a hazard for humans. Even if peroxisome proliferation is only a marker of liver cell involvement in the carcinogenic process, it is clear that human cells have a qualitatively different reaction to the rodent proximal carcinogen. Thus, humans are unlikely to show a carcinogenic response to trichloroethylene due to significantly lower production of trichloroacetic acid and the absence in humans of the critical biological response, the proliferation of peroxisomes.

In a recent study by Klaunig et al. (1989), the effects of trichloroethylene and its metabolites (trichloroacetic acid, trichloroethanol, and chloral hydrate) on intercellular communication in cultured B6C3F1 mouse and F344 rat hepatocytes were assessed. Trichloroethylene and trichloroacetic acid inhibited intercellular communication in mouse hepatocytes but not in rat hepatocytes. Trichloroethanol and chloral hydrate had no effect on hepatocyte intercellular communication in either rat or mouse cells. The authors concluded that while the species-dependent effect of trichloroethylene on intercellular communication may be correlated with different rates and extent of metabolism of trichloroethylene by rat and mouse hepatocytes, the inhibiting effect of trichloroacetic acid only on mouse hepatocytes suggests that other intrinsic factors in the male mouse make this species more susceptible to the effects of trichloroethylene and trichloroacetic acid on intercellular communication. These findings contribute to growing evidence for marked species differences in susceptibility to trichloroethylene-induced liver carcinogenesis.

While it has been suggested that peroxisome proliferation may not be a critical factor in the rat kidney response, it should be noted that the response observed was of very low incidence, questionable significance, and observed in studies judged to be inadequate for various reasons. The general lack of consistency of responses across species should be more fully discussed in the draft report. Recent investigations have

offered a tenable hypothesis for the formation of renal tubular adenocarcinomas in rats. These studies have provided evidence that the tumors may have been the result of hepatic metabolism of trichloroethylene by glutathione-S-transferase (Dekant et al., 1986), leading to the activation of the resulting conjugate by renal beta-lyase to a nephrotoxic and genotoxic entity (Green and Odum, 1985). Since the kidney tumors only appeared in conjunction with tubular cell cytomegaly in the 1988 NTP studies, however, the tumors may be a result of nephrotoxicity. In a recent paper by Brown et al. (accepted for publication in Regulatory Toxicology and Pharmacology), the authors reviewed the data on the occurrence of renal tubular adenocarcinomas in rats, and concluded that the kidney tumors are likely to be due to (1) a specific route of metabolic activation, (2) renal cytotoxicity, or (3) a combination of both. The authors further concluded that the occurrence of rat kidney tumors is a high-dose phenomenon, and that it has no relevance for human risk assessment.

The slight indications of testicular, leukemia, and renal cancers found in experimental animal studies are species-specific (rats), as are those for the lung and liver (mice). These data would suggest that promotional events are most critical in producing tumors in animals, rather than direct initiating events. The potential nonlinearity of these effects is critical in light of the high spontaneous tumor rates at most affected tumor sites.

Such species differences in metabolism and cellular factors

between mice and rats, and between rodents and humans, must be discussed at length in the draft report to place proper perspective on the carcinogenic potential of trichloroethylene at ambient exposure levels.

IV. Epidemiology

The results of the cohort mortality study by Shindell and Ulrich (1985) should be given greater weight than other epidemiologic studies reviewed in the draft report. The investigators followed 2646 employees who worked for three months or more during 1957-1983 in a manufacturing plant that used trichloroethylene as a degreasing agent. Although quantification of exposure during the early years of the study was not possible, recent monitoring data reveal conformance with OSHA standards. Groundwater in the area of the plant, from which drinking water for the workers was obtained, was found to contain 43 ppb trichloroethylene. In the total cohort, there were eight deaths observed from respiratory cancer compared with 11.4 expected, and 12 deaths observed from non-respiratory cancer as compared with 20.9 expected ($p < 0.05$). Mortality among the assemblers, a subgroup considered to have had the greatest opportunity for trichloroethylene exposure, conformed generally to the expected values for all causes. The mean length of follow-up was only 14.4 years, but could have ranged in excess of 26 years for some individuals. The Shindell and Ulrich study offers a far more extensive period of follow-up and a larger cohort than previous

studies, and thus adds substantially to the scientific data base concerning human health effects.

V. Genotoxicity

Many studies have been conducted on the mutagenic potential of trichloroethylene. The results of most of these tests have been called into question due to the purity of the sample and the presence of mutagenic epoxide stabilizers. Consequently, the relevance of these tests in assessing the mutagenic potential of pure trichloroethylene is ambiguous. Trichloroethylene does not appear to be a classic genotoxin and probably exerts its carcinogenic potential in animals via an epigenetic mechanism. The overall body of data on the mutagenic potential of trichloroethylene should be carefully reviewed in the draft report.

EPA, in its 1985 Health Assessment Document for Trichloroethylene, made the following conclusion about the mutagenic potential of the chemical:

The genotoxicity of trichloroethylene has been studied using a variety of assays, both in vitro and in vivo test systems. Available data provide suggestive evidence that commercial grade trichloroethylene is a weakly active, indirect mutagen. A conclusion about the mutagenic potential of pure trichloroethylene cannot be made. If trichloroethylene is mutagenic, the available data suggest that it would be a very weak indirect mutagen.

VI. Weight of the Evidence for Carcinogenicity

It would be scientifically inappropriate not to take all

available scientific evidence into consideration in assessing the carcinogenic potential of trichloroethylene. It should be noted that EPA has apparently not reached a final decision as to how to classify trichloroethylene. The conclusion in the 1985 Health Assessment Document for Trichloroethylene based on the draft EPA guidelines for carcinogen risk assessment was not consistent with the Science Advisory Board's review of earlier drafts of that document, or with its most recent statements (1988) that the weight of the evidence for trichloroethylene "lies on the continuum between the categories B2 and C of EPA's risk assessment guidelines." This conclusion should be reflected in the Executive Summary of the draft report.

Indeed, in its most recent review of trichloroethylene, IARC declined to classify trichloroethylene as either a probable or possible human carcinogen (Group 2A or 2B) and instead continued its classification in Group 3, unclassifiable as to human carcinogenicity. This conclusion is based on an evaluation of the animal evidence as limited and the human evidence as inadequate. All relevant studies were considered.

The recommendations of the SAB and IARC represent a consensus view by independent scientific experts that support the conclusion that ambient levels of trichloroethylene are unlikely to pose a carcinogenic risk to humans.

Kimbrough et al. (1985) and Ames et al. (1987, 1989) have addressed the relevance of the animal bioassay data to the

assessment of human risk from drinking water sources contaminated by trichloroethylene. Both authors have concluded that such potential exposures generally represent an insignificant risk. DHS should present this perspective in the draft report to achieve a balanced discussion of the experimental animal, metabolic, and pharmacokinetic data on trichloroethylene.

In light of these reviews, it is incomprehensible that the draft report would state (page 4-58) that the bioassay data "provide unambiguous support" for a classification of the animal evidence as sufficient. A more complete discussion of this question should be presented in the report. As recommended by EPA's Science Advisory Board, greater emphasis should be placed on the substantial number of negative studies, the inconsistencies among reported observations, and the marginal nature and uncertainties of the positive results. We urge a thorough reevaluation of the data and development of a revised draft report before submission to the Scientific Review Panel.

VII. Risk Assessment

The risk estimates presented in the draft report range from 8×10^{-7} to 9×10^{-6} . In comparison, EPA has proposed unit risk estimates of 1.7×10^{-6} by inhalation and 1.3×10^{-7} by ingestion (1985 Health Assessment Document for Trichloroethylene). The draft report should explain why the EPA and DHS estimates differ, and why the draft report proposes risk estimates that are greater than those adopted by the federal government.

The draft report should better incorporate physiologically-based pharmacokinetic (PB-PK) information to develop a more plausible estimate of potential risk. In a recent meeting of the California Air Resources Board concerning the proposed identification of methylene chloride as a toxic air contaminant, Chairwoman Jananne Sharpless stated that such an estimate would "help this Board try to interpret the information on how we go about controlling it" (July 13, 1989). Sharpless also alluded to the upcoming reviews of other chlorinated solvents (i.e., trichloroethylene and others), and expressed her desire on behalf of the Board that a "most plausible" risk estimate be developed. HSIA encourages DHS to develop such an estimate by better reflecting pharmacokinetic information.

Use of body-surface area correction factors are not appropriate in the case of trichloroethylene. Surface area scaling assumes that humans are more sensitive than rodents, despite the fact that carcinogenic responses in rodents after exposure to trichloroethylene are unlikely to be observed in humans. Body weight provides a better basis for dose adjustment.

VIII. OTHER COMMENTS

In the opening paragraph of the Executive Summary, the draft report states that trichloroethylene is flammable. Trichloroethylene does not support combustion and lacks a measurable flashpoint. Indeed, it is widely used by industry precisely because of its low flammability.

The Evaluation Highlights section of the draft report mentions assessments by EPA, IARC, and the National Institute of Occupational Safety and Health (NIOSH). It is odd that the workplace regulations of the Occupational Safety and Health Administration (OSHA), which are enforceable, are omitted, while the NIOSH guidelines are highlighted. The OSHA permissible exposure limit (PEL) was lowered from 100 ppm to 50 ppm (8-hour time-weighted average) (54 Fed. Reg. 2332; January 19, 1989). The OSHA PEL is now consistent with the threshold limit value recommended by the American Conference of Governmental Industrial Hygienists (ACGIH); neither organization considers trichloroethylene to be a carcinogen in the workplace.

Moreover, OSHA specifically considered the bioassay evidence discussed in the draft report and rejected establishing a lower PEL based on carcinogenicity. OSHA stated that "it is premature to establish a PEL for trichloroethylene based on evidence of its carcinogenicity, given the uncertainties in the evidence" (54 Fed. Reg. 2332, 2433).

REFERENCES

- Ames, B.N., Magaw, R., Gold, L.S., Ranking Possible Carcinogens: One Approach to Risk Management, In: The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies, (Ed.) Paustenbach, D.J., John Wiley & Sons, New York, 1989.
- Ames, B.N., Morgan, R., Gold, L.S., Ranking Possible Carcinogenic Hazards, *Science* 236: 271-280 (1987).
- Bell, Z.G., Olson, K.H., Benya, T.J., Final Report of Audit Findings of the Manufacturing Chemists Association: Administered Trichloroethylene in a Chronic Inhalation Study at Industrial Biotest Laboratories, Inc., Decatur, IL, Unpublished (1978).
- Brown, L.P., Farrar, D.G., de Rooij, C.G., Health Risk Assessment of Environmental Exposure to Trichloroethylene (accepted for publication in *Reg. Toxicol. Pharmacol.*, 1989).
- California Air Resources Board, Transcript of the Public Hearing to Consider the Adoption of a Regulatory Amendment Identifying Methylene Chloride as a Toxic Air Contaminant, Sacramento (July 13, 1989).
- Dekant, W., Metzler, M., and Henschler, D., Identification of S-1,2-dichlorovinyl-N-acetyl-cysteine as a Urinary Metabolite of Trichloroethylene: Possible Explanation for its Nephrocarcinogenicity in Male Rats, *Biochem. Pharmacol.* 35: 2455-2458 (1986).
- Elcombe, C.R., Species Differences in Carcinogenicity and Peroxisome Proliferation Due to Trichloroethylene: A Biochemical Human Hazard Assessment, *Arch. Toxicol., Suppl.* 8: 6-17 (1985).
- Fukuda, K., Takemoto, K., and Tsuruta, H., Inhalation Carcinogenicity of Trichloroethylene in Mice and Rats, *Ind. Health* 21: 243-254 (1983).
- Green, T., and Odum, J., Structure/Activity Studies of the Nephrotoxic and Mutagenic Action of Cysteine Conjugates of Chloro- and Fluoroalkenes, *Chem. Biol. Interact.* 54: 15-31 (1985).
- Green, T., and Prout, M.S., Species Differences in Response to Trichloroethylene. II. Biotransformation in Rats and Mice, *Toxicol. Appl. Pharmacol.* 79: 401-411 (1985).

- Henschler, D., Elsasser, H., Romen, W., and Eder, E.,
Carcinogenicity Study of Trichloroethylene, With and Without
Epoxide Stabilizers, in Mice, J. Cancer Res. Clin. Oncol.
107: 149-156 (1984).
- Henschler, D., Romen, W., Elsasser, H., Reichert, D., Eder, E,
and Radwan, Z., Carcinogenicity Study of Trichloroethylene
by Long Term Inhalation in Three Animal Species, Arch.
Toxicol., 43: 237-248 (1980).
- Herren-Freund, S.L., Pereira, M.A., Olsen, G., and DeAngelo,
A.B., The Carcinogenicity of Trichloroethylene (TCE) and Its
Metabolites, Trichloroacetic Acid (TCA) and Dichloroacetic
Acid (DCA), in Mouse Liver, Proc. Am. Assoc. Cancer Res.,
Vol. 27 (1986).
- Kimbrough, R.D., Mitchell, F.L., and Houk, V.N.,
Trichloroethylene: An Update, J. Toxicol. Environ. Health
15:369-383 (1985).
- Klaunig, J.E., Ruch, R.J., and Lin, E.L.C., Effects of
Trichloroethylene and Its Metabolites on Rodent Hepatocyte
Intercellular Communication, Toxicol. Appl. Pharmacol. 99:
454-465 (1989).
- Maltoni, C., Lefemine, G., and Cotti, G., Experimental Research
on Trichloroethylene Carcinogenesis, In: Archives of
Research on Industrial Carcinogenesis, (Ed.) Maltoni, C.,
and Mehlman, M.A., Princeton Scientific (1986).
- Monster, A.C., Difference in Uptake, Elimination, and Metabolism
in Exposure to Trichloroethylene, 1,1,1-Trichloroethane, and
Tetrachloroethylene, Int. Arch. Occup. Environ. Health 42:
311-317 (1979).
- National Cancer Institute (NCI), Bioassay of Trichloroethylene
for Possible Carcinogenicity, U.S. Department of Health,
Education, and Welfare, Bethesda, MD, NCI TR 13 (1976).
- National Toxicology Program (NTP), Carcinogenesis Bioassay of
Trichloroethylene in F344 Rats and B6C3F1 Mice, NTP 81-84,
NIH Publication No. 82-1799 (1982).
- National Toxicology Program (NTP), Toxicology and Carcinogenesis
Studies of Trichloroethylene in Four Strains of Rats (ACI,
August, Marshall, Osborne-Mendel), NTP TR 273, NIH
Publication No. 88-2529 (1988).
- Occupational Safety and Health Administration (OSHA), U.S.
Department of Labor, Final Rule on Air Contaminants, 54
Federal Register 2332-2983 (January 19, 1989).

Science Advisory Board (SAB), U.S. Environmental Protection Agency, Letter and Report to William D. Ruckelshaus, EPA Administrator, from Drs. Griffin and Nelson, EPA Environmental Health Committee of the SAB (December 17, 1984).

Science Advisory Board (SAB), U.S. Environmental Protection Agency, Letter and Report to Lee M. Thomas, EPA Administrator, from Drs. Nelson, Griesemer, and Doull, EPA Halogenated Organics Subcommittee of the SAB (March 9, 1988).

Shindell, S., and Ulrich, S., A Cohort Study of Employees of a Manufacturing Plant Using Trichloroethylene, J. Occup. Med. 27: 577-579 (1985).

U.S. Environmental Protection Agency (EPA), Health Assessment Document for Trichloroethylene, Washington, D.C. (1985).

Van Duuren, B.L., Goldschmidt, B.M., Loewengart, G., Smith, A.C., Melchionne, S., Seldman, I., and Roth, D., Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice, J. Nat'l. Cancer Inst. 63: 1433 (1979).



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Subject: *Review of Draft "Proposed Identification of Trichloroethylene as a Toxic Air Contaminant"*

Dear Sir:

The Lawrence Livermore National Laboratory (LLNL) has reviewed the draft document and offers the following comments and suggestions:

PART A

- (1) Page A-5: Has a chemical mechanism for conversion of "chlorinated hydrocarbon" diesel fuel additives to TCE been postulated? Is there any experimental evidence? If not, then this assertion should be omitted from the report.
- (2) Page A-7, Paragraph 3: It says on this page that the Halogenated Solvent Industry Alliance (HSIA) reported that approximately 4,650 tons of TCE were used in California in 1983. In Appendix A, on the other hand, the HSIA is quoted as saying that its members shipped 4,880 tons of TCE into the state and that 10 percent of this was shipped out of the state, leaving only 4,392 tons of TCE for all uses. The discrepancy between the 4,650-ton and 4,392-ton figures should be resolved. In addition, the report should make it clear that the TCE import figures correspond to HSIA member firms only, and should discuss how much TCE, if any, comes from non-HSIA sources.
- (3) Page A-7, Paragraph 3: Change "the fungicide production of difolatan" to the production of the fungicide difolatan."
- (4) Page A-10, Last Paragraph: Where is the documentation for the statement that "trichloroethylene is used in many paint and coating formulations?" A review by Science Applications International Corporation (Rogozen and Baca, 1989) of the National Paints and Coatings Association (NPCA) data base on paint and coatings solvents showed no formulations using TCE. While some TCE may have been included in the NPCA category "miscellaneous solvents," it is unlikely that the compound is used in "many" formulations.
- (5) Page A-13, Paragraph 1: It is assumed here that all of the TCE sold in California was sold by the distributors in the ARB's survey. Were there any direct sales from manufactures, without going through third-party distributors? Also, did the ARB attempt to estimate the amount of TCE sold by distributors who did not respond to the survey? The uncertainty in the 1,023-ton value should be stated in the report. Also, the statement (here and on Page Appendix A-2) that an estimated 2,300 tons of trichloroethylene were sold through distributors in California in 1983 is not documented anywhere in the report.

PART A (continued)

- (6) Page A-13, Section 3, Line 3: Change "are being treated" to "is being treated."
- (7) Page A-13, Section 3, Line 8: Shouldn't it say "volatilization process" instead of "volatile process?"
- (8) Page A-13, 4th Line from Bottom: Insert a comma between "soil" and "contaminating."
- (9) Page A-14, First 2 Full Paragraphs: These could use some re-writing. For example it isn't necessary to mention twice in one paragraph that there are 10 facilities in the Bay Area Air Quality Management District with air strippers. Also change "most of the contaminants will be transferred to the fresh air from a concentration gradient" to "a concentration gradient drives the transfer of contaminants from the water to the fresh air."
- (10) Page A-16, Consumer Products: Rogozen and Baca (1989) identified one household metal cleaner formulation containing TCE.
- (11) Chapter IV, Figures IV-1 and IV-2: These figures are illegible in the draft copy and should be upgraded for the final version.
- (12) Page A-48, Section F.1: Change "a person breathe" to "a person breathes."

PART B

- (1) The sections on carcinogenicity in animals and humans is well organized and written, and the summaries at the ends of the sections are useful. In contrast, the discussions of pharmacokinetics and metabolism and non-carcinogenic toxic effects lack a good narrative thread something of tie them together; they consist mainly of summaries of individual research projects.
- (2) Figure 3-1: The leftmost "C" on the chloral molecule should be a "Cl."
- (3) Page 4-14, Line 11: Change "6000 TCE ppm" to "6000 ppm TCE."
- (4) Page 4-21, Line 3: The referenced tables should be 4-1 and 4-2, not 2-1 and 2-2.
- (5) Page 4-49, 11 Lines from Bottom: Change "stains" to "strains."

If you have any questions, or would like additional information, please contact me at (415) 423-8853.

Sincerely,



Judy Steenhoven, Leader
Permits and Regulatory Affairs Group

II.

Air Resources Board Staff Responses to Comments on the Preliminary Draft Part A

A) Halogenated Solvents Industry Alliance, September 8, 1989

Comments received were all directed to Part B

B) Lawrence Livermore National Laboratory, September 27, 1989

1) **Comment:** "Page A-5: Has a chemical mechanism for conversion of "chlorinated hydrocarbon" diesel fuel additives to TCE been postulated? Is there any experimental evidence? If not, then this assertion should be omitted from the report."

Response: The sentence regarding "chlorinated hydrocarbons as diesel fuel additives" has been omitted.

2) **Comment:** "Page A-7, Paragraph 3: It says on this page that the Halogenated Solvents Industry Alliance (HSIA) reported that approximately 4,650 tons of TCE were used in California in 1983. In Appendix A, on the other hand, the HSIA is quoted as saying that its members shipped 4,880 tons of TCE into the state and that 10 percent of this was shipped out of the state, leaving only 4,392 tons of TCE for all uses. The discrepancy between the 4,650-ton and 4,392-ton figures should be resolved. In addition, the report should make it clear that the TCE import figures correspond to HSIA member firms only, and should discuss how much TCE, if any, comes from non-HSIA sources."

Response: Appendix A does not quote HSIA as reporting 10 percent of 4,880 tons of TCE being shipped out of state. Instead, Appendix A indicates that 2,580 of the original 4,880 tons of TCE imported into the state were shipped to Chevron Chemical Company in Richmond. HSIA estimated that 10 percent of the remaining TCE was shipped out of state (not 10 percent of the original 4,880 tons). Therefore:

$$(4,880 \text{ tons} - 2,580 \text{ tons}) = 2,300 \text{ tons,}$$

$$(2,300 \text{ tons})(1.00 - 0.10) = 2,070 \text{ tons,}$$

$$2,070 \text{ tons} + 2,580 \text{ tons} = 4,650 \text{ tons of TCE available for use in 1983.}$$

Regarding the amount of TCE imported from non-HSIA sources, HSIA represents both of the U.S. producers of TCE. Therefore, the only unreported imports of TCE into California would be from foreign producers and HSIA does not believe that foreign producers are importing any significant amounts of TCE into California.

3) **Comment:** "Page A-7, Paragraph 3: Change "the fungicide production of difolatan" to "the production of the fungicide difolatan.""

Response: This change has been made.

4) **Comment:** "Page A-10, Last Paragraph: Where is the documentation for the statement that "trichloroethylene is used in many paints and coating formulations?" A review by Science Applications International Corporation (Rogozen and Baca, 1989) of the National Paints and Coatings Association (NPCA) data base on paint and coatings solvents showed no formulations using TCE. While some TCE may have been included in the NPCA category "miscellaneous solvents," it is unlikely that the compound is used in "many" formulations."

Response: An ARB survey of California halogenated solvent distributors (ARB, 1989) indicated that 68 tons of TCE were distributed to paint and coating facilities in 1987 (see page A-7, paragraph 5). However, since Rogozen and Baca (1989) showed no paint and coating formulations using TCE, the first sentence of the last paragraph on page A-10 has been changed to read "Trichloroethylene is used in paint and coating formulations."

5) **Comment:** "Page A-13, Paragraph 1: It is assumed here that all of the TCE sold in California was sold by the distributors in the ARB's survey. Were there any direct sales from manufacturers, without going through third-party distributors? Also, did the ARB attempt to estimate the amount of TCE sold by distributors who did not respond to the survey? The uncertainty in the 1,023-ton value should be stated in the report. Also, the statement (here and on Page Appendix A-2) that an estimated 2,300 tons of trichloroethylene were sold through distributors in California in 1983 is not documented anywhere in the report."

Response: While there may be some direct sales from manufacturers, the ARB staff believes that the amount of TCE distributed in this manner is minimal in comparison to the major distributors.

Since all major distributors responded to the survey, the ARB did not attempt to estimate the amount of TCE sold by distributors who did not respond to the survey.

The last sentence of the fourth paragraph on page A-7 reads "Because all major distributors responded to the survey, the ARB staff believes that the data received accounted for most of the TCE distributed in California." The uncertainty of the 1,023-ton value is stated in this sentence.

Information received from HSIA (Cleary et al., 1986) indicated that 4880 tons of TCE were shipped into California in 1983. Of this initial value, 2580 tons of TCE were shipped directly to Chevron Chemical Company in Richmond for use as a chemical intermediate in the production of fungicide. The remaining TCE (2300 tons) was available for distribution. The third paragraph on page A-7 has been rewritten and rearranged to clarify this matter.

The following group of comments were considered and incorporated into the text:

6) **Comment:** "Page A-13, Section 3, Line 3: Change "are being treated" to "is being treated.""

7) **Comment:** "Page A-13, Section 3, Line 8: Shouldn't it say "volatilization process" instead of "volatile process?""

8) **Comment:** "Page A-13, 4th Line from Bottom: Insert a comma between "soil" and "contaminating.""

9) **Comment:** "Page A-14, First 2 Full Paragraphs: These could use some re-writing. For example it isn't necessary to mention twice in one paragraph that there are 10 facilities in the Bay Area Air Quality Management District with air strippers. Also change "most of the contaminants will be transferred to the fresh air from a concentration gradient" to "a concentration gradient drives the transfer of contaminants from the water to the fresh air.""

10) **Comment:** "Page A-16, Consumer Products: Rogozen and Baca (1989) identified one household metal cleaner formulation containing TCE."

11) **Comment:** "Chapter IV, Figures IV-1 and IV-2: These figures are illegible in the draft copy and should be upgraded for the final version."

12) **Comment:** "Page A-48, Section F.1: Change "a person breathe" to "a person breathes.""

III.

Responses by DHS Staff to Public Comments on Trichloroethylene

Comments on the Draft Technical Support Document on trichloroethylene (TCE) were made by the Halogenated Solvents Industry Alliance (HSIA), an association of users, distributors, and producers of chlorinated solvents, including TCE. To quote them, "Our comments include a summary of the pertinent literature on the carcinogenic potential of trichloroethylene in animals and humans, a discussion of the importance of species differences in metabolism of this chemical, and a recommendation to develop a more plausible estimate of potential risk by better reflecting pharmacokinetic information."

Comment 1. Trichloroethylene (TCE) is unlikely to pose a carcinogenic risk to humans at ambient environmental or occupational exposure levels.

Response. Based on evidence of genotoxicity and carcinogenicity from many animal experiments (Chapter 4), staff has concluded that trichloroethylene may pose a risk to human health. Staff has calculated that the carcinogenic risk due to exposure to ambient levels of TCE is small (Chapter 5), but it is not zero. This is in agreement with the EPA's Science Advisory Board which stated in a March 9, 1988 letter to EPA Administrator Lee M. Thomas: "Trichloroethylene has the potential to cause cancer in humans, but its potency is low." Estimates of risk based on occupational exposure levels were not calculated.

Comment 2. Epidemiological studies of workers show no increase in cancer mortality. In the most important study (Shindell S and Ulrich S, J. Occup.

Med. 27:577-579, 1985) a cohort of 2600 workers was examined at a manufacturing plant that used TCE as a degreasing agent and no increased risk of cancer was found when compared to a comparable group of unexposed workers.

Response. The comment says that no studies indicate elevated cancer risk. The document reviews several epidemiological studies in Chapter 4. Some studies of laundry workers and of metal workers have shown increased incidences of cancer but these workers had other exposures. These and most other studies suffer from small sample size, incomplete information on exposure, exposure of the workers to other chemicals, and weak statistical power. HSIA identifies the paper by Shindell and Ulrich as a study deserving greater weight. In this study, 21 cancer cases (9 respiratory, 12 nonrespiratory) were observed where 36.7 cases (12.1 respiratory, 24.6 nonrespiratory) were expected, based on "national mortality experience" for the United States (not on a comparable group of unexposed workers as stated in the comment). Measurements indicated that the facility was in compliance with OSHA requirements for TCE at the time of the study. Assuming all of the 2,646 workers included in the study were exposed to the current OSHA PEL of 50 ppm for 8 hours per days, 5 days per week for a 6.2 year employment period (16332 person years/2,646 individuals), the following calculations can be made:

$$\begin{aligned} 50 \text{ ppm} \times 5.38 \text{ mg/m}^3/\text{ppm} &= 269 \text{ mg/m}^3 = \text{concentration of TCE at TLV} \\ 269,000 \text{ ug/m}^3 \times 8/24 \times 5/7 \times 48/52 \times 6.2/70 &= 5236 \text{ ug/m}^3 \text{ lifetime} \\ &\text{equivalent exposure} \\ 5236 \text{ ug/m}^3 (8 \times 10^{-7} - 9 \times 10^{-6}) (\text{ug/m}^3)^{-1} &= (.004-.047) \text{ individual risk} \\ (.004-.047) \times 2646 &= 11 - 125 \text{ excess cancer cases predicted} \end{aligned}$$

(Conformance to the previous PEL of 100 ppm would double the range.) Thus, if workers were exposed to a time-weighted-average of 50 ppm, 11 to 125 excess cancers would be predicted to develop eventually, based on the range of risk in the DHS staff report. However, if the average daily workplace exposure was less than 50 ppm, predicted cases would decline in direct proportion (e.g., 5 ppm yields 1-12 excess cancer cases). In addition, persons who got their average 6.2 years of TCE exposure during the latter period of the study which ended in July 1983 would have been in the latency phase at the time of the study which was published in 1985. If they were to develop cancer from their exposure, the manifestation would occur several years after the study was completed. Furthermore, according to the paper, all office employees (who presumably were non-exposed) were included in the cohort but their proportion of the cohort was not stated. Again the more office workers included, the fewer cancer cases expected. Thus, based on the uncertainties in this study about actual exposure, the number of employees exposed, and the latency period needed to develop cancer following TCE exposure, the study cannot be considered conclusive in establishing the noncarcinogenicity of TCE in humans. Unfortunately it is very difficult to prove a negative. "Since the study was diluted by the inclusion of office employees and incompletely reported with regard to the health experience of the various subgroups, and since exposure levels to TRI were unknown, this study contributes little if any relevant information." (Axelson, O. Epidemiological studies of workers with exposure to tri- and tetrachloroethylenes. In: New Concepts and Developments in Toxicology (Chambers PL, Gehring P, Sakai F, eds.), Elsevier Science Publishers, 1986, pp.223-230). Thus staff does not agree that the existing epidemiological studies provide strong negative evidence. DHS staff

acknowledges that the epidemiological data are inadequate either to establish or to rule out the carcinogenicity of trichloroethylene in humans.

An update of the 1978 epidemiological study of Axelson et al. (J. Occup. Med. 20:194-196, 1978) was presented in 1984 at the International Conference on Solvent Toxicity in Stockholm (Axelson et al., Cancer morbidity and exposure to trichloroethylene). The update indicated excess cancer morbidity with increases in urinary tract and haemolymphatic organ cancer in their TCE cohort, but there was a deficit of total cancer deaths compared to expected. In this cohort the role of TCE stabilizers in causing the cancers is unclear. Hopefully a more complete report of these findings will be forthcoming. [According to a manuscript titled Health Risk Assessment of Environmental Exposure to Trichloroethylene, which accompanied the comments and which will appear in Regulatory Toxicology and Pharmacology in December, 1989, Axelson in a personal communication to the manuscript's authors said that he did not think that the excess cancers were compound related. It will be of interest to see a followup paper by Axelson.]

The number of negative studies needed to demonstrate that a chemical is not a carcinogen is dependent on the type of studies and the quality of the studies. The factors that are involved with regards to evaluating the quality and the significance of a study in terms of cancer risk assessment were presented in "Guidelines for Chemical Carcinogen Risk Assessment and their Scientific Rationale." To rule out carcinogenicity on the basis of human data, for any compound, would require multiple, well-designed, negative studies. Such studies would need to have historical exposure information (e.g., 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 to allow for latency, and substantial data on confounding (by other chemicals, by cigarette smoking, etc.). In light of the carcinogenicity of trichloroethylene in animals, additional negative epidemiologic data, superior to that which currently exists, would be needed to distinguish the animal and human responses.

Comment 3. The report quotes the NIOSH guidelines which recommended a workplace level of 25 ppm, but not the enforceable OSHA PEL. The OSHA PEL has been lowered from 100 to 50 ppm, consistent with the ACGIH TLV. Neither ACGIH nor OSHA considers TCE to be a carcinogen. Moreover, OSHA rejected the bioassay evidence as necessitating a further lowering of the PEL to protect against possible carcinogenicity.

Response. DHS has a different mandate from OSHA. Development of an OSHA standard is closer to promulgating a control strategy than in identifying a carcinogen. OSHA standards may consider factors other than risk such as feasibility, costs, and benefits. Workers have some control over the risks they choose to take to derive benefits from their jobs. OSHA did not say that TCE was not a carcinogen, rather that "... OSHA finds that it is premature to establish a PEL for trichloroethylene based on evidence of its carcinogenicity, given the uncertainties in the evidence." (Federal Register 54:2432-2434, 1989) The ACGIH's 1986 documentation for the TLV for TCE did not include the 1982 NTP gavage study and the 1983 paper by Fukuda et al. (Ind Health 21:243-254, 1983). Thus the ACGIH may not have considered all the

available data. The Health and Welfare Agency in its Proposition 65 activities has also concluded that TCE produces a carcinogenic risk to humans. In evaluating TCE in the toxic air contaminant program, Department of Health Services staff has considered all available scientific data including data from international and federal agencies.

Comment 4. TCE does not appear to be a classic genotoxin and probably exerts its carcinogenic potential in animals via an epigenetic effect. The comment also refers to EPA's conclusions: 1) Commercial grade TCE is a weakly active, indirect mutagen. 2) If pure TCE is mutagenic, it would be a very weak indirect mutagen.

Response. Staff acknowledges that there is varying evidence on TCE's genotoxicity. The genetic toxicity of TCE has been reviewed recently (Crebelli R, Carere A. Genetic toxicology of 1,1,2-trichloroethylene. Mutation Research 221:11-37, 1989) and summarized by IARC (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, Supplement 6, 1987). When radioactive TCE is incubated with DNA and a microsomal preparation, radioactivity becomes bound to DNA, an effect seen with many classic genotoxins. Although both positive and negative studies on mutation have been published, several studies with 0.33% and higher concentrations of epoxide-free TCE have shown mutations in Salmonella (Ames test). (The halogenated solvent carbon tetrachloride, a known carcinogen, has been negative in the Ames test.) Positive results have been seen with several in vitro and in vivo eukaryotic systems (e.g., SCE, unscheduled DNA synthesis,

mouse spot test, transformation) and in fungal mutagenicity assays, while other studies have been negative. Although there is a possibility that TCE acts epigenetically, there is evidence that it can act through genotoxic mechanisms as well. Thus, TCE could act by both genotoxic and epigenetic mechanisms. It is imprudent for a public health agency to discount the genotoxic evidence for TCE on the basis that it is only weakly genotoxic. The chemical may act by more than one mechanism. Existing test methods do not consider all genotoxic mechanisms. In addition two metabolites of TCE in its principal metabolic pathway in rodents and man, chloral hydrate and trichloroacetic acid, have genotoxic activity. These may not be formed in adequate amounts in the presence of the S9 fraction during the Ames test to show a mutagenic response. Trichloroacetic acid and another metabolite of TCE in a different metabolic pathway, dichloroacetic acid, have carcinogenic activity. Finally, glutathione derivatives of TCE in still another metabolic pathway are mutagenic and possibly carcinogenic.

Comment 5. The various animal bioassays for carcinogenicity are listed, commented on, and interpreted. Many positive results of carcinogenicity are discounted due to use of corn oil gavage, contaminating substances in the TCE, the original authors' interpretation of the data, and lack of peer review, especially for the Maltoni et al. studies. The comment further notes the species differences in responses. The conclusion of the commentor is that the positive studies should be considered limited, not sufficient, evidence of carcinogenicity.

Response. In the draft report all the various animal studies of carcinogenicity mentioned in the comment are discussed on pages 4-44 through 4-59. The data from the studies are compiled in tabular form in Appendix B. The comment repeats many facts about the assays that are in the draft report, except for the issue of corn oil vehicle for gavage. The vehicle used to deliver TCE may affect uptake and toxicity since TCE exhibits greater hepatotoxicity and lethality after subacute trichloroethylene exposure with aqueous gavage than with corn oil gavage vehicles in B6C3F1 mice (Merrick BA, Robinson M, Condie LW. J Appl Toxicol 9:15-21, 1989). In the cancer assays using gavage, TCE may be less likely to be absorbed from corn oil than from a water-based vehicle. As indicated on p.3-4 of the draft report, the study of Withey et al. (1983) showed that the maximum concentration of TCE in blood was almost 15 times greater when TCE was administered in water compared to corn oil. The area under the blood concentration-time curve was 218 times greater for TCE in water. Thus, instead of corn oil contributing to the carcinogenicity of TCE, TCE in corn oil may underestimate the cancer risk of TCE in water.

Obesity in test animals due to high fat intake (such as from corn oil) is thought to contribute to carcinogenicity. Staff believes that the induction of obesity by corn oil gavage as a contributor to carcinogenicity may not be relevant to the studies of TCE. In the 1976 NCI study the highest dosed male mice received 2339 mg/kg TCE in corn oil. According to the 1985 EPA Health Assessment Document for TCE the material had 24% TCE. Thus a 30 gram mouse would receive approximately 70 mg (0.048 ml) TCE and 222 mg (about 0.2 ml) corn oil. An EPA allometric equation for food intake ($F = 0.055 W^{0.6611}$)

indicates that a 30 g mouse eats 5.4 grams food per day of which the corn oil would comprise 4% of the food intake by weight.

However, DHS staff based its risk assessment on 4 inhalation studies, not on the gavage studies. The range of potencies (q_1^*) for the inhalation studies is 0.0098 - 0.098 (mg/kg/day)⁻¹, based on metabolized dose. For the gavage studies in mice, the range of potencies presented in the document is 0.0098 - 0.036 (mg/kg/day)⁻¹, based on metabolized dose (Table 5-1). The EPA obtained a range of 0.0069 - 0.036 (mg/kg/day)⁻¹, based on metabolized dose (Table 5-2). Based on applied dose, the EPA obtained a range of 0.0058 - 0.019 (mg/kg/day)⁻¹ for the inhalation studies (Table 5-2), while DHS staff obtained a range of 0.004 - 0.034 (mg/kg/day)⁻¹ (Table 5-3, revised). Thus there is much overlap in the ranges of potencies obtained for TCE from the gavage and inhalation routes using both metabolized and applied dose. Although some experimental evidence is conflicting and there are deficiencies in some studies, there is evidence for carcinogenicity of TCE in two species (rats and mice), by two routes (oral and inhalation), at multiple sites in studies done in different laboratories.

Comment 6. It is incomprehensible that the draft report would state (page 4-58) that the bioassay data "provide unambiguous support" for a classification of the animal evidence as sufficient. A more complete discussion of this question should be presented in the report.

Response. The word "unambiguous" has been deleted from the report. But, as stated above, there is evidence for TCE's carcinogenicity in two animal

species, by two routes, at several sites, in studies done in different laboratories. The World Health Organization, in its document Environmental Health Criteria 50 Trichloroethylene, published in 1985, states that there is clear evidence that trichloroethylene is carcinogenic in mice.

Comment 7. The most significant finding to surface from the many long-term animal studies is liver cancer in mice, but not in rats or humans. The proximal carcinogen is trichloroacetic acid, a metabolite, which induces proliferation of peroxisomes in liver cells. The level of peroxisome proliferation in rodents corresponds closely to the level of trichloroacetic acid production. Following exposure to trichloroethylene, blood levels of trichloroacetic acid are 7-fold greater in mice than in rats (Green and Prout, 1985). Monster (1979) has shown that rats, in turn, metabolize trichloroethylene at a 20-fold greater rate than humans. Humans produce less trichloroacetic acid than mice and rats and do not exhibit the critical biological response of peroxisome proliferation which is responsible for the formation of liver tumors in rodents.

Response. TCE does induce liver cancer in mice but there is additional evidence for carcinogenicity in mice and some in rats, by two routes (oral and inhalation), and at multiple sites including liver, lung, lymph system, kidney, and testes. Staff does not agree that peroxisome proliferation is the only method by which TCE may induce carcinogenicity. There is a correlation with peroxisome proliferation and hepatomas, but a causal relationship is unproven. [Staff was unable in the references given to verify the fold differences in trichloroacetic acid formation stated in the comment.] Other

studies showing animal cancer should not be discounted because they do not fit the peroxisome theory of tumor formation. In another section of the comments, the commentor mentions that the unique, mutagenic glutathione derivatives of TCE may be responsible for renal tumors when TCE is given at high dose levels. If these tumors result from the genotoxic properties of glutathione derivatives of TCE, this would be a mechanism of carcinogenicity not dependent on peroxisome proliferation. The draft report discusses the metabolism of these glutathione derivatives in Chapter 3.

Comment 8. EPA has apparently not reached a final decision as to how to classify TCE. The weight of evidence for TCE "lies on the continuum between the categories B2 and C of EPA's risk assessment guidelines."

Response. EPA has published unit risk factors for TCE in existing documents. EPA continues to update its potency values as new data are developed. DHS staff has reviewed the previous EPA documents and included more recent data in its update. It is unlikely that new risk numbers developed by EPA in the future will be much different from current values unless substantial, new data are published. TCE is currently considered by the EPA to be a category B2 carcinogen. A change in placement of TCE from the B2 to the C category would not impact the California toxic air contaminant identification process. TCE is already listed as a chemical known to the state of California to cause cancer for the purposes of Proposition 65.

Comment 9. The slight indications of testicular and renal cancers and of leukemia found in experimental animal studies are species-specific (rat), as

are those for lung and liver (mice). These data would suggest that promotional events are most critical in producing tumors in animals, rather than direct initiating events. The potential nonlinearity of these effects is critical in light of the high spontaneous tumor rates at most affected tumor sites.

Response. These differences might be due to promotional events. In some experiments the background tumor rates are quite high, up to 20% for liver cancer, but in some experiments the background rates have been low or zero. The observed rates for many human cancers, for which the causes are not clear such as breast, lung, and colorectal cancer, are high; promotion of such cancers would be of public health concern. In addition TCE may act by one or more genotoxic mechanisms as well. The so-called "species-specific" results cannot be attributed solely to promotion of existing cancers.

Comment 10. IARC (in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7, 1987, pp. 364-366, which was based on the March 1987 meeting of the working group) has continued its classification of TCE in Group 3 due to limited evidence of animal carcinogenicity and inadequate evidence of human carcinogenicity. All relevant studies were considered.

Response. Staff has acknowledged the IARC classification. The IARC working group had access to Maltoni's results (at least in book form since the book by Maltoni et al. on TCE is given as a reference in IARC Supplement 7) and

considered the data (van Duuren BL, An update: IARC carcinogenicity evaluations of vinylidene chloride, methylene chloride and trichloroethylene, Environmental Research 49:333-334, 1989). The IARC working discounted the increased incidence of lymphomas in female mice reported in the 1980 paper by Henschler. The EPA's SAB noted that "it is not clear whether all the studies reviewed by EPA were considered by IARC."

Comment 11. Body-surface area correction factors are not appropriate, since they assume that humans are more sensitive than rodents, despite the fact that carcinogenic responses observed in rodents after TCE exposure are unlikely to be observed in humans.

Response. This is an a posteriori argument. In the absence of decisive empirical evidence to the contrary, DHS has used a surface area extrapolation factor to extrapolate between species. This procedure is described in the document "Guidelines for Chemical Carcinogen Risk Assessment and their Scientific Rationale" prepared by the Health and Welfare Agency. Compelling evidence to change this position has not been presented to the Department and is not available in the scientific literature. Such a correction factor can serve as an uncertainty factor for extrapolation between species, for allowance of variation in sensitivity among humans, and for use of weakly validated assumptions in the pharmacokinetic model.

Comment 12. HSIA recommends a more plausible estimate of potential risk by better reflecting pharmacokinetic information which will reduce the uncertainties inherent in the risk assessment process.

Response. DHS staff used both applied dose and pharmacokinetic considerations in developing its risk assessment. The pharmacokinetic approach is detailed in Chapter 3. Because TCE is metabolised completely and similarly in man and rodents, the risk estimates by these approaches are quite similar. This is different from, for example, methylene chloride where a 9-fold difference is obtained since that solvent is metabolized differently in man from rodents. The pharmacokinetic approach used in the DHS document has recently been published by K. T. Bogen (Pharmacokinetics for regulatory risk analysis. The case of trichloroethylene. Regulatory Pharmacology and Toxicology 8:447-466, 1989).

Comment 13. EPA proposes a unit risk estimate of $1.7 \times 10^{-6} (\text{ug}/\text{m}^3)^{-1}$ by inhalation which differs from the DHS number.

Response. DHS and ARB have no mandate to produce unit risks equal to those of EPA. As required in the AB 1807 process, DHS is providing a range of risk ($8 \times 10^{-7} - 1 \times 10^{-5} (\text{ug}/\text{m}^3)^{-1}$), based on both applied dose and pharmacokinetic approaches from 4 animal studies of cancer induced by the inhalation route (Chapter 5). The range includes the original EPA unit risk for inhalation, $1.3 \times 10^{-6} (\text{ug}/\text{m}^3)^{-1}$, which was calculated from the incidence of hepatomas in the Bell et al. (1978) study and human dose data based on the study of Monster et al. (1976), which appeared in the 1985 EPA Health Assessment Document for Trichloroethylene, and the value of $1.7 \times 10^{-6} (\text{ug}/\text{m}^3)^{-1}$ based on mouse lung tumors which appeared in the EPA addendum. The range also includes the unit risk of $3.3 \times 10^{-6} (\text{ug}/\text{m}^3)^{-1}$ used to derive the risk specific intake of 60

ug/day, presently in use as a temporary regulation for Proposition 65. As a best estimate of risk, staff has determined the geometric mean of the risks obtained from the four animal inhalation studies. Based on pharmacokinetic analysis, a value of $2 \times 10^{-6} \text{ (ug/m}^3\text{)}^{-1}$ was obtained, whereas based on applied dose considerations a value of $3 \times 10^{-6} \text{ (ug/m}^3\text{)}^{-1}$ was obtained.

Comment 14. Kimbrough and co-workers and Ames and co-workers have addressed the relevance of the animal bioassay data to risk assessment of drinking water and concluded that such potential exposures generally represent an insignificant risk.

Response. The current risk assessment is for air exposure, not water. Risks from air do not necessarily follow the pattern for risks from water. Notwithstanding the route of exposure, the risks addressed by Ames may be small compared to much other (larger) risks, but they may be measurable. Ames' lowest risk is a HERP of 0.001% for 1 liter of tap water containing 83 ug chloroform. Chloroform, an animal carcinogen, is the principal trihalomethane present in chlorinated drinking water. Epidemiological studies of people drinking chlorinated surface water or non-chlorinated ground water indicate a higher incidence of bladder cancer in those drinking chlorinated water (Cantor KP, et al., Bladder cancer, drinking water source, and tap water consumption: a case-control study. JNCI 79:1269-1279, 1987). The increase in bladder cancer is thought to be due to by-products of chlorination including chloroform. If an epidemiological study can detect a difference, the increase in cancer is most likely at least statistically significant. According to Ames the risk for drinking water from the well worst contaminated by

trichloroethylene in Silicon Valley is estimated to have a risk 4 times (HERP - .004%) that of chloroform. Thus, the risk from TCE in drinking water may also be significant, although chloroform is a more potent carcinogen than TCE. In the case of chlorination of drinking water the significant cancer risk may be a lesser problem than exposing oneself to the risk of other diseases due to organisms present in non-chlorinated water.

Comment 15. In the Executive Summary the draft report states that TCE is flammable. It is not flammable.

Response. The words "flammable" has been changed in the revised draft report to "nonflammable."

PART C ADDENDUM

**PUBLIC COMMENTS AND RESPONSES TO THE
DRAFT TRICHLOROETHYLENE REPORT**

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

August 1990

Part C Addendum contains the comments received from the public during the March 29, 1990 to April 9, 1990 public review period for the Draft report on Trichloroethylene. The responses of the Air Resources Board and the Department of Health Services to those comments are also contained in this Addendum.

CONTENTS OF THE ADDENDUM TO PART C

- I. Comment Letter Received from the Public on the Draft Trichloroethylene Report:
 - o Halogenated Solvents Industry Alliance (HSIA)
- II. Air Resources Board Staff Responses to Summarized Comments on the Draft Part A and the Executive Summary
- III. Department of Health Services Staff Responses to Summarized Comments on the Draft Part B

I.

Comment Letter Received from the Public on the
Draft Trichloroethylene Report

HSIA HALOGENATED SOLVENTS INDUSTRY ALLIANCE

1225 19th Street, N.W., Suite 300, Washington, D.C. 20036-2411 • (202) 223-5890

April 9, 1990

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

Dear Ms. Shiroma:

The Halogenated Solvents Industry Alliance (HSIA) offers these comments on the Executive Summary and on Part B (Health Effects of Trichloroethylene) of the final draft Technical Support Document for the Proposed Identification of Trichloroethylene as a Toxic Air Contaminant. We ask that these comments be provided to the Scientific Review Panel in advance of its scheduled April 16 review of trichloroethylene.

HSIA commented on a previous draft of the Technical Support Document on September 8, 1989. We urge the Panel to review these comments, reprinted in Part C of the Technical Support Document, as they have largely been disregarded.

HSIA is an association of users, distributors, and producers of chlorinated solvents, including trichloroethylene. Our members, as well as other users of trichloroethylene, have a vital interest in the accuracy and scientific validity of the Technical Support Document. Decisions made by the Board on the basis of the Technical Support Document will have a significant effect on actions taken by local air districts in California to regulate trichloroethylene. As a consequence of those actions, a large number of industrial and commercial users of trichloroethylene will be affected, as will the public that benefits from the applications of the chemical.

According to the Executive Summary (page 2), concentrations of trichloroethylene in ambient air range from 0.14 to 0.26 parts per billion (ppb) in California. The available scientific evidence indicates that the actual risk of exposure to trichloroethylene at such ambient levels is negligible. Therefore, we urge the Scientific Review Panel to recognize that the conclusion as stated on page 1 of the Executive Summary ("at ambient concentrations, trichloroethylene may cause or contribute to an increase in mortality or serious illness and may therefore pose a potential hazard to human health") is almost certainly overstated. It is clearly inconsistent with most scientific reviews, which generally have agreed with the scientists from the Centers for Disease Control, who concluded after a thorough review that "[t]he risk associated with exposure to trace amount (ppb) concentrations of trichloroethylene in water appear to be minimal or perhaps negligible" (Kimbrough, et al., Trichloroethylene: Update, J. Tox. Env. Health 15:369-383, 1985). This statement made in the context of incidents of groundwater contamination at low part per billion levels is even more true for ambient air exposure at fractions of a part per billion.

We also request that a statement be added to page 4 of the Executive Summary under the heading "What is the Risk Assessment for Exposure to TCE?" The second sentence in this paragraph should read "[t]his is a 95% upper confidence limit estimate of plausible excess cancer cases; the actual cancer risk cannot be calculated and may be negligible." This statement would be consistent with the language concerning upper confidence limit potency estimates on page 1-6 of the draft Part B report.

We are also concerned that the unit risk estimate will be misinterpreted. For example, in a May 5, 1989, memorandum on methylene chloride, the Department of Health Services provided an estimate of potential risk that was endorsed by the Scientific Review Panel as the most plausible estimate of risk. As the enclosed memorandum indicates, the California Division of Occupational Safety and Health viewed this information as "new scientific evidence for lowering the exposure limits for methylene chloride" and included the issue of revising the workplace limit for methylene chloride as a major topic for a meeting of its Advisory Committee on Airborne Contaminants. In this instance, an upper-bound estimate of potential risk is being used to suggest that exposure to methylene chloride at the existing California workplace limit (100 ppm) will cause cancer in four out of every 100 workers, even though high quality published epidemiology studies show no overall increase in cancer among workers exposed to an average of 26 ppm of methylene chloride for over 30 years.

Ms. Genevieve Shiroma

April 10, 1990

Page 3

Our earlier comments describe scientific research that has shown that results observed in mice are unlikely to be seen in humans because of differences in metabolism and mechanism of action. We enclose with these comments a report of this work by the toxicologist who conducted it, along with the article by Kimbrough, et al. mentioned above. We urge the Panel to give careful consideration to these papers as it reviews the draft Part B Report.

Sincerely,



Paul A. Cammer, Ph.D.
President

Enclosures

II.

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

o Halogenated Solvents Industry Alliance (HSIA)

1. **Comment:** The risk of exposure to TCE is negligible. References furnished by HSIA conclude that the risk from exposure to TCE in water is minimal or negligible at ppb levels; therefore the risk is even lower at ambient air concentrations of fractions of ppbs.

Response: The DHS risk assessment concluded that there is a small risk from exposure to TCE at ambient concentrations. Parts per billion in water and air are not equivalent. Breathing 20 m³ of air containing 0.14 to 0.26 ppb TCE (as measured in California's ambient air) would result in an intake of 15 to 28 μ g TCE. Drinking two liters of water containing 5 ppb TCE, (the USEPA's maximum contaminant level [MCL]), would result in a slightly smaller intake of 10 μ g of TCE.

2. **Comment:** HSIA requests that a statement be added to page 4 of the Executive Summary under the heading "What is the Risk Assessment for Exposure to TCE?" The second sentence in this paragraph should read "This is a 95 percent upper confidence limit estimate of plausible excess cancer cases; the actual cancer risk cannot be calculated and may be negligible."

Response: Since the Summary portion of Part B of the technical support document for TCE contains this language, we think it is not necessary to place this statement in the Executive Summary.

III.

Department of Health Services Staff Responses to Summarized Comments on the Draft Part B

o Halogenated Solvents Industry Alliance (HSIA)

1. **Comment:** Ambient concentrations of TCE range from 0.14 to 0.26 ppb. The available scientific evidence indicates that the risk of exposure to these levels is negligible. Therefore, the conclusion stated on page 1 of the Executive Summary ("at ambient concentrations, trichloroethylene may cause or contribute to an increase in mortality or serious illness and may therefore pose a potential hazard to human health") is almost certainly overstated. Scientists from the Center for Disease Control conclude that "the risk associated with exposure to trace amount (ppb) concentrations of trichloroethylene in water appear to be minimal or perhaps negligible." This statement made in the context of incidents of groundwater contamination at low parts per billion levels is even more true for ambient air exposure at fractions of a part per billion.

Response: As a public health agency we relied on the evidence that TCE may act by a genotoxic mechanism and that TCE administration causes several types of tumors in both mice and rats. We agree that TCE is a weak carcinogen and we predict at least a small probability of carcinogenesis. In addition, ppb in water and air are not equivalent (see response to comment 1, Section II).

2. **Comment:** HSIA's earlier comments describe scientific research that has shown that results observed in mice are unlikely to be seen in humans because of differences in metabolism and mechanism of action.

Response: Please see the response to comment 1.