The Vinyl Institute
A Division of The Society of The Plastics Industry, Inc.

May 29, 1990

TO: The VI Health, Safety & Environment Committee

RE: California Air Resources Board - Draft Report on Vinyl Chloride

I received today the May 1990 three-part draft report on the "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant" from the California Air Resources Board.

Enclosed are the following items from each of the sections:

Part A: Public Exposure To, Sources and Emissions of Vinyl Chloride in California
- Executive Summary
- Table of Contents

Part B: Health Effects of Airborne Vinyl Chloride
- Table of Contents
- Executive Summary

Part C: Public Comments and Responses to the Preliminary Draft Report
- Responses to comments filed by the Vinyl Institute.
- A copy of the comments filed 9/8/89 by the VI.

If after reviewing the enclosed, you wish to receive any specific sections of the report, please let me know and I will forward them to you.

Sincerely yours,

Meredith

Meredith N. Scheck
Assistant Director

MNS/pmb
cc: P. de la Cruz
J. Krokowsky
C. Bush

R&S150644

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Assistant Director

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cc: P. de la Cruz, J. Krokowsky, C. Bush

(Note to C. Bush: BFGoodrich also filed comments that were signed by K. Stimler in government affairs - she should also have a complete copy of the report.)

R&S150645

TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT

DRAFT REPORT

EXECUTIVE SUMMARY AND PART A

May 1990

State of California
Air Resources Board
Stationary Source Division

R&S150646

EXECUTIVE SUMMARY

What is a toxic air contaminant?

According to Section 39655 of the California Health and Safety Code, a toxic air contaminant is "an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health." In addition, "substances which have been identified as hazardous air pollutants pursuant to Section 7412 of Title 42 of the United States Code shall be identified by the state board as toxic air contaminants."

Does the Air Resources Board (ARB) staff recommend identification of vinyl chloride as a toxic air contaminant?

Yes, we recommend that vinyl chloride be identified as a toxic air contaminant because:

- there is sufficient evidence that exposure to vinyl chloride poses a public health hazard,
- vinyl chloride is detected in ambient and indoor air near known emission sources and does not break down in the atmosphere at a rate that would significantly reduce public exposure, and
- vinyl chloride shall be identified as a toxic air contaminant pursuant to Section 39655 of the California Health and Safety Code because it is listed as a hazardous air pollutant by the federal government pursuant to Section 7412 of Title 42 of the United States Code.

Why does the ARB staff recommend the identification of vinyl chloride as a toxic air contaminant when a state ambient air quality standard already exists?

The state ambient air quality standard of 10 ppb averaged over 24 hours merely reflects the limit of detection (LOD) for vinyl chloride ambient air concentration analysis in 1978 when the standard was promulgated. This technology-based standard is not recognized as health-protective. The identification of vinyl chloride as a toxic air contaminant would allow health-protective control measures to be implemented at concentrations below 10 ppb.

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

Acute exposure to vinyl chloride has lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis, and death. Chronic exposure of workers to vinyl chloride has induced acro-steolysis, vasospasm of the hands, dermatitis, circulatory and CNS alterations, thrombocytopenia, splenomegaly, and changes in liver function. However, these noncarcinogenic effects occur at vinyl chloride concentrations near or above 10 ppm which is far greater than either the California average ambient level of less than 0.5 ppb or measured ambient hot spot concentrations of about 10 to 15 ppb. Therefore, the DHS staff do not expect noncarcinogenic adverse health effects to occur from exposures to current concentrations of vinyl chloride found in ambient air.

The International Agency for Research on Cancer (IARC), the United States Environmental Protection Agency (EPA), and the California Department of Health Services (DHS) have designated vinyl chloride a chemical for which there is sufficient evidence of carcinogenicity in both humans and experimental animals. Epidemiological studies of occupationally exposed human workers have linked vinyl chloride exposure to the development of a rare cancer, liver angiosarcoma, and have suggested a relationship between exposure and cancers of the lung and brain. Chronic inhalation and oral exposures of rats, mice, and hamsters to vinyl chloride have been associated with an increased incidence of malignant and benign tumors at several sites including the liver, lungs, mammary glands, and the nervous system. Vinyl chloride is mutagenic in both prokaryotic and eukaryotic test systems.

Is there a threshold level for vinyl chloride?

Since vinyl chloride is mutagenic and there is not sufficient evidence at this time to support the designation of an exposure level below which no significant adverse health impacts are anticipated, the DHS staff recommend that vinyl chloride be treated as having no threshold exposure level.

What are the findings of the Scientific Review Panel?

(To be added.)

Is vinyl chloride produced or used in California?

Vinyl chloride is not produced in California, however, it is estimated that several thousand tons are used each year by two facilities producing polyvinyl chloride. Polyvinyl chloride is used by fabricators for the production of materials employed by the construction, packaging, electrical, and transportation industries.

What are the sources of vinyl chloride emissions?

Landfills, polyvinyl chloride production and fabrication facilities, and sewage treatment plants are the major sources of vinyl chloride emissions in California.

Landfills represent California's largest source of vinyl chloride emissions. Section 41805.5 of the 1986 California Health and Safety Code required testing landfills for specified compounds including vinyl chloride. Vinyl chloride was detected at or above a statistically determined detection limit of 106 ppbv in the internal gas of about half of the 340 landfills tested thus far.

Vinyl chloride emissions estimates have been made for two landfills in the South Coast Area Basin: BKK Landfill and Operating Industries Incorporated (OII) Landfill. The test data for the BKK Landfill was obtained from January 1986 through December 1986, while data for the OII Landfill was obtained from January 1987 through December 1987. Assuming that emissions do not vary significantly from year to year, it is estimated that cumulative vinyl chloride emissions from these two landfills could range from about 50 to 250 tons per year. Landfill emissions occur by two mechanisms: 1) direct vinyl chloride emissions from disposed wastes which contain vinyl chloride, and 2) indirect emissions due to the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons.

What is the persistence of vinyl chloride in the atmosphere?

Vinyl chloride is estimated to be degraded in 1.6 to 3.9 days through its reaction with hydroxyl radicals in the atmosphere. Therefore, vinyl chloride is sufficiently persistent to be transported throughout an air basin before it is degraded.

What is the ambient concentration of vinyl chloride?

Vinyl chloride in California poses a potential near-source risk as detectable levels are limited only to locations near identified emission sources such as landfills. The South Coast Air Quality Management District (SCAQMD) obtained ambient monitoring data from locations near two landfills in the South Coast Air Basin. At the BKK Landfill from January through December of 1987, 24-hour average concentrations of vinyl chloride ranged from below the LOD to 15 ppb with a mean of 1.2 to 2.6 ppb. The SCAQMD's

LOD for ambient vinyl chloride monitoring was 2 ppb. At the Operating Industries Incorporated (OII) Landfill from January through December of 1986, 24-hour average concentrations of vinyl chloride ranged from below the LOD to 9.8 ppb with a mean of 1.0 to 2.0 ppb.

What is the exposure level of people living near sources such as landfills?

Population-weighted exposure results, based on computer modeling by ARB staff, show that approximately two million people living near the BKK Landfill were exposed to estimated annual average vinyl chloride concentrations ranging from 0.08 to 0.34 ppb in 1987. The maximum exposed individual living near BKK was estimated to be exposed to an average annual concentration of 2.3 to 10.3 ppb. For the OII Landfill, the population-weighted exposure results show that approximately four million people were exposed to an estimated annual average vinyl chloride concentration ranging from 0.004 to 0.06 ppb in 1986. The maximum exposed individual living near OII Landfill was estimated to be exposed to an annual average vinyl chloride concentration ranging from 0.6 to 8.7 ppb. Insufficient data are available at this time to determine the population-weighted exposure to vinyl chloride near other California landfills.

Is there evidence of indoor air exposure to vinyl chloride?

In California, indoor air vinyl chloride has been detected only in houses near landfills. Some homes near landfills have been shown to accumulate vinyl chloride to the extent that indoor concentrations are several times greater than general outdoor concentrations. Landfill gas containing vinyl chloride may contribute to indoor air concentrations by direct outdoor air influx or by underground migration and subsequent entrance through the substructures of homes.

In 1985, elevated levels of vinyl chloride in the water meter boxes of several homes adjacent to the OII Landfill prompted a South Coast Air Quality Management District indoor air grab-sample study. Indoor air sampling results showed vinyl chloride concentrations ranging from 8 to 100 ppb. Since 1985, the OII Landfill installed a gas collection system and significant levels of landfill gas are no longer detected in the water meter boxes of homes near the landfill. Presently, indoor vinyl chloride concentrations in the residences near the landfill are believed to be substantially lower due to the OII Landfill's gas collection system.

The ARB is currently sponsoring research to assess the presence of vinyl chloride in homes not located near landfills; to date, no vinyl chloride has been detected.

Are there other routes of exposure to vinyl chloride?

Exposure to vinyl chloride may also occur from ingestion of food and water that contain residues of the substance. Since vinyl chloride is not

typically detected in drinking water or food products, exposure through these routes is not expected to significantly contribute to the cancer burden attributed to vinyl chloride.

What is the risk assessment for exposure to vinyl chloride?

The DHS analyzed many human occupational and animal studies in the cancer risk assessment for vinyl chloride exposure. Predictions from the majority of the studies of humans exposed to vinyl chloride occupationally are uncertain due to inadequate exposure data, insufficient follow-up time, and methodological problems. Based on the exposure estimates for vinyl chloride workers in the Waxweiler, et al. (1976) study, the 95% upper confidence limit on the lifetime unit risk of contracting cancer from vinyl chloride ranged from $2.5 \times 10^{-5} ppb^{-1}$ to $4.5 \times 10^{-5} ppb^{-1}$. Evaluation of animal experiments using the linearized multistage model leads to predictions of upper confidence limits on unit risks for humans ranging from $3.7 \times 10^{-5} ppb^{-1}$ to $20 \times 10^{-5} ppb^{-1}$. Considering tumorgenicity data as well as the results of human and animal studies, the DHS staff conclude that the overall range of upper confidence limits on cancer unit risk is $2.5 \times 10^{-5} ppb^{-1}$ to $20 \times 10^{-5} ppb^{-1}$. In order to ensure protection of public health, the DHS has identified the best estimate of cancer unit risk to be $20 \times 10^{-5} ppb^{-1}$, the top of the upper confidence limits range.

Because vinyl chloride has not been detected in statewide ambient air monitoring, hot spot concentrations detected by monitors near two South Coast landfills were used to assess the probable impact of vinyl chloride on the cancer burden in California. Population-weighted estimates of peak exposure concentrations for maximally exposed receptors ranged from 2 to 10 ppb at the BKK Landfill and from 0.6 to 9 ppb at the OII Landfill. An estimated 17,000 to 131,000 persons were exposed to 1 ppb of vinyl chloride near the BKK Landfill where the highest exposures were predicted from the monitoring results of 1987. Using the upper confidence limits range of risks, the DHS estimates that 3 to 36 cancers may occur in 131,000 persons due to lifetime exposure to 1 ppb of vinyl chloride.

All of the above estimates represent the upper range of plausible excess cancer risk. Estimates of actual risks at exposures near 1 ppb are uncertain and could be much lower.

Based on the evidence of vinyl chloride-induced carcinogenicity and the results of the risk assessment, the staffs of the DHS and the ARB find that vinyl chloride, in concentrations near certain hot spot locations in California, meets the definition of a toxic air contaminant in the California Health and Safety Code Section 39655.

What are the alternatives to identifying vinyl chloride as a TAC?

Government Code Section 11346.14 requires agencies to descibe alternatives to the regulation considered by the agency and the agency's reasons for rejecting those alternatives. The only alternative to identifying vinyl chloride is not to identify it. We are not recommending this alternative because we believe that vinyl chloride meets the definition of a toxic air contaminant.

What would be the environmental impact of the identification of vinyl chloride as a toxic air contaminant?

The identification of vinyl chloride as a toxic air contaminant is not itself expected to result in any impact on the environment. The Board's identification of vinyl chloride as a toxic air contaminant may result in the adoption of control measures according to the California Health and Safety Code Sections 39665 and 39666. Implementation of control measures would benefit the public health by reducing vinyl chloride emissions resulting in a reduced health risk due to vinyl chloride exposure.

Environmental impacts identified with respect to specific control measures will be included in the consideration of such control measures pursuant to the California Health and Safety Code Sections 39665 and 39666.

DRAFT
TECHNICAL SUPPORT DOCUMENT
PART A

PUBLIC EXPOSURE TO, SOURCES, AND EMISSIONS OF VINYL CHLORIDE IN CALIFORNIA

REPORT TO THE AIR RESOURCES BOARD ON VINYL CHLORIDE

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Stationary Source Division

May 1990

DRAFT

PRELIMINARY EXPOSURE TO, AND SOURCES OF ATMOSPHERIC VINYL CHLORIDE IN CALIFORNIA

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TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT

DRAFT REPORT
PART B

May 1990

State of California
Air Resources Board
Stationary Source Division

R&S150657

HEALTH EFFECTS OF AIRBORNE VINYL CHLORIDE

CALIFORNIA DEPARTMENT OF HEALTH SERVICES

May, 1990

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1.0 EXECUTIVE SUMMARY

Vinyl chloride is a short-chain halogenated hydrocarbon used predominantly in the manufacture of polyvinyl chloride and various packaging and construction products. Vinyl chloride has a very low degree of acute toxicity, with two-hour inhalation LD_{50} values ranging from 27,419 ppm in mice to 236,215 ppm in rabbits and guinea pigs. Exposure to high concentrations can lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis and death. Several human deaths have been attributed to occupational exposure to very high levels of vinyl chloride. Autopsies of these patients revealed congestion of the liver, spleen and kidneys. Acute toxicity symptoms are thought to occur above 100 ppm.

Chronic exposure of workers to vinyl chloride has been shown to lead to "vinyl chloride disease", characterized by occupational acro-osteolysis, vasospasm of the hands similar to Raynaud's syndrome, dermatitis, circulatory and central nervous system alterations, thrombocytopenia, splenomegaly and changes in liver function. Eight symptoms commonly reported by workers exposed to vinyl chloride (including dizziness, headaches and nausea) were observed even at dose levels below 50 ppm.

Vinyl chloride has been shown to induce cancer in animals *in utero*, but has not been shown to cause any other reproductive or developmental effects in rats, mice and rabbits. Epidemiologic studies of families of vinyl chloride workers or communities having vinyl chloride processing facilities

suggested the possibility of an increased incidence of birth defects and spontaneous abortions among people at risk; however, subsequent reviews of these studies have concluded that there is inadequate evidence to link environmental or paternal exposure to vinyl chloride with birth defects or spontaneous abortions in humans.

The noncarcinogenic effects occur at concentrations near or above 10 ppm, which is greater than four orders of magnitude above possible general ambient levels in California (0.5 ppb). The noncarcinogenic effects also occur at concentrations greater than 3 orders of magnitude above the highest concentrations measured near landfills (10 ppb). Consequently, DHS staff do not expect noncarcinogenic adverse health effects to occur from acute or chronic exposures to vinyl chloride in ambient air.

The International Agency for Research on Cancer (IARC), the United States Environmental Protection Agency (EPA) and the California Department of Health Services (CDHS) have identified vinyl chloride as a chemical for which there is sufficient evidence of carcinogenicity in both humans and experimental animals. Chronic inhalation and oral exposures of rats, mice and hamsters to vinyl chloride have been associated with an increased incidence of malignant and benign tumors at several sites including the liver, lung, mammary gland and the nervous system. In humans, epidemiological studies of occupationally exposed workers have linked vinyl chloride exposure to development of a rare cancer, liver angiosarcoma, and have suggested a relationship between exposure and lung and brain cancers.

Although pharmacokinetic studies in humans exposed to vinyl chloride are rare, limited evidence indicates that, following inhalation of low levels of vinyl chloride (3 to 24 ppm), up to 71% (with a mean value of 42%) of the given dose may be absorbed. Vinyl chloride absorption appears to depend on its metabolism, which is a dose-dependent, saturable process. Due to saturation of the enzyme systems responsible for the metabolism of vinyl chloride (cytochrome P-450 and alcohol dehydrogenase), exposure to concentrations above approximately 250 ppm would not necessarily be expected to lead to a perceptibly increasing incidence of tumor development. Metabolism of vinyl chloride leads to formation of chloroethylene oxide and chloroacetaldehyde, two reactive intermediates which undergo covalent binding to cellular macromolecules and are thought to be responsible for the toxic effects of vinyl chloride. These and other metabolites may be further metabolized and excreted in the urine. Unmetabolized vinyl chloride is eliminated primarily in exhaled air.

Vinyl chloride is mutagenic in both prokaryotic and eukaryotic test systems, with significantly greater genotoxicity seen after metabolic activation. DHS staff have found no evidence of a carcinogenic threshold level and the staff recommends that vinyl chloride be considered as not having a threshold for carcinogenicity.

Several studies of carcinogenicity of vinyl chloride in animals and in occupationally exposed workers have been analyzed for risk assessment purposes. The lowest lifetime equivalent concentration associated with an increased incidence of tumors in laboratory animals is 0.06 ppm or 6 to 60-fold above potential human exposure concentrations. Although measurements

of actual exposure levels are not available for vinyl chloride, worker exposure estimates have been used to evaluate the Waxweiler et al. (1976) study. Based on these estimates, the present analysis calculates that the 95% upper confidence limit (UCL) on lifetime unit risk of contracting cancer from vinyl chloride, assuming liver, brain and lung cancer are all related to vinyl chloride exposure, is 4.5×10^{-5} ppb^{-1}. In the case that only liver cancer is assumed to be linked to exposure, the UCL on unit risk is 2.5×10^{-5} ppb^{-1}. These predictions are uncertain due to inadequate exposure data, follow-up time and other methodological problems. Evaluation of animal experiments by the linearized multistage model yields predictions of UCLs on unit risks for humans to be in the range of 3.7×10^{-5} to 20×10^{-5} ppb^{-1}. Evaluation of animal tumorigenicity data indicates that vinyl chloride's carcinogenic potency is dependent on sex, tumor site and age of exposure. Taking all these factors into account, DHS staff conclude that the best estimate to use in order to assure the public health is the top of the range of animal UCLs of unit risk, 20×10^{-5} ppb^{-1}. The overall range of UCLs on unit risk suitable for regulatory purposes is 2.5×10^{-5} to 20×10^{-5} ppb^{-1}.

Vinyl chloride has not been detected in the ambient air of California (limit of detection = 0.5 ppb) except at certain "hot spots". Air Resources Board (ARB) staff has monitored vinyl chloride emissions from the BKK hazardous waste site in West Covina and the OII landfill in Monterey Park. Estimates of peak exposure concentrations for maximally exposed receptors range from 2 to 10 ppb at the BKK landfill and from 0.6 to 9 ppb at the OII site. Air Resources Board staff has estimated that between 17,000 and 131,000 individuals may be exposed to 1 ppb at the BKK site.

The model predicts that the 95% upper confidence limit on cancers due to lifetime exposure of 131,000 residents to 1 ppb would be in the range of 3 to 36. Based on the finding of vinyl chloride-induced carcinogenicity and the results of the risk assessment, DHS staff finds that vinyl chloride is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

1.1 Vinyl Chloride Highlights

I. National and International Evaluation (Other Agencies' Evaluation)

A. International Agency for Research on Cancer (IARC)

1. Short-Term Tests: Sufficient evidence of mutagenic activity exists, both with and without an exogenous metabolic activation system.

2. Animal carcinogenicity bioassays: Sufficient evidence of animal carcinogenicity by oral administration or inhalation exists.

3. Human evidence: Sufficient evidence of carcinogenicity to humans exists. Occupational exposure to vinyl chloride has been linked with development of angiosarcoma of the liver, and has been associated with tumors of the brain and lung and of the hematopoietic and lymphatic

systems. Vinyl chloride is grouped under IARC category 1, meaning that it is causally associated with cancer in humans.

B. U.S. Environmental Protection Agency (EPA)

1. Short-Term Tests: Sufficient evidence of mutagenic activity exists, both with and without an exogenous metabolic activation system, for both DNA damage and mutation.

2. Animal carcinogenicity bioassays: Sufficient evidence of animal carcinogenicity by administration orally or by inhalation exists.

3. Human data: A number of epidemiological studies have linked vinyl chloride with angiosarcoma and other forms of neoplasms. Sufficient evidence exists to indicate that vinyl chloride is a human carcinogen by inhalation.

C. Conclusions: Both EPA and IARC have concluded there is ample evidence that vinyl chloride is genotoxic and is carcinogenic in both animals and humans.

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Response to Comments: Vinyl Institute

I. General comment

Comment: "There are at least two areas of discussion that are inadequately treated.....They are the pharmacokinetic knowledge of vinyl chloride in the risk assessment approach and a total inadequate treatment of the large number of studies in the published literature." (sic)

Response: DHS staff note the usefulness of the commenter's general suggestions advocating more explicit consideration of the pharmacokinetic model and of the epidemiological data in the quantitative risk assessment. Therefore, in the revised document, DHS staff have described quantitatively the Michaelis-Menten kinetic model, as developed by Gehring et al. (1978), which the commenters specifically mention. The model has been included in the risk analysis of the major epidemiological study and in the quantitative analysis of the animal studies.

II. Specific comments

A. Concerning the assertion that the risk assessment does not adequately treat pharmacokinetic knowledge of vinyl chloride:

1. Comment: The DHS risk assessment did not cite several pharmacokinetically oriented studies. One such study was Anderson et al. (1980). Another was Bolt et al. (1981).

Response: DHS considered both the references that the commenter mentioned. The original DHS risk assessment cited one of these two references, as well as many other references on pharmacokinetics. See pages 2-1 through 2-17, and especially page 2-4, where Bolt et al. (1981) is cited. The original public announcement listed the Anderson et al. (1980) paper, but the DHS risk assessment did not cite that reference because the original DHS risk assessment did not use the pharmacokinetic approach in the quantitative modelling of risk predictions. That reference obtained a multistage risk estimate in the lower end of the range of risks, consistent with the DHS calculations for the early Maltoni data that Anderson et al. used. The revised risk assessment now cites Anderson et al. (1980).

2. Comment: "The DHS document fails to incorporate any of the established pharmacokinetic information in its treatment of theoretical risk for vinyl chloride."

Response: The revised document now includes a pharmacokinetic model in the quantitative prediction of risk. The original version of the document included on pages 8-1 and 8-6 a summary of the implications of the pharmacokinetic information and concluded that the pharmacokinetic analysis is not quantitatively necessary (for laboratory rodents) because of sufficient bioassay data at exposures below the saturation concentration for rats. This view is consistent with an independent analysis of Krewski et al.

(1987). They reported that when basing the quantitative risk analysis for rats on doses below 200-500 ppm, which is within the linear range of dose response, there is virtually no difference between unit risks obtained using administered dose and delivered dose, as obtained in a pharmacokinetic model. The revised analysis did find a greater difference, and the revised version of the document performs the analysis using a pharmacokinetic model.

3. Comment: A reactive metabolite is probably responsible for VC toxicity.

Response: DHS agrees. The original vinyl chloride risk assessment document stated at page 8-1, "the oncogenicity of vinyl chloride appears to be due to one or more reactive metabolites, rather than the parent molecule". Also, the first sentence in Chapter 2, Metabolism and Pharmacokinetics, stated, "Experimental evidence has suggested that vinyl chloride must undergo transformation to a reactive metabolite(s) by the liver to be toxic."

4. Comment: "It is currently thought that VC is metabolized by epoxidation with subsequent production of chloroacetaldehyde. The further oxidation and conjugation with glutathione are responsible for the metabolites found in the urine."

Response: The risk assessment mentioned both the epoxidation process and the conjugation with glutathione -- on pages 2-1 and 2-13 respectively. Both also appeared in the IARC diagram, which is Fig. 2.1.

5. Comment: Gehring found that several models overpredicted the risk to man unless corrected for varying rates of metabolism and for surface area differences of the different species.

Response: In 1978 Gehring et al. used pharmacokinetics in fitting a probit model to observed cancer rates in the rat bioassay. Those authors then went on to use surface area scaling on the assumed rate of metabolism to extrapolate the results from rats to compare to a human risk measurement, derived from an occupational study (Fox and Collier, 1977). In 1979 Gehring et al. used the same pharmacokinetics in fitting four models to observed cancer rates in the rat bioassay. Those authors then went on to extrapolate all four results from rats to compare to an occupational risk study that was then recently completed by Equitable Environmental Health (EEH, 1978). The comparison by Gehring et al. considered the probit prediction to be in satisfactory agreement with the new human measurement without any scaling of risk by surface area. Of the remaining three models, the authors reported one as being too low and the other two as being too high. A follow up study of the occupational group (Wong et al., 1986; see comment B-2 below) subsequently indicated much higher rates of human liver angiosarcoma than had the earlier study. These last two occupational studies (EEH, 1978 and Wong et al., 1986) remain unpublished.

B. Concerning the assertion that the risk assessment does not adequately treat the large number of epidemiology studies in the published literature:

1. Comment: To dismiss the large number of epidemiology studies and to relegate them only to comparisons with animals is unacceptable. "DHS demonstrates a bias towards the utilization of animal experiments as a priority over human evidence in their approach to risk assessment. This results in a dramatic overestimate of likely human risk at the low environmental levels being addressed by the document." The DHS judges that risk extrapolations based on the human data are comparable to those of the animal predictions, yet differences of an order of magnitude or two in risk assessment can often have a dramatic practical effect. "When adequate or substantial human evidence exists, that data should be given preferential treatment in the risk assessment process."

Response: The original document pointed out at pages 1-4, 7-55, 8-7, B-2 and B-3 that the epidemiological data are important to consider in the risk assessment but mostly are not sufficient to construct reliable dose-response functions. One of the main reasons for this limitation is the inability of the occupational studies to account for the effects of sex, tumor site and age of exposure, all of which are found to be important in the animal carcinogenicity results. Also, there are large uncertainties of exposure in the occupational studies. The original document did make the comparative statement that, taking all the limitations of the occupational studies into account, "the human risk estimates are consistent with those obtained for laboratory animals." (page 1-4). See also page 8-10. Using suggestions of the commenter about pharmacokinetics, DHS has revised the estimate f lifetime unit risk for all cancers to be 4.5×10^{-5} ppb^{-1}, based on an occupational study by Waxweiler et al. (1976). This estimate is only a factor of four less than the best animal predictions. Such a result represents reasonable consistency, considering that the occupational results may not take proper account of the greater sensitivity found in females, the greater risk to children, and the inability of the human studies to detect any, except relatively large increases, in any specific type of tumor. The DHS has revised the document to include the two most reliable human results, both from the Waxweiler et al. (1976) study, which do now overlap the narrowed range of risk for animals.

2. Comment: Two updated epidemiology studies, one of over 10,000 workers, are cited in support of the commenter's position that "DHS's approach to dismiss human epidemiology evidence in their risk assessment is inadequate."

Response: The original document reviewed epidemiology studies on pages 7-31 through 7-55 and developed quantitative analyses in Appendices B and C. The document cited both the studies mentioned by the commenter. The first is the paper of Daher et al. (1988), which is cited at page 7-46. This paper, which is less than two pages in length, continues to follow the same 593 Dow employees as did the study of Ott et al. (1975). The number of persons in the study is still too small to expect to detect any effect. The second study mentioned by the commenter is the epidemiological follow up for the Chemical Manufacturers Association (CMA), which was summarized in the Tables B-1 and B-2 of the original document. This study recorded 359 cancer deaths. The SMR for liver and biliary cancer was very large, 641, and the SMR for brain cancer, 180, was statistically significant. On page B-10 that study

was also cited as providing some evidence against a relationship between lung cancer and vinyl chloride exposure. This work for the CMA was listed in the original bibliography by the corporate author, Environmental Health Associates (1986). The risk assessment has been revised to use a consistent means of referencing this unpublished work as Wong et al. (1986). DHS staff has not put much weight on this work because it does not appear to be proceeding to the peer reviewed literature and it is problematic to relate most of the studies to exposure.

3. Comment: Liver angiosarcoma "is the most suitable end-point for analysis of risk of exposure to vinyl chloride."
   (a) The "most reasonable interpretation of the data is consistent with the causal association of vinyl chloride and an excess of brain cancer; however, the relative risk calculation for brain cancer is much lower than that for liver cancer."
   (b) "Only two out of eight studies on lung cancer yield statistically-significant results, and because studies with the higher power were negative, a causal association is unlikely." (sic)
   (c) "Vinyl chloride angiosarcoma is a rare cancer in unexposed populations, thereby making the utilization of angiosarcoma as a demonstration of vinyl chloride exposure on the basis of work history truly a reasonable approach."
   (d) "Angiosarcoma has been demonstrated to occur both in animals and humans when exposed to vinyl chloride."

Response: Liver angiosarcoma plays a major role in the current risk assessment, for the reasons given by the commenter. Nevertheless, other sensitive indicators of carcinogenesis, such as breast cancer observed in rodents and several cancers in humans are also considered.

4. Comment: A recent paper by Purchase et al. (1987) "demonstrates a much more studied and scientifically defensible approach to assessing risk of exposure to vinyl chloride."

Response: The approach of Purchase et al. is not defensible by current standards of risk assessment in the U.S. The models that they use in their risk assessment to interpret animal data have become of marginal importance compared to the multistage (or single stage) model, which has more biological plausibility and also provides more stable estimates of confidence limits on risk. Expressing their results as dose producing one-in-a-million risk, they use the marginal models to produce an excessively large range of dose, with the highest dose being 10^{10} the lowest dose. The higher doses are said to be consistent with the occupational experience, but there is no support for that statement in spite of a lengthy analysis of data on liver angiosarcoma in vinyl chloride workers in several countries prior to 1982. The only dose that the paper derives from the human studies is from a sketchy environmental effects analysis of Barr (1982). See the next item.

5. Comment: Barr (1982) conducted an analysis of liver angiosarcoma cases that could be located among populations inferred to be living in the vicinity of VCM production facilities. The results suggest that "100 ppb represented the

estimated dose representing a 1 x 10^{-6} lifetime risk in man. That value is similar to the highest estimate derived from the animal data when taking biotransformation into account."

Response: The risk assessment did not cite the study of Barr (1982) with its brief analysis of liver angiosarcoma because that analysis is so unsubstantial epidemiologically and the work remains unpublished in the peer-reviewed literature. As a counter to Barr's brief analysis, a well considered recent assessment by the Committee on the Evaluation of Carcinogenic Substances, National Health Council of the Netherlands (1987), published in the scientific literature, has found carcinogenic risk based on published occupational studies to be one in a million per ppb, which was about the same as found in the original DHS risk assessment, 2.1 x 10^{-6}/ppb, before revising the model to take account of the pharmacokinetics of vinyl chloride.