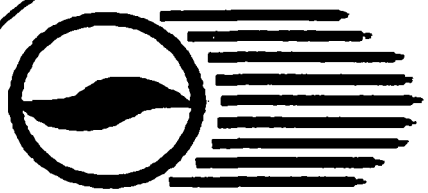
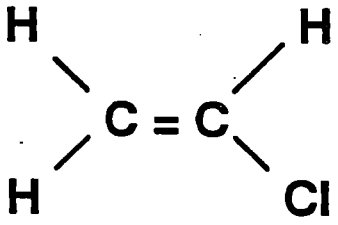


STAFF REPORT/EXECUTIVE SUMMARY

PROPOSED IDENTIFICATION OF



VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California
Air Resources Board
Stationary Source Division

This report has been reviewed by the staffs of the California Air Resources Board and the Department of Health Services and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board or the Department of Health Services, nor does mention of trade names of commercial products constitute endorsement or recommendation for use.

California State University, Fullerton
Fullerton, California 92634

Department of Chemistry and Biochemistry
(714) 773-3621

Correspondence to:
P.O. Box 668
San Clemente, CA 92674-668
Phone: (714) 361-1132 FAX: (714) 361-1283

October 22, 1990

Mr. William C. Lockett, Chief
Office of External Affairs
California Air Resources Board
1102 Q Street
Sacramento, California 95814

Dear Bill:

The Scientific Review Panel on Toxic Air Contaminants has reviewed the Report on Vinyl Chloride and has formulated its findings regarding the report. I am formally submitting the Scientific Review Panel's findings to the Air Resources Board.

Sincerely,

Dr. James N. Pitts, Jr.
Chair, Scientific Review Panel

Enclosure

cc: Scientific Review Panel

3. Based on the interpretation of available scientific evidence, the OHS staff estimated that the upper 95 percent confidence limits on the lifetime risk of cancer from vinyl chloride ranged from 2.5×10^{-5} ppb^{-1} to $20 \times 10^{-5} ppb^{-1}$. The OHS staff identified the best estimate of vinyl chloride cancer unit risk as the top of the upper confidence limits range, $20 \times 10^{-5} ppb^{-1}$ or $7.8 \times 10^{-5} (ug/m^3)^{-1}$. Table 1 compares the best estimate of vinyl chloride cancer unit risk with those of other compounds recently reviewed by the SRP.

TABLE 1

Compound	Unit Risk (ppb^{-1})	Unit Risk $(ug/m^3)^{-1}$
Vinyl chloride	20×10^{-5}	7.8×10^{-5}
Chloroform	2.6×10^{-5}	6.3×10^{-6}
Trichloroethylene	1.1×10^{-5}	2×10^{-6}
Inorganic arsenic	particulate	3.3×10^{-3}
Methylene chloride	3.5×10^{-6}	1×10^{-6}

Upper bound excess lifetime risks are health-protective estimates; the actual risk may well be below these values.

4. Landfills, publicly-owned treatment works, and polyvinyl chloride producers and fabricators are the major identified sources of vinyl chloride emissions in California's outdoor air.

5. Based on its gas-phase reactivity with hydroxyl radicals, vinyl chloride's estimated tropospheric lifetime ranges from 1.6 to 3.9 days.

6. Vinyl chloride has not been detected by the ARB's statewide ambient toxic air contaminant monitoring network. However, vinyl chloride has been detected in the ambient air near emission sources such as landfills.

Scientific Review Panel Findings on the Vinyl Chloride Report

As Adopted at the Panel's October 19, 1990 Meeting

In accordance with California Health and Safety Code Section 39661, the Scientific Review Panel (SRP) has reviewed the report prepared by the staffs of the Air Resources Board (ARB) and the Department of Health Services (DHS) on the public exposure to, and health effects of vinyl chloride. The Panel has also reviewed the public comments received on this report. Based on this review, the SRP finds that the report on vinyl chloride is without serious deficiencies and agrees with the staffs of the ARB and the DHS that:

1. There is strong evidence that exposure to vinyl chloride results in animal and human carcinogenicity. The United States Environmental Protection Agency (USEPA) assigned vinyl chloride to Group A of its classification scheme for carcinogens. In explaining its Group A category, the EPA states, "This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The International Agency for Research on Cancer (IARC) assigned vinyl chloride to Group 1 of its classification scheme for carcinogens. In introducing its list of Group 1 carcinogens which included vinyl chloride, the IARC states, "The Working Group concluded that the following agents are carcinogenic to humans." Based on available scientific data, the Panel agrees with the EPA's and the IARC's classification of vinyl chloride as a human carcinogen.

2. Based on available scientific information, the DHS staff found no evidence of a vinyl chloride exposure level below which no carcinogenic effects are anticipated.

7. The limited monitoring conducted in the Landfill Gas Testing Program which began in 1987 was designed to identify landfill sites that pose a potential risk to public health. Preliminary findings show that vinyl chloride concentrations ranging from the detection limit of 106 ppbv to 72,000 ppbv were detected in the internal gas of 160 (47 percent) out of the 340 landfills at which internal gas testing was performed. 24-hour averaged ambient vinyl chloride concentrations ranging from the detection limit of 2 ppbv to 15 ppbv were detected at 24 (10 percent) out of the 251 landfills at which ambient monitoring was performed. The limited testing conducted was designed to be used for screening purposes. For that reason, vinyl chloride may be present in the ambient air at additional landfills, but was not detected in the one to three days of ambient testing specified in the testing guidelines for the Program. Further interpretation of the data from specific landfill sites must also consider factors such as how the testing was carried out, along with location, size, and proximity to sensitive receptors.

8. Ambient vinyl chloride data from perimeter monitoring by the South Coast Air Quality Management District (SCAQMD) at two landfills in 1986 and 1987 were used in a model to estimate population-weighted exposures near the sites. These exposure estimates were based on ambient outdoor data and do not include any possible elevated indoor exposures that may occur inside homes near the landfills. The cancer risk from vinyl chloride exposure to people residing in the vicinity of the landfills may be determined using the DHS's best estimate of vinyl chloride cancer unit risk of $20 \times 10^{-6} ppb^{-1}$ (see Finding 3 above) and the modeled population-weighted exposure estimates.

   a. Population-weighted exposure for maximally exposed individuals living immediately adjacent to the landfills (at the fenceline) was estimated to range from an annual average of approximately 0.6 to 9 ppbv vinyl chloride at OII Landfill and from approximately 2 to 10 ppbv at BKK Landfill.

b. Modeled estimates of exposure (not population-weighted) for 0 to 6,000 people living close to OII and for 0 to 2,500 people living close to BKK are included to provide an idea of the predicted exposure levels and risk directly downwind from the landfills. According to the model, 0 to 6,000 people near OII may have been exposed to annual average vinyl chloride concentrations of at least 3 ppbv and 0 to 2,500 people near BKK may have been exposed to annual average concentrations of at least 7 ppbv. Using the DHS's best estimate of cancer unit risk, 0 to 4 or more cancers were estimated to occur among the 6,000 people living closest to OII; and 0 to 4 or more cancers were estimated to occur among the 2,500 people living closest to BKK.

c. Population-weighted exposure results were calculated for the people living within a 41 square-kilometer area (or, approximately 25 square-mile area) of each landfill. For OII Landfill, approximately 4 million people may have been exposed to average annual concentrations ranging from 0.004 to 0.05 ppbv. For BKK Landfill, approximately 2 million people may have been exposed to annual average concentrations ranging from 0.08 to 0.34 ppbv. Using the DHS's best estimate of cancer unit risk, 4 to 48 cancers were estimated for the 4 million people living within approximately 25 square miles of OII; and 32 to 135 cancers were estimated for the 2 million people living within approximately 25 square miles of BKK.

9. The limited data available indicate that the vast majority of homes have very low, often undetectable, indoor vinyl chloride concentrations. However, grab samples collected by the South Coast Air Quality Management District (SCAQMD) in 1985 showed concentrations ranging from 8 to 100 ppbv inside a few homes near OII Landfill mentioned in Finding 8. Current indoor concentrations in the homes studied by the SCAQMD in 1985 are expected to be lower because of the subsequent installation of a landfill gas collection and flare system.

In order to test this idea, additional indoor air monitoring at homes adjacent to the landfill is being considered.

Since vinyl chloride is not typically detected in indoor air, exposure through this route is not expected to significantly contribute to overall risk, except in the vicinity of certain landfills.

10. Non-carcinogenic health effects are not known to occur at: 1) the highest recorded 24-hour average outdoor concentration in California (15 ppbv) (see Finding 7), 2) the estimated outdoor average annual vinyl chloride concentrations (see Findings 6 and 8), or 3) the highest recorded vinyl chloride concentration from the air inside a California home (100 ppbv) (see Finding 9).

11. Prior to 1975, vinyl chloride monomer levels as high as 20 ppmw were found in food packaged in vinyl chloride polymer containers or materials. In 1986, the Food and Drug Administration (FDA) proposed to limit the maximum amount of residual vinyl chloride monomer in rigid and semi-rigid food containers to 10 ppbw and the maximum amount of vinyl chloride monomer allowed in polymeric coatings and films which contact food to 5 ppbw. According to an FDA official, the regulation was not promulgated because it was believed that monomer stripping processes leave no residue of vinyl chloride monomer. There is no further information available on the levels of vinyl chloride in food containers and packaging. The exposure estimates in Finding 8 do not account for potential exposure from polymeric food packaging.

In California, surface water and ground water from public water systems are generally free of vinyl chloride. Since it is not typically detected in drinking water, exposure through this route is not expected to significantly contribute to the cancer burden attributed to vinyl chloride.

12. Because vinyl chloride was identified as a hazardous air pollutant under Section 112 of the United States Clean Air Act, identification of vinyl chloride as a toxic air contaminant is required by California Health and Safety Code Section 39655.

13. Based on all available scientific evidence, including consistent animal and human studies and the small range of dose extrapolation (from the animal studies), we conclude that the data are overwhelming that vinyl chloride is a toxic air contaminant.

We agree with the ARB staff recommendation to its Board that vinyl chloride be listed as a toxic air contaminant.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on October 19, 1990.

Dr. James N. Pitts
Chairman, SRP

STAFF REPORT/EXECUTIVE SUMMARY

PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT

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

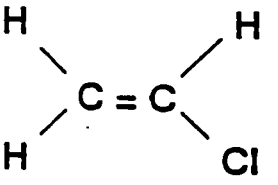
October 1990

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."

What is vinyl chloride?

Vinyl chloride is a readily flammable, sweet smelling, colorless gas at ambient temperature and pressure. Because vinyl chloride polymerizes in ultraviolet light or the presence of a catalyst, the monomer of this highly volatile compound is used in the commercial production of polyvinyl chloride (PVC).



Vinyl Chloride Monomer

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

Yes, the ARB staff recommends that the Board adopt the proposed amendment to section 9300, Titles 17 and 26 of the California Code of Regulations identifying vinyl chloride as a toxic air contaminant because:

- o there is sufficient evidence that exposure to vinyl chloride poses a public health hazard,
- o 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 eliminate public exposure,
- o vinyl chloride is listed as a hazardous air pollutant by the federal government pursuant to section 7412 of Title 42 of the United States Code; therefore, pursuant to section 39655 of the California Health and Safety Code, vinyl chloride is required to be identified as a toxic air contaminant, and
- o the Department of Health Services (DHS) staff recommends that vinyl chloride be identified as a toxic air contaminant and that vinyl chloride be treated as having no threshold exposure level below which no significant adverse health impacts are anticipated.

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 ppbv averaged over 24 hours reflects the limit of detection (LOD) for vinyl chloride ambient air concentration analysis in 1978 when the standard was promulgated (the method

for calculating the LOD is discussed in Section A, Chapter III, Part A, of the Technical Support Document). This technology-based standard was developed in response to information which associated the development of cancer in humans with vinyl chloride exposure and is not currently 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 ppbv.

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 central nervous system alterations, thrombocytopenia, splenomegaly, and changes in liver function. However, these noncarcinogenic effects occur at vinyl chloride concentrations near or above 10 ppmv. Because vinyl chloride has never been detected in samples collected from the ARB's 20-station ambient toxic air contaminant network and measured ambient hot spot concentrations range from 10 to 15 ppbv, the California Department of Health Services (DHS) staff do not expect noncarcinogenic adverse health effects from exposures to current concentrations of vinyl chloride found in ambient air.

The International Agency for Research on Cancer (IARC) lists vinyl chloride in Group 1 of its carcinogen classification scheme. The United States Environmental Protection Agency (EPA) lists vinyl chloride in Group A of its carcinogen classification scheme. The IARC, the EPA, and the 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 carcinogenic and 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.

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, publicly-owned treatment works (POTWs), and polyvinyl chloride (PVC) production and fabrication facilities are the major identified sources of vinyl chloride emissions in California.

In 1987, section 41805.5 of the California Health and Safety Code required the testing of landfills for specified compounds including vinyl chloride. The data gathered in the Landfill Gas Testing Program will be

used by air pollution control districts to provide a relative ranking of the sites based on the potential for emissions of toxic compounds and the potential for exposure. The data show that vinyl chloride concentrations ranging from a detection limit (the Testing Guidelines example method for calculating the detection limit is discussed in Chapter II, Part A of the Technical Support Document) of 106 ppbv to 72,000 ppbv were detected in the internal gas of 160 (47 percent) out of the 340 landfills at which internal gas testing was conducted. The presence of vinyl chloride in internal landfill gas represents a potential source of vinyl chloride emissions.

The South Coast Air Quality Management District (SCAQMD) conducted long-term, intensive ambient vinyl chloride monitoring on two landfills in the South Coast Area Basin (SCAB): Operating Industries Incorporated (OII) Landfill and BKK Landfill. OII Landfill is located near Monterey Park, California and BKK Landfill is located near West Covina, California. The test data for the OII Landfill was obtained from January 1986 through December 1986, while data for the BKK Landfill was obtained from January 1987 through December 1987. Based on 24-hour averaged ambient data from these testing periods, cumulative vinyl chloride emissions were estimated to range from 50 to 250 tons per year. The vinyl chloride emissions of OII and BKK are not likely to be typical of other California landfills. However, monitoring required by the Landfill Gas Testing Program mentioned above showed 24-hour averaged ambient vinyl chloride concentrations ranging from the detection limit (the Testing Guidelines example method for calculating the LOD is discussed in Chapter II, Part A of the Technical Support Document) of 2 ppbv to 15 ppbv at 24 (10 percent) out of the 251 landfills tested for ambient concentrations. Since the SCAQMD's study, the vinyl chloride emissions at OII and BKK landfills are expected to have decreased because subsequent ambient levels in perimeter monitoring samples were typically below the detection limit in the late 1980's. This decrease in ambient vinyl chloride concentrations near the landfills is attributed to the installation of gas collectors and flares.

POTWs emitted an estimated 1.7 tons of vinyl chloride in 1985. PVC production facilities emitted less than 0.5 tons of vinyl chloride in 1988 while PVC fabrication facilities emitted an estimated 0.75 tons of vinyl chloride in 1982.

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 has never been detected in samples collected at the 20 monitoring stations of the ARB's ambient toxic air contaminant monitoring network. Since detectable levels in California are limited to locations near identified emission sources such as landfills, vinyl chloride exposure poses a potential near-source risk rather than a statewide risk.

The monitoring required by the Landfill Gas Testing Program (section 41805.5 of the California Health and Safety Code effective in 1987) showed 24-hour average ambient vinyl chloride concentrations ranging from the detection limit (the Testing Guidelines example method for calculating the LOD is discussed in Chapter II, Part A of the Technical Support Document) of 2 ppbv to 15 ppbv at 24 out of 251 landfills tested for ambient concentrations.

The South Coast Air Quality Management District (SCAQMD) obtained vinyl chloride ambient monitoring from locations near two landfills in the South

Coast Air Basin. The LOD for the SCAQMD vinyl chloride monitoring study was 2 ppbv (the SCAQMD's method for calculating the LOD is discussed in Chapter III, Part A of the Technical Support Document). At the OII Landfill from January through December of 1986, 24-hour average concentrations of vinyl chloride ranged from below the LOD to 9.8 ppbv with a mean of 1.0 to 2.0 ppbv. The U.S. Environmental Protection Agency (EPA) states, "The Operating Industries, Incorporated (OII) Landfill is currently a federally listed Superfund site. Subsequent to the SCAQMD's vinyl chloride sampling during 1986, the Environmental Protection Agency (EPA) has implemented more stringent landfill gas control measures. The EPA has also selected a remedy for landfill gas control that is expected to substantially reduce landfill gas emissions from the OII Landfill. It is fully anticipated that these control measures will substantially lower the levels of vinyl chloride in the ambient air in the vicinity of the OII Landfill." At the BKK Landfill from January through December of 1987, 24-hour average concentrations of vinyl chloride ranged from below the LOD to 15 ppbv with a mean of 1.2 to 2.6 ppbv.

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

Population-weighted exposure estimates, based on computer modeling by the ARB staff, showed that 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 9 ppbv. Modeled cumulative population exposure estimates (not population-weighted) predicted that 0 to 6,000 people living close to OII may have been exposed to annual average concentrations of at least 3 ppbv (see Table I). Population-weighted exposure results estimated that approximately four million people living within about 25 square miles of OII Landfill may have been exposed to estimated annual average vinyl chloride concentrations ranging from 0.004 to 0.06 ppbv in 1986.

TABLE I

RANGE OF CUMULATIVE POPULATION EXPOSED
TO VINYL CHLORIDE NEAR OII

Range of Cumulative Population			Exposed to Vinyl Chloride Concentrations (ppbv) at or above:
Lower-bound Estimate[a]		Upper-bound Estimate[b]	
4,287,300	-	4,287,300	>0 but <0.01[c]
272,000	-	3,111,000	0.01
33,000	-	1,073,000	0.05
12,000	-	445,000	0.10
0	-	22,000	1.0
0	-	12,000	1.5
0	-	6,000	2.0
0	-	6,000	3.0

a - The exposure estimate is based on an emission rate of 0.31 ug/m^2s^{-1}.
b - The exposure estimate is based on an emission rate of 4.42 ug/m^2s^{-1}.
c - According to the model, the entire cumulative population studied was at least exposed to vinyl chloride concentrations between 0 and less than 0.01 ppbv. In addition, calculated population-weighted exposure for this population was estimated to range from an annual average of 0.004 to 0.06 ppbv vinyl chloride.

For the BKK Landfill, the population-weighted exposure results showed that the maximum exposed individual living near BKK was estimated to be exposed to an average annual concentration of 2 to 10 ppbv. Modeled cumulative population exposure estimates (not population-weighted) predicted that 0 to 2,500 people living close to BKK may have been exposed

to annual average concentrations of at least 7 ppbv (see Table II). Population-weighted exposure results estimated that approximately two million people living within about 25 square miles of BKK Landfill may have been exposed to annual average vinyl chloride concentrations ranging from 0.08 to 0.34 ppbv in 1987.

TABLE II

RANGE OF CUMULATIVE POPULATION EXPOSED TO VINYL CHLORIDE NEAR BKK

Range of Cumulative Population			Exposed to Vinyl Chloride Concentrations (ppbv) at or above:
Lower-bound Estimate[a]		Upper-bound Estimate[b]	
2,154,000	-	2,154,000	>0 but <0.01[c]
2,026,000	-	2,154,000	0.01
732,000	-	1,970,000	0.05
374,000	-	1,431,000	0.1
17,000	-	131,000	1.0
0	-	54,000	2.0
0	-	28,000	3.0
0	-	20,000	4.0
0	-	14,000	5.0
0	-	7,000	6.0
0	-	2,500	7.0

a - The exposure estimate is based on an emission rate of 0.75 ug/m^2s^{-1}.
b - The exposure estimate is based on an emission rate of 3.32 ug/m^2s^{-1}.
c - According to the model, the entire population was at least exposed to vinyl chloride concentrations between 0 and 0.01 ppbv. In addition, the calculated population-weighted exposure for this population was estimated to range from an annual average of 0.08 to 0.34 ppbv vinyl chloride.

These exposure estimates are based on ambient data only and do not include any possible elevated indoor exposures that may occur inside homes near landfills.

Is there evidence of indoor air exposure to vinyl chloride?

In California, vinyl chloride in indoor air has been detected only in houses near landfills. In 1985, a South Coast Air Quality Management District (SCAQMD) indoor air grab-sample study showed vinyl chloride concentrations ranging from 8 to 100 ppbv in some homes near OII Landfill. Present indoor vinyl chloride concentrations in the residences near OII are believed to be lower due to OII's installation of gas collectors and flares subsequent to the SCAQMD study. In order to test this idea, additional indoor air monitoring at homes adjacent to the landfill is being considered. To date, no indoor vinyl chloride has been detected in studies of homes not located near landfills.

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.

Prior to 1975, vinyl chloride monomer levels as high as 20 ppmw were found in food packaged in vinyl chloride polymer containers or materials. In 1986, the Food and Drug Administration (FDA) proposed to limit the maximum amount of residual vinyl chloride monomer in rigid and semi-rigid food containers to 10 ppbw and the maximum amount of vinyl chloride monomer allowed in polymeric coatings and films which contact food to 5 ppbw. According to an FDA official, the regulation was not promulgated because it was believed that monomer stripping processes leave no residue of vinyl chloride monomer. An estimate of the potential for vinyl chloride exposure from food ingestion is not possible because, to our knowledge, current

information on the levels in food and food packaging is not available. The vinyl chloride exposure estimates in this Staff Report/Executive Summary and in the accompanying Technical Support Document do not account for potential exposure from polymeric food packaging.

In California, surface water and ground water from public water systems are generally free of vinyl chloride. Since it is not typically detected in drinking water, exposure through this route 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. Using the best estimate of cancer unit risk, an estimated 200 cancers may occur in one million people exposed to 1 ppbv of vinyl chloride for a 70-year lifetime.

Because vinyl chloride has not been detected in statewide ambient air monitoring, 24-hour averaged hot spot concentrations detected by monitors

near two South Coast landfills were used in a model to estimate annual average outdoor concentrations and to assess the probable impact of vinyl chloride on the cancer burden for people living near these landfills. Population-weighted modeled estimates of peak exposure concentrations for maximally exposed receptors ranged from 0.6 to 9 ppbv at the OII Landfill and from 2 to 10 ppbv at the BKK Landfill.

An estimated 17,000 to 131,000 persons were exposed to 1 ppbv 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 estimated that 3 to 36 cancers may occur in 131,000 persons due to lifetime exposure to 1 ppbv of vinyl chloride.

All of the above estimates represent the upper range of plausible excess cancer risk. Estimates of actual risks could be much lower.

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

California Government Code section 11346.14 requires agencies to describe 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 and because vinyl chloride is listed as a hazardous air pollutant by the federal government pursuant to section 7412 of Title 42 of the United States Code; therefore, pursuant to section 39655, vinyl chloride is required to be identified as 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. Subsequent to identification, the 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.

What are the findings of the Scientific Review Panel?

In accordance with California Health and Safety Code Section 39661, the Scientific Review Panel (SRP) has reviewed the report prepared by the staffs of the Air Resources Board (ARB) and the Department of Health Services (DHS) on the public exposure to, and health effects of vinyl chloride. The Panel has also reviewed the public comments received on this report. Based on this review, the SRP finds that the report on vinyl chloride is without serious deficiencies and agrees with the staffs of the ARB and the DHS that:

1. There is strong evidence that exposure to vinyl chloride results in animal and human carcinogenicity. The United States Environmental Protection Agency (USEPA) assigned vinyl chloride to Group A of its classification scheme for carcinogens. In explaining its Group A category, the EPA states, "This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The International Agency for Research on Cancer (IARC) assigned vinyl chloride to Group 1 of its classification scheme for carcinogens. In introducing its list of Group 1 carcinogens which included vinyl chloride, the IARC states, "The Working Group concluded that the

following agents are carcinogenic to humans." Based on available scientific data, the Panel agrees with the EPA's and the IARC's classification of vinyl chloride as a human carcinogen.

2. Based on available scientific information, the DHS staff found no evidence of a vinyl chloride exposure level below which no carcinogenic effects are anticipated.

3. Based on the interpretation of available scientific evidence, the DHS staff estimated that the upper 95 percent confidence limits on the lifetime risk of cancer from vinyl chloride ranged from 2.5×10^{-5} ppb^{-1} to $20 \times 10^{-5} ppb^{-1}$. The DHS staff identified the best estimate of vinyl chloride cancer unit risk as the top of the upper confidence limits range, $20 \times 10^{-5} ppb^{-1}$ or $7.8 \times 10^{-5} (ug/m^3)^{-1}$. Table III compares the best estimate of vinyl chloride cancer unit risk with those of other compounds recently reviewed by the SRP.

TABLE III

Compound	Unit Risk (ppb^{-1})	Unit Risk $(ug/m^3)^{-1}$
Vinyl chloride	20×10^{-5}	7.8×10^{-5}
Chloroform	2.6×10^{-5}	5.3×10^{-6}
Trichloroethylene	1.1×10^{-5}	2×10^{-6}
Inorganic arsenic	particulate	3.3×10^{-3}
Methylene chloride	3.5×10^{-6}	1×10^{-6}

Upper bound excess lifetime risks are health-protective estimates; the actual risk may well be below these values.

4. Landfills, publicly-owned treatment works, and polyvinyl chloride producers and fabricators are the major identified sources of vinyl chloride emissions in California's outdoor air.

5. Based on its gas-phase reactivity with hydroxyl radicals, vinyl chloride's estimated tropospheric lifetime ranges from 1.6 to 3.9 days.

6. Vinyl chloride has not been detected by the ARB's statewide ambient toxic air contaminant monitoring network. However, vinyl chloride has been detected in the ambient air near emission sources such as landfills.

7. The limited monitoring conducted in the Landfill Gas Testing Program which began in 1987 was designed to identify landfill sites that pose a potential risk to public health. Preliminary findings show that vinyl chloride concentrations ranging from the detection limit of 106 ppbv to 72,000 ppbv were detected in the internal gas of 160 (47 percent) out of the 340 landfills at which internal gas testing was performed. 24-hour averaged ambient vinyl chloride concentrations ranging from the detection limit of 2 ppbv to 15 ppbv were detected at 24 (10 percent) out of the 251 landfills at which ambient monitoring was performed. The limited testing conducted was designed to be used for screening purposes. For that reason, vinyl chloride may be present in the ambient air at additional landfills, but was not detected in the one to three days of ambient testing specified in the testing guidelines for the Program. Further interpretation of the data from specific landfill sites must also consider factors such as how the testing was carried out, along with location, size, and proximity to sensitive receptors.

8. Ambient vinyl chloride data from perimeter monitoring by the South Coast Air Quality Management District (SCAQMD) at two landfills in 1986 and 1987 were used in a model to estimate population-weighted exposures near the sites. These exposure estimates were based on ambient outdoor data and do not include any possible elevated indoor exposures that may occur inside homes near the landfills. The cancer risk from vinyl chloride exposure to people residing in the vicinity of the landfills may be determined using the DHS's best estimate of vinyl chloride cancer unit risk of $20 \times 10^{-5} ppb^{-1}$ (see Finding 3 above) and the modeled population-weighted exposure estimates.

a. Population-weighted exposure for maximally exposed individuals living immediately adjacent to the landfills (at the fenceline) was estimated to range from an annual average of approximately 0.6 to 9 ppbv vinyl chloride at OII Landfill and from approximately 2 to 10 ppbv at BKK Landfill.

b. Modeled estimates of exposure (not population-weighted) for 0 to 6,000 people living close to OII and for 0 to 2,500 people living close to BKK are included to provide an idea of the predicted exposure levels and risk directly downwind from the landfills. According to the model, 0 to 6,000 people near OII may have been exposed to annual average vinyl chloride concentrations of at least 3 ppbv and 0 to 2,500 people near BKK may have been exposed to annual average concentrations of at least 7 ppbv. Using the DHS's best estimate of cancer unit risk, 0 to 4 or more cancers were estimated to occur among the 6,000 people living closest to OII; and 0 to 4 or more cancers were estimated to occur among the 2,500 people living closest to BKK.

c. Population-weighted exposure results were calculated for the people living within a 41 square-kilometer area (or, approximately 25 square-mile area) of each landfill. For OII Landfill, approximately 4 million people may have been exposed to average annual concentrations ranging from 0.004 to 0.06 ppbv. For BKK Landfill, approximately 2 million people may have been exposed to annual average concentrations ranging from 0.08 to 0.34 ppbv. Using the DHS's best estimate of cancer unit risk, 4 to 48 cancers were estimated for the 4 million people living within approximately 25 square miles of OII; and 32 to 136 cancers were estimated for the 2 million people living within approximately 25 square miles of BKK.

9. The limited data available indicate that the vast majority of homes have very low, often undetectable, indoor vinyl chloride concentrations. However, grab samples collected by the South Coast Air Quality Management District (SCAQMD) in 1985 showed concentrations

ranging from 8 to 100 ppbv inside a few homes near OII Landfill mentioned in Finding 8. Current indoor concentrations in the homes studied by the SCAQMD in 1985 are expected to be lower because of the subsequent installation of a landfill gas collection and flare system. In order to test this idea, additional indoor air monitoring at homes adjacent to the landfill is being considered.

Since vinyl chloride is not typically detected in indoor air, exposure through this route is not expected to significantly contribute to overall risk, except in the vicinity of certain landfills.

10. Non-carcinogenic health effects are not known to occur at: 1) the highest recorded 24-hour average outdoor concentration in California (15 ppbv) (see Finding 7), 2) the estimated outdoor average annual vinyl chloride concentrations (see Findings 6 and 8), or 3) the highest recorded vinyl chloride concentration from the air inside a California home (100 ppbv) (see Finding 9).

11. Prior to 1975, vinyl chloride monomer levels as high as 20 ppmw were found in food packaged in vinyl chloride polymer containers or materials. In 1986, the Food and Drug Administration (FDA) proposed to limit the maximum amount of residual vinyl chloride monomer in rigid and semi-rigid food containers to 10 ppbw and the maximum amount of vinyl chloride monomer allowed in polymeric coatings and films which contact food to 5 ppbw. According to an FDA official, the regulation was not promulgated because it was believed that monomer stripping processes leave no residue of vinyl chloride monomer. There is no further information available on the levels of vinyl chloride in food containers and packaging. The exposure estimates in Finding 8 do not account for potential exposure from polymeric food packaging.

    In California, surface water and ground water from public water systems are generally free of vinyl chloride. Since it is not typically

detected in drinking water, exposure through this route is not expected to significantly contribute to the cancer burden attributed to vinyl chloride.

12. Because vinyl chloride was identified as a hazardous air pollutant under Section 112 of the United States Clean Air Act, identification of vinyl chloride as a toxic air contaminant is required by California Health and Safety Code Section 39655.

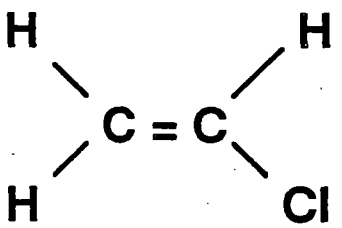
13. Based on all available scientific evidence, including consistent animal and human studies and the small range of dose extrapolation (from the animal studies), we conclude that the data are overwhelming that vinyl chloride is a toxic air contaminant.

We agree with the ARB staff recommendation to its Board that vinyl chloride be listed as a toxic air contaminant.

TECHNICAL SUPPORT DOCUMENT

PART A

PROPOSED IDENTIFICATION OF



VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California

Air Resources Board

Stationary Source Division

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October 1990

This report has been reviewed by the staff of the California Air Resources Board and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Air Resources Board, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

In preparing this report, the staff reviewed pertinent literature published through December 1989.

TECHNICAL SUPPORT DOCUMENT
PART A

REPORT TO THE AIR RESOURCES BOARD ON VINYL CHLORIDE

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

Project Coordinator
Barbara Cook

Principal Investigators
Richard Corey
Tom Parker
Barbara Cook

Contributors
Paul Allen
Renee Capouya
Steve Hui
Chris Nguyen
and
Roger Atkinson, Ph.D. (University of California, Riverside)

Reviewed and Approved by:

Joan Denton, Ph.D., Manager
Substance Evaluation Section

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch

Peter D. Venturini, Chief
Stationary Source Division

October 1990

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

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INDOOR AIR EXPOSURE/OTHER ROUTES OF EXPOSURE ASSESSMENT FOR VINYL CHLORIDE

I. BACKGROUND

Health and Safety Code Section 39660.5 directs the Board, in its toxic air contaminants identification process, to assess exposures to toxic air contaminants in indoor as well as outdoor environments. Indoor exposure assessment has become increasingly important as an integral part of air exposure assessment because (ARB 1987, 1989):

1. people spend a predominant proportion of their time indoors; and

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

Indoor air exposure data, combined with outdoor air exposure data, can provide a realistic estimate of personal exposure through the air environment. A more detailed discussion of indoor air exposure is contained in Appendix A.

Indoor air data can be obtained either by personal air sampling or by fixed-site air sampling. In personal sampling, the sampling equipment is carried by an individual and air samples are taken wherever the individual may be. In contrast, fixed-site air samplings refer to air samples taken at a fixed location. Personal air sampling data generally provide a more realistic estimate of individual exposure. Since most people spend 80-90% of their time in indoor environments, personal air sampling data are strongly weighted by indoor air exposure data.

While the main objective of this report is to define exposure through the air, this report also presents personal exposure data through other media. The inclusion of these data will provide an useful perspective of the overall exposures to toxic air contaminants through environmental media. The need for total exposure assessment and some of the issues and concepts involved in total exposure estimates are discussed in Appendix B.

II. INDOOR AIR EXPOSURE TO VINYL CHLORIDE

A. PERSONAL AIR SAMPLING

Personal air sampling data for most organic compounds come from the Total Exposure Assessment Methodology (TEAM) studies conducted by the Environmental Protection Agency (EPA) during 1980-85 (Wallace, 1987; USEPA 1987a,b; Wallace & Clayton, 1987; Wallace et al., 1986; Pellizzari et al., 1986). Although vinyl chloride was included in the initial pilot study (Phase I) of the TEAM project, vinyl chloride was deleted from the subsequent main studies (Phase II and III). The deletion of vinyl chloride was due to two factors (Pellizzari, 1987). First, Tenax, the most cost-effective sampling

medium which could collect a number of compounds of concern, was not suitable for vinyl chloride collection. In addition, the alternative sampling method used to collect vinyl chloride in the pilot study did not provide the required reliability for detecting low vinyl chloride concentrations.

Consequently, the pilot study provides the only available personal air sampling data for vinyl chloride. Based on this limited information, indoor air exposure to vinyl chloride is apparently low. In monitoring nine subjects in New Jersey and three from North Carolina for several days on three separate visits over a 6-month period, all of the 138 air samples (collected in 5 to 10 hour sampling periods) were below the reported limit of detection (LOD) of 20 ppb (51 ug/m^3)[1] (Wallace et al. 1984). The procedure for calculating the LOD was not described in the paper and the subcontractor who conducted the monitoring could not be located for the information.

B. FIXED-SITE AIR SAMPLING

As part of a recent follow-up TEAM study in California, fixed-site monitoring stations were installed to monitor indoor and outdoor air concentrations of a number of organic compounds (Pellizzari, et al., 1989). Specially designed stainless steel canisters were used for collecting vinyl chloride air samples from homes in the Los Angeles area for two seasons. Ten homes were sampled in the Winter season and eight of the original homes were sampled in the Summer season. Canister air samples were collected indoors and outdoors at each home during two, 12-hour periods. Samples obtained in the Winter season did not provide reliable data due to technical problems. All outdoor or indoor samples, a total of 32 samples, obtained in the Summer season indicated that vinyl chloride air concentrations were below the limit of detection. The samples were analyzed by two analytical methods with limits of detection at about 0.2 and 58 ppb (0.55 and 148 ug/m^3), respectively. The LOD, as defined by Pellazzari, et al., is a value where the measured signal of the analyte is three times that of the noise of the instrument. Therefore, values below the LOD are not reported.

A similar TEAM study was conducted in Baltimore. Indoor air concentrations of vinyl chloride in about 160 homes were monitored by fixed-site sampling stations. Based on partially analyzed results, vinyl chloride was not detected in indoor air environments. The limit of detection was quoted by the researcher as 10 to 16 ppb (26 to 40 ug/m^3) (Pellizzari, 1987).

C. SPECIAL SITUATION AIR MONITORING

In 1981, the South Coast Air Quality Management District (SCAQMD) collected 24-hour bag samples in the vicinity of the BKK landfill (a Class I site) in West Covina. A total of more than 500 air samples were taken at two outdoor sites and at four sites inside downwind residences (SCAQMD, 1982). All the samples (24% of the total sampled) that equaled or exceeded the state vinyl chloride air quality standard of 10 ppb (26 ug/m^3) were taken inside the

---

1 $1\ ug/m^3 \times (0.0245/MW) \times 10^3 = 1$ ppb

residences. The highest recorded indoor vinyl chloride concentration was 50 ppb (130 ug/m^3). The limit of detection was 2 ppb (5.2 ug/m^3) (see Section A, Chapter III for the SCAQMD method of calculating the LOD).

In late 1984, the SCAQMD staff screened for landfill gas migration from Operating Industrial, Inc. (OII) Landfill by taking about ten grab-samples inside the water meter boxes of residences adjacent to the landfill (SCAQMD, 1985a). A water meter box is a below-ground, enclosed box containing an apparatus which measures the amount of water used by a household. Grab samples from the water meter boxes showed vinyl chloride concentrations ranging from 13 to 36000 ppb (31.2-93600 ug/m^3). In 1985, the SCAQMD (1985b) conducted further monitoring by grab-samples inside some of the residences and found indoor vinyl chloride air concentrations at 8 to 100 ppb (20.8 to 260 ug/m^3). Present indoor concentrations of vinyl chloride in these residences near OII landfill may be lower since monitoring of water meter boxes has not detected significant levels of landfill gases due to improvements in OII's landfill gas collection system (Coy, 1987).

C. SUMMARY

Except for houses near landfills, the vinyl chloride concentration in indoor air appears to be low. However, this conclusion is based on the evaluation of a very limited database. In addition, the sampling and analytical procedures for vinyl chloride indoor air monitoring are less than satisfactory as evidenced by the wide range for reported limits of detection. The limit of detection, 0.2 ppb (0.55 ug/m^3), reported in the latest California TEAM study appears to be the most reliable. This limit of detection will be used to estimate the upper limit exposure for houses not adjacent to landfills (see Section II B of this appendix for the TEAM study method of calculating the LOD).

For houses near landfills, the measured high indoor vinyl chloride air concentrations may indicate the potential impact of nearby emission sources to indoor environments. A more detailed discussion of landfill emissions as a source of indoor vinyl chloride is presented in section III(C).

III. POTENTIAL SOURCES OF INDOOR VINYL CHLORIDE

A. PLASTIC MATERIALS AND CONSUMER PRODUCTS

Vinyl chloride has not been used in any consumer products since 1974 when vinyl chloride was banned as a propellant in household aerosol products and as an ingredient of drug and cosmetic products (IARC, 1979).

Because of its versatility, plastic products made of polyvinyl chloride (PVC) and other vinyl chloride polymers are ubiquitous in any household. Before being made into different products, PVC polymer is in the form of a resin that is made by chemically linking the vinyl chloride molecules. Individual vinyl chloride molecules are also called vinyl chloride monomer (VCM). Unreacted VCM can remain in the PVC resin for some time depending on the initial amount of the unreacted VCM. Therefore, an indirect source of vinyl chloride indoors may come from the release of unreacted VCM from these plastic products. For example, during 1975 to 1976, VCM concentrations

ranging from below 2 ppb to 1.2 ppm (5.2 to 3,077 ug/m^3) were measured in automobile interior air space under experimental conditions (U.S.EPA, 1976; 1977).

Emissions of unreacted VCM have been greatly reduced due to improvements in monomer stripping technology (Wheeler, 1981). In the past, residual VCM concentrations in the PVC resins at the time of shipment ranged as high as 2000 ppm (5,128 mg/m^3). Currently, PVC resins contain about 10 ppm (26 mg/m^3) residual VCM at the time of shipment and may lose VCM at a rate of 20 to 50% per month during storage. In addition, most of the VCM will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products. Thus, commercial products made of PVC resins do not now contain significant residual vinyl chloride for later emission.

B. VAPORIZATION FROM WATER SOURCES

Water can serve as a medium to carry pollutants from outdoor to indoor environments. Once in contact with air indoors, volatile chemicals such as vinyl chloride can leave the water and enter the air. Human activities such as using water for cooking, heating or showering can promote rapid vaporization of vinyl chloride from water. Industrial solvent contaminated surface or ground water may, therefore, bring outdoor vinyl chloride indoors via the water supply.

In California, surface water is generally free of vinyl chloride (Sharrp, 1987). In assessing ground water quality, the California Department of Health Services (CDHS, 1986) reported that only one out of the 2,947 wells for large public water systems was contaminated with vinyl chloride. The maximum concentration found in that well was 23 ug/l with a median value of 20 ug/l. Vinyl chloride has not been detected in wells used for small public water systems (CDHS, 1987). The limit of detection of vinyl chloride in water is 0.5 ug/l. Based on this information, vinyl chloride in the water supply will have an insignificant impact on the indoor vinyl chloride air concentration.

C. VINYL CHLORIDE FROM LANDFILL GAS

Homes built on or near landfills containing vinyl chloride or related chlorinated hydrocarbons may have high indoor air concentrations of vinyl chloride. Vinyl chloride emission from landfills can be caused by the vaporization of vinyl chloride that was originally disposed there. Class I landfills that are designated for toxic waste are likely to contain vinyl chloride waste. In addition, microbiological conversion of chlorinated hydrocarbons can produce and emit vinyl chloride <u>in situ</u> (Molton, Hallen and Pyne, 1987).

Wood and Porter (1987) reported their evaluations of over 20 Class II landfills that are designated only for municipal waste. Ninety percent of these landfills contained measurable amounts of vinyl chloride and the concentrations at half of these landfills were above 1000 ppb (2,564) ug/m^3). These high concentrations were measured by grab-sampling, an instant filling of a two-liter evacuated flask, at ground levels or at landfill gas collection points. For five of the landfills, 24-hour bag sampling was also conducted. Only one of these five landfills produced measurable 24-hour concentrations of vinyl chloride off-site.

There are at least two ways that vinyl chloride from landfills may contribute to indoor vinyl chloride concentrations of nearby residential houses. First, houses that are located downwind from landfills can receive vinyl chloride through direct outdoor air influx into indoor environments. Secondly, landfill gases, carrying vinyl chloride, can migrate underground and enter houses through substructures. The rate of accumulation of vinyl chloride indoors depends heavily on the soil permeability, source strength, air exchange rate and structure of the house. Higher indoor than outdoor vinyl chloride concentrations may occur because vinyl chloride is more rapidly destroyed in outdoor than indoor air. Outdoor destruction proceeds more quickly because vinyl chloride's reaction with hydroxyl radicals is the compound's dominant atmospheric removal mechanism and because hydroxyl radicals are formed in the presence of direct sunlight.

As discussed in Section II(B), houses located near Class I landfills had higher indoor than outdoor air concentrations of vinyl chloride. The accumulation of high vinyl chloride concentrations in the water meter boxes indicated that landfill gas containing vinyl chloride can migrate underground and enter nearby indoor environments. Controlled release or combustion of landfill gas on site may slow down vinyl chloride subterranean migration.

D. OTHER FACTORS THAT MAY INFLUENCE INDOOR CONCENTRATIONS

A minute amount of vinyl chloride has been identified in the smoke of cigarettes (1.3-16 ng/cigarette) and of little cigars (14-27 ng/cigar) (IARC, 1985; Hoffmann, Patrianakos and Brunnemann, 1976). The vinyl chloride level in the mainstream smoke may be determined by the total inorganic chloride content of the tobacco. The contribution from tobacco smoke appears to have insignificant impact on the indoor air concentration of vinyl chloride.

E. SUMMARY

In general, there are very few, minor emission sources of vinyl chloride indoors. However, houses that are situated near landfills may accumulate vinyl chloride in the indoor environment due to subterranean gas migration and direct air infiltration. Some of these houses may have indoor air levels of vinyl chloride higher than the State of California Ambient Air Quality Standard for outdoor vinyl chloride.

The results from the SCAQMD's five hundred 24-hour bag samples (the highest measured 24-hour averaged concentration was 50 ppb or 130 ug/m^3) can be used to estimate the upper limit of indoor air exposure to vinyl chloride in houses near landfills (SCAQMD, 1982). The results obtained by grab-sample monitoring, however, are not necessarily reflective of long-term indoor exposure to vinyl chloride.

IV. OTHER ROUTES OF VINYL CHLORIDE EXPOSURE

A. WATER INGESTION

The major source of drinking water for California is surface water which does not have detectable vinyl chloride concentrations. Ground water used for public water systems is also relatively free of vinyl chloride (CDHS, 1987, 1986). The detectable limit of vinyl chloride in water is 0.5 ug/l (0.5 ppb). Based on this information, vinyl chloride exposure through drinking water is judged to be insignificant under ordinary situations.

B. FOOD INGESTION

Vinyl chloride is not one of the compounds that have been monitored routinely in U.S. food and food products. However, before 1973, vinyl chloride was found in food and beverages marketed in vinyl chloride polymer containers or packaging materials (IARC, 1979). At that time, levels as high as 20 mg/kg (ppm) of vinyl chloride monomer were present in alcoholic beverages packaged in this material. Vinyl chloride was also found in edible oils, butter and margarine at 0.05-14.8 mg/kg.

When cleaner PVC resins became available after 1975, vinyl chloride polymer containers contained only about 10 ppb of residual vinyl chloride monomer. In its recent rule-making proposal, the Food and Drug administration (FDA) (1986) estimated vinyl chloride exposure from food and beverages packaged with vinyl chloride polymer materials. These materials include liquor bottles, wine bottles, oil bottles, vinyl chloride homopolymer film, and materials made with vinyl chloride-vinylidene chloride copolymers. Based on a conservative approach, the FDA's estimated lifetime-averaged individual exposure to vinyl chloride would not exceed 25 nanograms per day.

V. ESTIMATES OF TOTAL EXPOSURE FROM INDOOR AIR AND OTHER ROUTES

The estimated daily dose of vinyl chloride from different environmental media are presented in Table 1. From the Table, exposure to vinyl chloride in general indoor air, food and water appears to be insignificant. However, exposure to vinyl chloride indoors in homes near landfills may be the major portion of total vinyl chloride exposure.

A. INDOOR AIR EXPOSURE

The average concentration of vinyl chloride indoors in houses not near landfills is estimated to be below the limit of detection (0.2 ppb or 0.55 ug/m^3). For homes that are located near landfills, the highest observed daily average measurement, 50 ppb or 130 ug/m^3, is used for a conservative estimate.

B. FOOD INGESTION

The estimate of daily dose reported by FDA (1986) is directly used.

APPENDIX III

ESTIMATE OF TOTAL EXPOSURE TO VINYL CHLORIDE FROM INDOOR AIR

The quantitiy $^2\sigma_{BLOD}(K+1)$, the average squared deviation of the below-LOD portion of the distribution, is computed from the following equation:

$$^2\sigma_{BLOD}(K+1) = \sigma^2(K)^*[1-Z(K)^*(f(Z(K))/F(Z(K)))],$$
$$\text{where } Z(K)=((L-\mu(K))/\sigma(K)).$$

Gleit's method nearly always converges in a few steps unless there are only a few distinct values above the detection limit, in which case it may converge very slowly. Gleit's method and closely related methods appear to be the best available estimators of the mean when the sample includes values below the LOD, as is demonstrated by the simulations reported in Gleit's paper.

* See Appendix VII for the ARB Monitoring and Laboratory Division's method for calculating the LOD and Section A. Chapter III for the South Coast Air Quality Management District laboratory's method for calculating the LOD.

DESCRIPTION OF GLEIT'S METHOD

Gleit's method accounts for the concentrations below the LOD* by setting them equal to the 'below-LOD mean" μ_{BLOD}, the mean of the portion of the normal distribution below the LOD. Setting the unknown concentrations to their average value seems intuitively reasonable, and the simulations reported in Gleit's paper show that his method is more accurate than other commonly used approximations.

The below-LOD mean of a normal distribution of a variable with a limit of detection L is given, in terms of L and the mean μ and the standard deviation σ of the distribution, by equation 1:

$$\mu_{BLOD} = \mu - \sigma^{*}[f((L-\mu)/\sigma)/F((L-\mu)/\sigma)] \qquad (1)$$

In equation (1), f and F are, respectively, the probability density function and cumulative distribution function of the standard normal distribution. The "Estimated Concentrations for Samples Below the LOD" reported in Table II-2 are the below-LOD means of the assumed lognormal distributions of the concentrations. These below-LOD means are computed from equation (2) in terms of parameters of the associated normal distribution: the LOD L, the mean concentration from Table II-2, and the estimated standard deviation (which is not tabulated).

$$\exp(\mu+0.5^{*}\sigma^{2})^{*}F((L-\mu-\sigma^{2})/\sigma)/F(L-\mu/\sigma) \qquad (2)$$

We now describe how Gleit's method estimates the mean and variance of the assumed normal distribution. The mean and variance cannot be estimated by merely substituting into standard formulas, if below-LOD concentrations are to be set to the below-LOD mean. On the one hand, the mean and variance must be known in order to calculate the below-LOD mean from (1); on the other hand, the below-LOD mean must be known if it is to be used in the calculation of the mean and variance. Statistical theory, by asserting that a "best-fitting" mean and variance for the distribution exist, provides a way out of this dilemma. Gleit uses a simple iterative

procedure to compute these best-fitting parameters. Since his procedure can be simply described in words, a written description is given, supplemented where necessary by equations written in a notation more convenient than Gleit's.

Starting with initial guesses $\mu(0)$ and $\sigma^2(0)$ for the mean and variance, the procedure repeatedly generates new estimates of the mean and variance by the two-step computation described below until successive estimates of the mean and variance converge sufficiently (The K-th pair of estimates are denoted by $\mu(K)$ and $\sigma^2(K)$.). The two steps are:

(a) the K+1-st below-LOD mean $\mu_{BLOD}(K+1)$ is computed by substituting $\mu(K)$ and $\sigma(K)$ (the square root of $\sigma^2(K)$) into equation (1).

(b) The K+1-st estimate of the mean, $\mu(K+1)$, is computed in the usual way with $\mu_{BLOD}(K+1)$ substituted for the sample values below the LOD. The K+1-st estimate of the variance, $\sigma^2(K+1)$, is also computed in the usual way, with an analogous substitution for sample values below the LOD: the squared deviations from the mean of concentrations below the LOD are set equal to the average squared deviation from the mean of the below-LOD portion of the distribution.

Let the N sample items be X(1),.....,X(N), and let p be the number of sample items below the LOD. $\mu(K+1)$ is computed by:

$$\mu(K+1) = (1/N)\ \Sigma\ Y(J), \text{ where } Y(J)=X(J) \text{ if } X(J)\ R\ L$$
$$\text{and } Y(J)= \tilde{\mu}_{BLOD}(K+1) \text{ otherwise}$$

$\sigma^2(K+1)$ is computed by:

$$\sigma^2(K+1)=(1/N)\ \Sigma\ D^2(J), \text{ where } D^2(J)=(X(J) - \mu(K+1))^2$$
$$\text{if } X(J)\ L, \text{ and } D^2(J)= \sigma^2_{BLOD}(K+1) \text{ otherwise.}$$

APPENDIX II

DESCRIPTION OF GLEIT'S METHOD

VINYL CHLORIDE ANALYSIS -- METHOD A

Instrument: Hewlett Packard 5700A Gas Chromatograph

Detector: Flame Ionization

Injection System: Two Carle valves, a 10-port and a 4-port, are plumbed to contain a 4 ml, 1/4" stainless steel sample loop with pre-column, back-flush and pressure balance. See Figure D for valve plumbing.

GC Conditions:

Detector Temp. -	200°C
Oven Temp. -	60°C
Analytical Column -	6' x 1/4" ss, Chromosil 310, 60/80 mesh
Pre-Column -	6' x 1/8" ss, Durapack n-octane/Porasil C, 100/120 mesh
Carrier Gas -	80/100 ml/min nitrogen

Data Gathering: A Hewlett Packard 3388A Integrator is used to calculate concentration by peak area comparison to an external standard.

Valve Timing: Timing and switching events are performed by the integrator. 1.4 minutes after injection both valv are switched to the back-flush or initial position

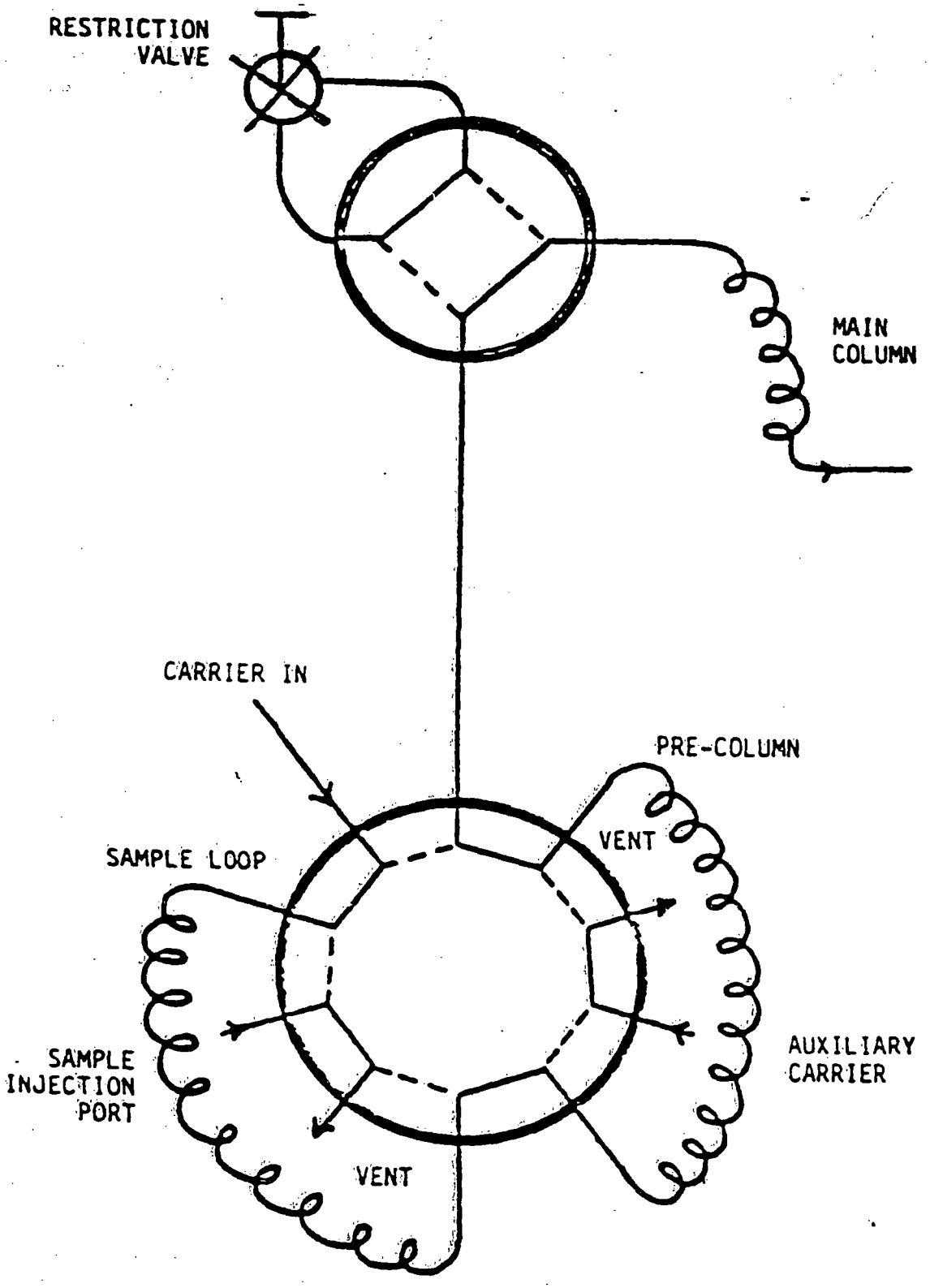


FIGURE C:
Valve Plumbing

Standard: Approximately 1 ppm vinyl chloride is prepared by Scott Environmental Technology and certified to ±2% analysis.

Range: 2 ppb to 1% vinyl chloride

Accuracy: ± 1 ppb in the range 2 - 50 ppb, ± 2 in the range 50 ppb to 1%

AMBIENT AIR SAMPLES AT LANDFILL PARIMETER

(REQUIRED BY SUBPARAGRAPH (c)(4)(D) OF RULE 1150.1)

SAMPLING FREQUENCY

Once per month or at less frequent intervals to be determined by the Executive Officer. The landfill owner/operator must file a written request with the Executive Officer if he wants to sample at intervals less frequent than monthly. Such a request must be supported with previous sampling results and other documentation. In determining if the requested sampling frequency is appropriate, the Executive Officer will consider previous ambient air sampling results, landfill surface sampling results, landfill gas composition and other pertinent data. The Executive Officer will notify the landfill owner/operator of his decision in writing.

NUMBER OF SAMPLES

The number of ambient air samples required will depend upon the topography and the size of the landfill. At a minimum, samplers will be sited to provide good meteorological exposure to the predominant offshore (drainage land breeze) and onshore (sea breeze) wind flow patterns. In areas with significant slopes,

local nightly drainage patterns will also be sampled. All sampling locations must be approved by the Executive Officer prior to sampling.

SAMPLING CONDITIONS

Ambient air sampling will be conducted on days when stable (offshore drainage) and unstable (onshore sea breeze) meteorological conditions are representative for the season. Preferable sampling conditions are characterized by the following meteorological conditions:

1. Clear cool nights with wind speeds two (2) miles per hour or less.
2. Onshore sea breezes with wind speeds 10 miles per hour or less.

No sampling will be conducted if the following adverse meteorological conditions exist:

1. Rain
2. Average wind speeds greater than 15 miles per hour for any 30 minute period.
3. Instantaneous wind speeds greater than 25 miles per hour.

Continuously recorded on site wind speed and direction measurements will characterize the micrometeorology of the site and serve to verify that the meteorological criteria have been

met during sampling.

EQUIPMENT DESCRIPTION

An ambient air sampling unit consists of a 10-liter Tedlar (Dupont trade name for polyvinyl fluoride) bag, a DC operated pump, stainless steel capillary tubing to control the sample rate to the bag, a bypass valve to control the sample flow rate (and mimimize back pressure on the pump), a rotameter for flow indication to aid in setting the flow, a 24-hour clock timer to shut off the sampler at the end of the 24-hour sampling period, and associated tubing and connections (made of stainless steel, teflon, or borosilicate glass to minimize contamination and reactivity). The physical layout of the sampler is shown in Figure 5 (see Appendix A).

EQUIPMENT SPECIFICATIONS

A. Power -- one 12V DC marine battery

The marine battery provides 12V DC to the pump and the clock.

B. Pump -- one 12V DC pump

The diaphragm is made of non-lubricated Viton (Dupont trade name for co-polymer of hexafluoropropylene and vinylidene fluoride) rubber. The maximum pump unloaded flow rate is

4.5 liters per minute.

C. Bag -- one 10-liter Tedlar bag with a valve

TEDLAR BAG IS ENCLOSED IN A LIGHT-SEALED CARDBOARD BOX TO PREVENT PHOTOCHEMICAL REACTIONS FROM OCCURING DURING SAMPLING AND TRANSPORTATION. The valve is a push-pull type constructed of aluminum and stainless steel, with a Viton o-ring seal.

D. Rotameter

Rotameter is made of borosilicate glass and has a flow range of 3 to 50 cubic centimeters per minute. The scale is in millimeters with major graduations (labeled) every 5 mm and minor graduations every 1 mm.

E. Air flow control orifice -- 316 stainless steel capillary tubing

F. Bypass valve

G. Fittings, tubing, and connectors -- 316 stainless steel or teflon

H. Clock timer

Accuracy should be better than 1%.

I. Wind speed and direction monitor with continuous recorder

1. Wind speed -- 3 cup assembly, range 0 - 50 miles per hour with a threshold of 0.75 mile per hour or less.
2. Wind direction -- Vane, range 0 - 540 degrees with a threshold of 0.75 mile per hour or less.

SAMPLING PROCEDURES

Ambient air samples will be collected at the perimeter of the landfill over a 24-hour period beginning between 10 A.M. and 11 A.M. using the above described self-contained portable sampling units. The samplers will be placed at the approved locations as described previously. One or more wind speed and direction monitors with continuous recorders will be installed and operated in areas approved by the Executive Officer to measure wind speed and direction throughout the entire sampling period. The wind direction transmitter must be oriented to true north using a compass.

QUALITY CONTROL PROCEDURE

The following quality control procedure is required for the ambient air sampling operation:

A. Assign an identification number to each sampling bag.

B. Clearly mark sampling locations on a landfill topographic map which is drawn to scale.

C. Document the date and time that the bag was put into operation, the sampling location, and the date and time that it was pulled from service.

D. Check the clock timer. The clock time and the actual time should agree within $\pm$ 3 minutes.

E. Check whether or not the pump is running.

F. Check the rotameter reading. The float (measured at the middle) should be within +3 and -6 minor graduations of the marked setting for 6.0 cubic centimeters per minute. If the rotameter setting exceeds the above limits adjust the bypass valve to correct the flow rate. Make sure that the flow has stabilized (at least three minutes at constant flow) since there may be a lag time between the adjustment and final flow.

G. Check whether the bag valve is in the open position. If the valve is in the closed position open the valve and and record the time on the quality control sheet.

H. Remove the bag for analyses at the end of the 24-hour period. KEEP THE BAG IN A LIGHT-SEALED CONTAINER AT ALL TIMES.

Data for each sample collected must be entered on a quality control sheet as shown in Figure 3 (see Appendix A). Prior to use, the Tedlar bags should be evacuated and filled with purified nitrogen three times to flush out the old sample. Before sending the bags into the field, they should be checked to make sure that the vacuum has been maintained. Remove from service any bag that has experienced any leakage.

ANALYTICAL PROCEDURES

Bag samples collected must be analyzed within 72 hours of collection, or shorter period if notified by the Executive Officer, for total organic compounds and toxic air contaminants using analytical methods identified in Table 1 (see Appendix A) or equivalent methods approved by the Executive Officer. NOTE THAT ALL BAG SAMPLES MUST BE KEPT IN LIGHT-SEALED CONTAINERS TO AVOID PHOTOCHEMICAL REACTIONS.

REPORTING OF THE RESULTS

The following data must be submitted to the Director of Engineering within 45 days after the end of the quarterly reporting period for the landfill or 45 days after the analytical results are available whichever is sooner. A different submittal time may be implemented upon approval of the Executive Officer.

A. Volume concentration of total organic compounds (reported as methane and total non-methane hydrocarbons).

B. Volume concentration of toxic air contaminants identified in these guidelines.

C. Barometric sea level pressure (inches of mercury) on the days the samples were collected. If a barometer is not available at the landfill site, use the National Weather Service data at the nearest station.

D. Wind speed and direction data.

E. A drawn to scale landfill topographic map with sampling locations clearly marked and numbered.

F. Quality control data sheets.

APPENDIX I

SCAQMD'S ANALYTICAL METHOD FOR SAMPLING AND ANALYSIS OF ATMOSPHERIC VINYL CHLORIDE

APPENDICES

October 1990

I.

INTRODUCTION

Vinyl chloride (CH_2=CHCl) is a colorless, flammable gas at ambient temperature and pressure. The United States Environmental Protection Agency (EPA) lists vinyl chloride as a Group A carcinogen (Human Carcinogen) and the International Association for Research on Cancer (IARC) lists vinyl chloride as a Group 1 carcinogen (Agent of Human Carcinogenicity).

Part A of this report is an evaluation of vinyl chloride's uses, emission sources, ambient and indoor air concentrations, and population exposure in California. Also included are discussions of the physical properties and atmospheric persistence of vinyl chloride. California Health and Safety Code section 39655 (Assembly Bill 1807, 1983) states that substances listed by the EPA as hazardous air pollutants (section 112 of the Clean Air Act) shall be identified as toxic air contaminants (TACs) by the Air Resources Board (ARB). Therefore, because the EPA has listed vinyl chloride as a hazardous air pollutant, the ARB is directed by statute to identify vinyl chloride as a TAC.

The ARB is the state agency responsible for the identification of TACs in their non-pesticidal uses. The California Health and Safety Code section 39655 defines a TAC as "an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness or which may pose a present or potential hazard to human health". The findings of the Part A report are considered with the health effects findings (Part B report) of the Department of Health Services (DHS) to determine if a compound should be identified as a TAC by the ARB.

Several different limit of detection (LOD) values are mentioned in this report, including those used for: the establishment of the 1978 ambient air quality standard, the South Coast Air Quality Management District (SCAQMD) investigation of BKK and Operating Industries, Incorporated (OII) landfills, the Landfill Gas Testing Program, indoor air studies, and the ARB 20-station ambient toxic air contaminant monitoring network. These LODs indicate levels at or above which vinyl chloride concentrations are not only detectable, but are also quantifiable. In a number of the analyses listed, vinyl chloride was detected below the LODs. This report discusses the derivation of the LOD for each of the analyses.

In 1978, the ARB adopted an ambient air quality standard for vinyl chloride of 10 ppbv averaged over a 24-hour period in response to information associating the development of human cancer with exposure to vinyl chloride. The standard represents the limit of detection (LOD) for vinyl chloride in 1978 and is not currently recognized as health-protective. The standard specifies an analytical procedure with the same method of calculating the LOD as that used by the ARB's Monitoring and Laboratory Division (see Section A, Chapter III and Appendix VII). The identification of vinyl chloride as a toxic air contaminant would allow the implementation of health-protective control measures at concentrations below 10 ppbv.

Vinyl chloride is primarily used for the production of polyvinyl chloride (PVC). PVC is fabricated for use in several products of which many are used by the construction industry. Finished commercial PVC products are not expected to be significant sources of vinyl chloride due to current processing and shipping procedures. In California, the identified sources of vinyl chloride emissions are: landfills, publicly-owned treatment works (POTWs), and PVC production and fabrication facilities.

Available information shows that landfills are a potential major identified source-category of vinyl chloride emissions in California. Vinyl chloride has been detected in the ambient air near landfills as well as in the internal gas of landfills. Additional studies have shown that vinyl chloride can be formed in the many landfills where chlorinated organic compounds were disposed as well as landfills where vinyl chloride and halogenated industrial waste were disposed.

In this report, ambient monitoring data and meteorological data are used with an atmospheric dispersion model to estimate population exposure to vinyl chloride near two California landfills. The modeling estimates show that people living near these landfills may have been exposed to elevated levels of vinyl chloride. Also, preliminary data from the Landfill Gas Testing Program required by section 41805.5 of the 1986 California Health and Safety Code are presented (see Appendix VI for a table of the Landfill Gas Testing Program data). The results indicate there is a potential for elevated ambient vinyl chloride exposure for people residing near other landfills.

In addition to estimating ambient air exposure, this report also evaluates indoor air exposure to vinyl chloride. Based on limited monitoring data, indoor air exposure to vinyl chloride is probably not significant for the majority of the population. However, for people residing near some landfills, inhalation of indoor air may represent the most significant source of vinyl chloride exposure. This is because vinyl chloride can migrate underground from landfills and accumulate in nearby structures.

II.

PRODUCTION, USES AND EMISSIONS

Although vinyl chloride is not produced in California, several thousand tons are used each year in the state for the production of polyvinyl chloride (PVC). The PVC which is produced is primarily used by fabricators for the production of materials used by the construction, packaging, electrical, and transportation industries.

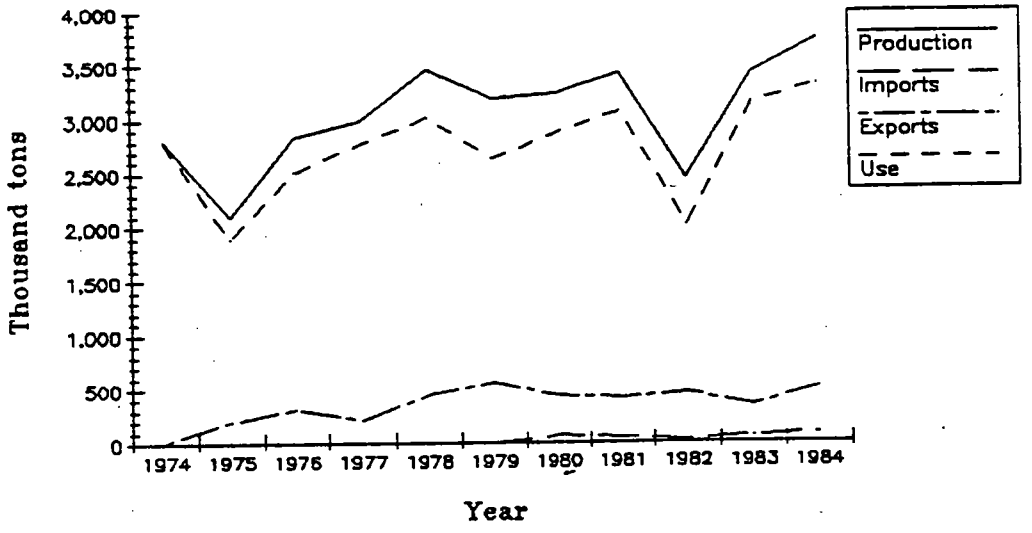
Based on available data, landfills are a potential major identified source-category of vinyl chloride emissions in California. Other known emission sources of vinyl chloride in the state include PVC production and fabrication facilities, and sewage treatment plants.

A. PRODUCTION

Commercial production of vinyl chloride in the United States began in 1936. During the first year of production, two thousand tons were produced (CEN, 1984). With a reported annual U.S. production of 3.8 million tons, vinyl chloride ranked 21st on a list of the most produced chemicals in the United States in 1984 (CEN, 1985a). Figure II-1 shows the production, imports, exports, and use of vinyl chloride from 1974 through 1984 (CEN, 1985a: US DOC, 1985a; and US DOC, 1985b]. During this 10-year period, vinyl chloride production increased at an average annual rate of 3% (CEN, 1985a). More recent estimates for U.S. vinyl chloride production are 4.7 million tons and 4.2 million tons for 1985 and 1986, respectively (CEN, 1987).

FIGURE II-1

NATIONAL VINYL CHLORIDE PRODUCTION, IMPORTS, EXPORTS, AND USE



Two facilities in California currently use vinyl chloride to produce PVC. Two other facilities in the state that were producing PVC ceased production, one in 1982 and the other in 1985 (Personal Communication, 1985a, 1985b, 1985c; and Zwiacher, W. et al., 1983).

B. CURRENT AND PROJECTED USES

About 96 Percent of the vinyl chloride produced in the U.S. is used to manufacture PVC. The remainder is either exported or used to manufacture 1,1,1-trichloroethane (methyl chloroform) (U.S, DH&HS, 1978; and McPherson, W., 1979). Sixty percent of the PVC is used for fabricating various plastic materials used by the construction industry. Specifically, PVC is used by the construction industry for pipe fittings, flooring, paneling, and roofing. PVC is also used by the packaging, electrical, furnishings, transportation, recreation, apparel, and medical industries.

The growth of the vinyl chloride industry is closely tied to PVC use. Historical data for California show the number of housing units in the construction industry increased from approximately 1.0 million units in 1981 to 1.8 million units in 1986 (U.S, DOC, 1987). If this growth in the construction industry continues, the PVC use by this industry is also expected to increase. Data are not available to forecast the use of PVC in other sectors. However, the total United States demand for PVC has been forecasted to increase by approximately 3 to 5 percent annually from 1985 to 1990 (CMR, 1985).

C. LANDFILLS: A POTENTIAL MAJOR EMISSION SOURCE

Landfills are estimated to be a potential major source-category of vinyl chloride emissions in California. However, because landfills vary in the amount and composition of wastes they accept as well as the waste disposal methods used, estimating total vinyl chloride emissions for the

state's hundreds of landfills is not possible. To better understand why all landfills are potential vinyl chloride emission sources, this section presents information on the types and number of landfills in California, the disposal methods employed, the causes of vinyl chloride emissions from landfills, vinyl chloride emission estimates for landfills, and some methods used to control landfill emissions.

1. Types of Landfills

There are three types of landfills in California: Class I sites (e.g., BKK, located in West Covina) which accept all types of wastes including hazardous materials; Class II sites [e.g., Operating Industries, Incorporated (OII), located in Monterey Park] which normally accept only "non-hazardous" wastes but can accept certain types of hazardous wastes (ARB, 1982b); and Class III (municipal or sanitary landfills) sites which can accept only household wastes. In California, there are twenty Class I sites (at present, only two of the 20 sites are accepting hazardous waste), approximately 200 Class II sites, and approximately 2000 unclassified and Class III sites (ARB, 1982b; WRQCB, 1990).

2. Land Disposal Methods

Landfarming, surface impoundments, and landcovering are often used as waste disposal methods in California. These disposal methods may be practiced by more than one type of landfill. For instance, any of the three types of landfills may employ landcovering as a disposal method. However, only Class I and II sites may contain surface impoundments. In addition, the same landfill may employ more than one disposal method. For landfarming, heavy oil sludge is spread several inches thick over the land. The sludge is then cultivated into the soil at frequent intervals. This cultivating process ensures a better aerobic decomposition of the wastes (Thibodeaux and Hwang, 1982). Surface impoundments, often called evaporation ponds or lagoons, are used to dispose of certain types of liquid wastes. As the name implies, surface impoundments allow the wastes to be evaporated into the atmosphere.

Landcovering is most often used at Class III sites or municipal landfills. In landcovering, wastes are spread over the land. At the end of each day, the wastes are covered with approximately six inches to 12 inches of cover. Ultimately, the wastes are covered with a layer of cover material that is at least four feet deep.

3. Landfill Emissions

Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emissions from disposed wastes which contain vinyl chloride; and 2) the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons. Other minor mechanisms by which vinyl chloride emissions may occur include chemical reactions such as pyrolysis, surface photolysis, and hydrolysis of trichloroethylene and other chlorinated hydrocarbons, and off-gassing of PVC (Molton et al., 1987).

Direct Emissions. Direct emissions of vinyl chloride can only occur at landfill sites where vinyl chloride containing wastes were previously disposed. Because vinyl chloride containing wastes cannot be legally disposed in Class II or Class III landfills, Class I landfills (e.g., BKK) at which vinyl chloride has been disposed are probably the largest source of direct emissions of vinyl chloride. However, because vinyl-chloride-containing wastes may have been illegally disposed, Class II and Class III landfills may also emit vinyl chloride directly.

Formation of Vinyl Chloride. Because vinyl chloride can be formed from the biodegradation of chlorinated wastes, emissions of vinyl chloride may occur from any landfill site including Class II and Class III sites where no vinyl chloride has been disposed. Of the three landfill disposal methods, it appears that landcovering and landfarming are most likely to produce the conditions necessary for the formation of vinyl chloride.

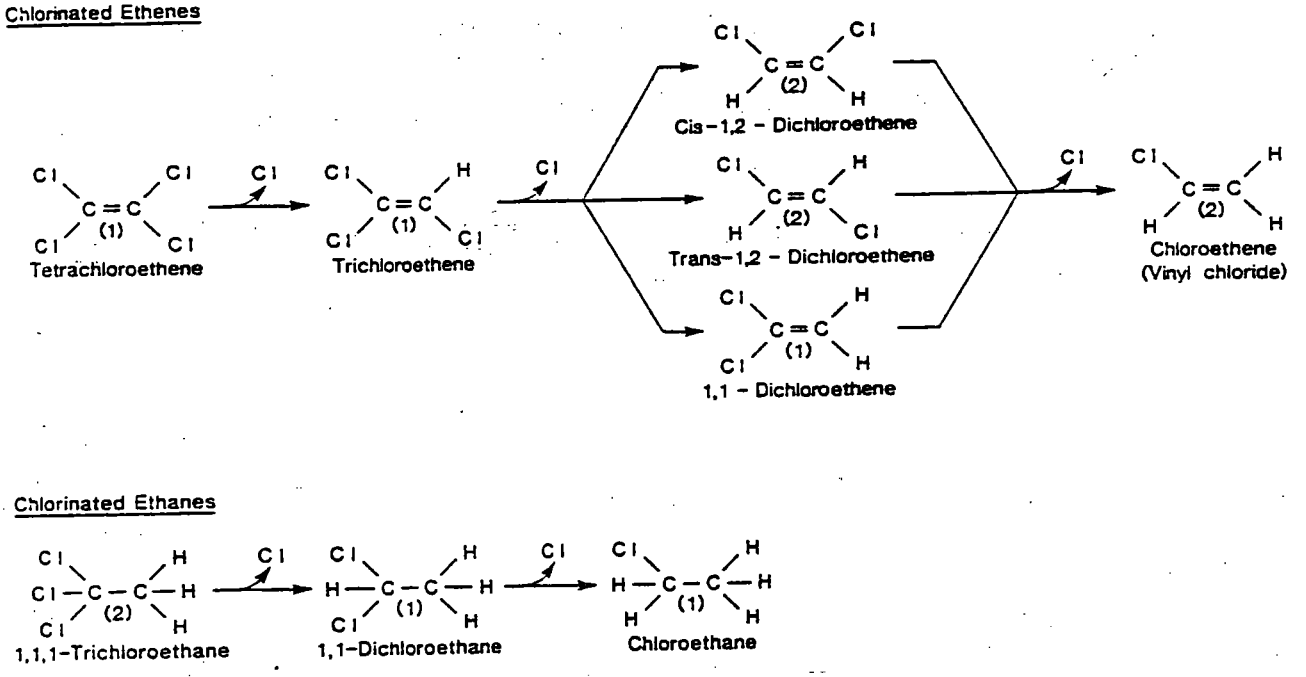
Results of an ARB sponsored study demonstrated the formation of vinyl chloride when soil samples from two municipal landfills were incubated with chlorinated hydrocarbons (Molten et al., 1987). Similar results were obtained when sludge samples were incubated with chlorinated hydrocarbons. The evaluation of the biological mechanism showed that vinyl chloride production occurred predominantly under anaerobic (without oxygen) conditions. Subsequent experimentation with carbon-13 labeled chloroethanes and chloroethenes yielded carbon-13 labeled vinyl chloride as well as other biodegradation products. These results are in agreement with other studies which evaluated the biodegradation of chlorinated hydrocarbons to produce vinyl chloride (Kleopfer, 1985; Beeman, et al., 1978; Wood et al., 1980; and Parsons et al., 1984). Figure II-2 illustrates the pathways by which vinyl chloride is formed from the dehalogenation (chlorine removal) of chlorinated ethenes and ethanes. In addition, the figure indicates the relative rate by which the various compounds are degraded. Not all of the compounds presented in this scheme have necessarily been unequivocally demonstrated to form vinyl chloride. However, given the current state of information, they should be regarded as vinyl chloride precursors.

Although the disposal of halogenated wastes from industrial operations is now substantially restricted, for decades these materials were disposed in Class I landfills as well as some Class II landfills throughout the state. The halogenated wastes are composed of many of the chlorinated compounds which can lead to the formation of vinyl chloride. However, the amount of halogenated wastes previously disposed in these facilities is unknown. Therefore, without monitoring data that shows otherwise, all Class I and Class II facilities (this includes open and closed facilities) should be regarded as potential vinyl chloride emission sources.

Industrially generated halogenated wastes were never permitted to be disposed in Class III facilities. However, many of the chlorinated compounds which can lead to the formation of vinyl chloride are used extensively in consumer products, which after use typically end up in Class III landfills. The amount of chlorinated compounds remaining in consumer products and disposed in landfills is not known. However, because of the widespread use of these compounds in consumer products, all Class III landfills (this includes open and closed facilities) should be regarded as potential vinyl chloride emission sources.

FIGURE II-2

ANAEROBIC BREAKDOWN SEQUENCE VIA REDUCTIVE DEHALOGENATION



(1) - Substantial degradation

(2) - Slow degradation

Source: Cline and Viste, 1984.

Methods of Estimating Landfill Emissions. Several models have been developed to estimate volatile organic gaseous emissions from hazardous waste landfills (Thidobeaux, 1981; Hwang, 1982; Shen, 1981; and Hartley, 1969). The models usually apply to specific landfill operations such as landfarming, surface impoundments, etc. However, these models are difficult to use because they require a number of input parameters such as waste composition, wind speed, and ambient conditions which are not commonly known. These models involve the use of Fick's Law (Fick's Law describes the diffusion of a species through a layer of fluid) and may be appropriate for estimating direct emissions of volatile compounds such as vinyl chloride. However, because the models do not consider factors such as formation, they may not be appropriate for estimating vinyl chloride emissions where formation is occurring.

A method to estimate vinyl chloride emissions where formation may be occurring is to establish monitoring stations around landfill sites to measure the 24-hour average ambient concentrations of the compounds of interest. The ambient concentrations along with appropriate meteorological data can then be used in dispersion models to back-calculate the emission rate from the landfill site. This is the method that was used to estimate vinyl chloride emissions from BKK and OII.

Landfill Emission Estimates. Table II-1 summarizes vinyl chloride emission estimates for the state's landfills. As indicated in the table, vinyl chloride emissions have been estimated for BKK and OII landfills. The vinyl chloride emission estimates for BKK and OII make several assumptions. These assumptions are: 1) vinyl chloride is emitted from an area of approximately 1,700,000 meters^2 for BKK and 330,000 meters^2 for OII; 2) annual average emission rates of vinyl chloride from BKK and OII are within the ranges estimated in Table III-4; and 3) emissions of vinyl chloride are uniform over the entire area of the landfill that is estimated to emit vinyl chloride.

Further testing is necessary to estimate emissions from landfills other than BKK and OII. Thus, for the 1987 and 1986 inventory years, total vinyl chloride emissions from California landfills were probably greater than those estimated in this report.

TABLE II-1

VINYL CHLORIDE LANDFILL EMISSION ESTIMATES*

Source	Source Type	Emissions (tons/year)	Inventory Year	Ref.
Class I Landfills				
BKK, West Covina	Area	44-197	1987	ARB,1988b
Other Sites	Area	NA		
Class II Landfills				
OII, Los Angeles	Area	4-51	1986	ARB, 1988b
Other Sites	Area	NA		
Class III Landfills	Area	NA		

* - These emission estimates assume that the vinyl chloride emission rates are uniform throughout the year over the area of the landfill that is estimated to emit vinyl chloride.
NA - Not Available

Based on 1987 monitoring data for BKK, ARB staff estimate a vinyl chloride emission rate ranging from 0.75 to 3.32 micrograms meter^{-2} second^{-1} (see Table III-4). For BKK landfill, this translates to estimated vinyl chloride emissions ranging from 44 and 197 tons per year. Over BKK's history it is not known how much vinyl-chloride-containing or halogenated wastes were disposed at the landfill. However, in 1984, BKK received approximately 136,000 tons of volatile or toxic wastes. An unknown portion of these wastes were halogenated solvents (ARB, 1982b). For OII, ARB staff estimated a vinyl chloride emission rate ranging from 0.31 to 4.42 micrograms meter^{-2} second^{-1} (Table III-4). For the OII landfill, this translates to estimated vinyl chloride emissions ranging from 4 to 51 tons per year. The amount of halogenated wastes disposed at OII over its history is unknown. However, in 1982, OII received 9,200 tons of volatile or toxic wastes. As with BKK, an unknown portion of these wastes were halogenated solvents (ARB, 1982a).

Monitoring results available for several other landfills are as follows: Flux measurements on the surface of the Scholl Canyon sanitary landfill (a former Class II landfill located in Glendale, California) showed vinyl chloride concentrations ranging from non-detectable to 180 ppbv (parts per billion by volume) at various locations (Todd and Propper, 1985). In addition, tests conducted by the SCAQMD at several other Class II landfill sites from 1981 to 1985 confirmed the presence of vinyl chloride in landfill surface gas or gas collection systems (Coy, 1985).

To partially address the lack of monitoring data from other landfills throughout the state, Health and Safety Code section 41805.5 (AB 3525 and subsequent amendments by AB 3374) required the development and implementation of landfill monitoring guidelines and the reporting of monitoring results. The law required the ARB to establish guidelines for landfill operators to monitor gas migration, gas constituency, and the ambient air at many of the hazardous and municipal waste landfills in California. The testing guidelines identified vinyl chloride as one of the compounds requiring monitoring. Although the choice of vinyl chloride analytical methods was left to individual laboratories performing the analysis, the guidelines specified an ambient vinyl chloride detection limit of 2 ppbv and provided an example of a vinyl chloride method with an achievable detection limit of 2 ppbv. In this example method, the limit of detection (LOD) is based on 3 standard deviations of runs near the method detection limit (within 10 standard deviations of the method detection limit) (ARB, 1986; ARB, 1987). This means of calculating the LOD is the same as that used by the ARB's Monitoring and Laboratory Division (see Appendix VII). 24-hour ambient vinyl chloride concentrations ranging from the detection limit of 2 ppbv to 15 ppbv were detected at 24 (10 per cent) out of the 251 landfills at which ambient monitoring was performed. Vinyl chloride concentrations ranging from the detection limit (see Appendix VI, Table 1 for the method of determining the detection limit) of 106 ppbv to 72,000 ppbv were detected in the internal gas of 160 (47 per cent) out of the 340 landfills at which internal gas testing was performed (Appendix VI).

4. Gas Collection Systems

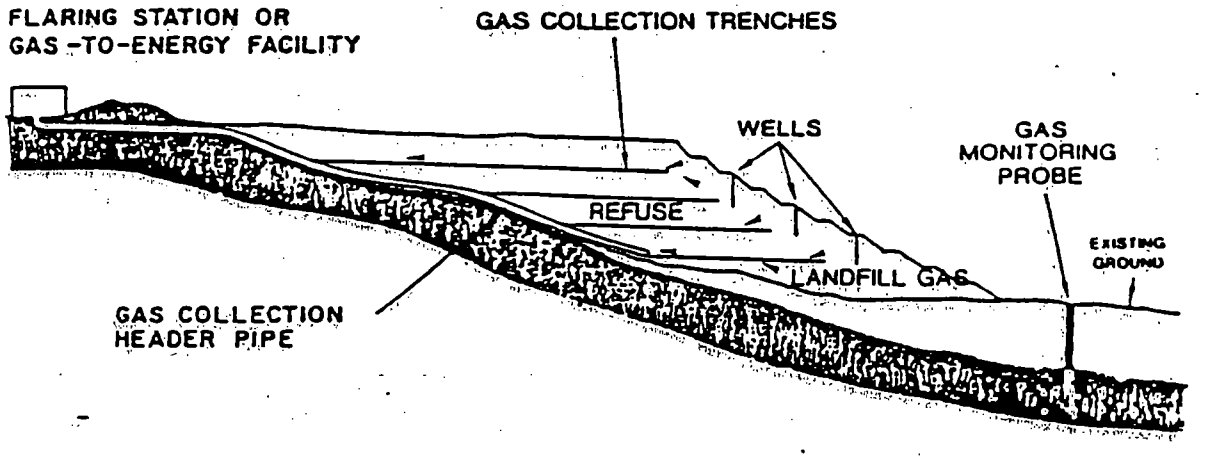
For some landfills, emissions are required to be controlled to reduce odors as well as emissions of methane and toxicants. However, gas

control systems have been installed at some landfills as a resource recovery and/or energy conservation measure. For example, BKK transmits collected landfill gases to either one of two flare stations and/or to a five megawatt gas turbine for use as a fuel in generating electricity. Both well (vertical piping) and trench systems (horizontal piping) are used to collect landfill gases. In 1983, BKK installed a number of wells and gas collection lines to help control gaseous emissions. Although there are still potential sources of gaseous emissions such as cracks at the landfill surface, pipe connections and valves, and burner exhaust, ambient concentrations of vinyl chloride near BKK have been declining. Since installing their gas collection system, BKK has continued to expand the system by adding wells and trenches. Since installing a gas collection system at OII, ambient concentrations at the perimeter of the facility have continued to decline. Due to the lack of violations of the state standard for vinyl chloride (10 ppbv), ambient monitoring at the perimeter of OII was discontinued by the SCAQMD in early 1987. Currently, OII Landfill is a federally listed superfund site managed by the EPA.

A well system consists of a network of wells drilled vertically into the refuse to collect the generated gases. These wells are connected to collection pipelines where gases are withdrawn from the buried layers of waste. In general, a vertical gas well is constructed by drilling a 30-inch diameter hole 50 to 100 feet deep into the wastes. Perforated PVC pipes are then placed inside the hole. The space between the pipe and the hole is backfilled with uncrushed gravel (Sanitation Districts of Los Angeles County, 1984). A typical gas control system showing both well and trench systems is shown in Figure II-3.

FIGURE II-3

LANDFILL GAS COLLECTION SYSTEM



Source: Sanitation Districts of Los Angeles, 1984.

In the trench system, a network of perforated pipelines is laid in trenches within the waste at approximately 200-foot intervals horizontally and 80-foot intervals vertically. To support the pipes and to allow the migration of the generated gases, approximately 2 feet of uncrushed gravel are packed around the pipelines. These pipelines are then connected to a main collection pipe where gases are withdrawn (Sanitation Districts of Los Angeles County, 1984).

D. OTHER KNOWN EMISSION SOURCES

Other than landfills, emissions of vinyl chloride occur from: PVC production and fabrication, publicly-owned treatment works (POTWs), ethylene dichloride production, vinyl chloride production, methyl chloroform production, caprolactam production, and incomplete incineration of chlorine containing materials (Sittig, M., 1981; Zwiacher, W., et al., 1983; and Lamorte, M., 1978). In California, the identified sources of vinyl chloride emissions that can be quantified are PVC production, PVC fabrication, and POTWs. Table II-2 provides estimates of vinyl chloride emissions for identified sources. Currently, there are no known vinyl chloride, ethylene dichloride, methyl chloroform (TCA) or caprolactam production facilities operating in the state.

TABLE II-2

SUMMARY OF VINYL CHLORIDE EMISSION ESTIMATES FOR OTHER SOURCES

Source	Source Type	Emissions Tons/Year	Inventory Year	Reference
PVC Production	Point	<0.5	1988	ARB, 1988b
PVC Fabrication	Point	0.75	1982	Zwiacher, et al., 1983
POTWs	Point	1.7	1985	Chang, et al., 1987
On-site Wastewater Treatment Plants	Point	NA		
Waste Incinerators	Point	NA		
Transportation and Accidental Spillage	Area	NA		

NA - Not Available

1. Polyvinyl Chloride (PVC) Production

Three PVC producers reported emitting a cumulative total of 3 tons of vinyl chloride in 1984 (Personal Communication, 1985a, 1985b, and 1985c). In 1982, vinyl chloride emissions from these producers were estimated to be 1.4 tons (Zwiacher, W., et al., 1983). All three producers reported that they were in compliance with the South Coast Air Quality Management District's (SCAQMD's) Rule 1163. This rule requires that vinyl chloride emissions from designated plants not cause ambient vinyl chloride levels to exceed 10 ppbv (parts per billion by volume) during any 24-hour period when measured beyond the plant's property line (Personal Communication, 1985a, 1985b, 1985c; and ARB, 1980). Rule 1163 was adopted by SCAQMD as part of their program to control vinyl chloride emissions to 10 ppbv.

In 1984, the PVC producers operating in the state reported using closed systems, incineration, routine leak surveys, and maintenance programs as control technologies to comply with existing standards for vinyl chloride emissions (Personal Communication, 1985a, 1985b, and 1985c). The primary control method used by the two PVC producers currently operating in California is incineration. One facility (facility A) uses an afterburner with an operating temperature of approximately 2000°F while the other facility (facility B) uses a catalytic-type incinerator. Both facilities have a monitoring system that continuously measures the vinyl chloride concentration within various areas of the plant. Portable hydrocarbon (HC) detectors are used to pinpoint leaks detected by the area monitoring system. These plants are also inspected at least once a year by the SCAQMD Enforcement Division to ensure compliance with district rules (Personal Communication, 1985d).

The SCAQMD periodically conducts ambient monitoring for vinyl chloride near the two PVC producers in California. In addition to the SCAQMD's monitoring program, the SCAQMD requires one of the PVC producers (facility A) to monitor the ambient air for vinyl chloride at the perimeter of their facility on a daily basis. The other PVC producer (facility B) is not required by the SCAQMD to conduct ongoing offsite ambient monitoring for vinyl chloride. This is because: 1) historically, the facility has not exceeded the ambient air quality standard for vinyl chloride; and 2) the process that is used to manufacture latex emulsions is not expected to result in vinyl chloride emissions as great as those associated with the other facility which produces PVC resins. Generally, 24-hour average concentrations near these facilities are below the 10 ppbv standard. However, in October of 1988, the SCAQMD reported concentrations as high as 20 ppbv for facility A (Molita, 1989). As a result, the SCAQMD plans to conduct ambient monitoring more frequently at this facility to ensure compliance with the ambient air quality standard for vinyl chloride. The SCAQMD's monitoring results indicate that this PVC producer may contribute to the public's exposure to vinyl chloride. Therefore, this facility should be investigated in more detail when considering control measures to reduce the public's exposure to vinyl chloride.

Table II-2 lists the cumulative vinyl chloride emissions estimates from the two PVC producers in California at less than 0.5 tons for 1987. This estimate is substantially lower than the 1984 estimate of 3 tons when three PVC producers were operating in California (Personal Communication, 1985a, 1985b, 1985c).

2. Polyvinyl Chloride Fabrication

Polyvinyl chloride (PVC) can be fabricated into several products such as PVC pipes, pipe fittings, plastics, etc. Some major fabrication processes are extrusion (to shape by forcing through a die), calendering (to press between rolling cylinders), molding, and bonding. PVC contains the vinyl chloride monomer as a residual from the PVC production processes. Residual vinyl chloride (RVC) in PVC ranges from 0.002 ppmw (parts per million by weight) to 10 ppmw (U.S. EPA, 1982). When PVC is fabricated into final products, vinyl chloride is emitted.

The SCAQMD identified 33 PVC handling and fabrication facilities under its jurisdiction with an estimated usage of 75,000 tons of PVC in 1982. The SCAQMD staff assumed that all vinyl chloride is emitted from the fabrication processes. Using this assumption and a maximum RVC of 10 ppmw in PVC, the SCAQMD estimated that these handling and fabrication facilities emitted approximately 0.75 ton of vinyl chloride in 1982 (Zwiacher, 1983). This estimate represents an upper-bound condition because the maximum RVC was used to estimate emissions, and because all RVC from the incoming PVC was assumed to be emitted from the fabrication processes. The vinyl chloride migration studies conducted by the Environmental Protection Agency (EPA) indicated a much smaller percentage of monomer is released during fabrication (U.S. EPA, 1982). A typical release of vinyl chloride in the extrusion process was only 10 percent of that in the PVC (U.S. EPA, 1982).

3. Publicly-owned Treatment Works

Publicly-owned treatment works (POTWs) are wastewater treatment plants that are owned by public entities, and which consist of wastewater collection systems, wastewater and sludge treatment facilities, and effluent and sludge disposal systems. Users that discharge wastewater into POTWs are normally classified as commercial, industrial, and residential. The two primary mechanisms that result in emissions of organic gases are volatilization and biodegradation. Because POTWs treat wastewater which can contain vinyl chloride and halogenated compounds from industries, vinyl chloride can be volatilized during the treatment processes. In addition, chlorinated hydrocarbons such as trichloroethylene and 1,2-dichloroethane could be biodegraded to vinyl chloride.

Halogenated hydrocarbons including vinyl chloride have been measured at wastewater treatment plants throughout the nation, including California (U.S. EPA, 1980). A preliminary study of two wastewater treatment plants, one in Los Angeles and another in the Sacramento Valley, indicated that vinyl chloride was present in the anaerobic digester tanks. Concentrations of up to 2.6 ppmv have been measured (ARB, 1985). These digester tanks are equipped with pressure/vacuum (P/V) valves to equilibrate the inside and outside pressure of the tanks. These P/V valves are potential sources of vinyl chloride emissions along with fugitive emissions associated with pipe fittings and valves.

In a study performed by the University of California at Davis (UCD), researchers used a mass balance approach to estimate that approximately 1.7 tons of vinyl chloride were emitted by POTWs in California in 1985 (Chang et al., 1987). Specifically, the difference between the concentration of vinyl chloride in the POTW influent and effluent was assumed to be emitted to the atmosphere. This approach may be useful in assessing which POTWs constitute a threat to public health. However, because this approach does not take into account the formation or degradation of vinyl chloride within POTWs, the resulting emission estimates should only be considered rough approximations. In response to the need for more information concerning emissions of toxicants from POTWs, ARB is currently funding a research contract. When the research is complete, the resulting report will contain the most recent information concerning the estimation of emissions of toxicants from POTWs and POTW collection lines. The report will also address the efficacy of POTW odor control systems on reducing emissions of toxic compounds.

E. OTHER POTENTIAL EMISSION SOURCES

Along with the sources discussed in Section D, there are several other potential sources of vinyl chloride emissions in California. These include on-site wastewater treatment plants, incineration of PVC materials, and transportation of vinyl chloride.

1. On-site Wastewater Treatment Plants

As presented in the discussion on POTWs, wastewater treatment facilities are sources of vinyl chloride emissions. At several industrial facilities such as oil refineries, chemical manufacturers, etc., industrial wastewater is normally treated before being discharged. These wastewater treatment plants are also potential sources of vinyl chloride emissions.

2. Waste Incinerators

Vinyl chloride has been identified as a combustion product in the flue gas of an incinerator burning plastics (Boettner et al., 1973). It has also been hypothesized to form upon the combustion of PVC materials (Ahling et al., 1978). PVC materials are used extensively in automobile's upholstery, bumper parts and floor mats. When these materials are incinerated, vinyl chloride is a likely pollutant in the incinerator exhaust. Hospital waste incinerators are another potential source of vinyl chloride emissions since much of the hospital waste such as syringes and plastic bags are PVC-containing materials.

3. Transportation and Accidental Spillage

Another potential source of emissions is the accidental spillage and/or leakage of vinyl chloride that is being transported either by rail car, tank car, or marine vessel. Vinyl chloride is transported by rail cars to the two PVC producers currently operating in California. As far back as records are available, there have been no reported accidents involving vinyl chloride in the state (Office Of Emergency Services, 1985; California Highway Patrol, 1985).

REFERENCES TO CHAPTER II

Ahling, B., Bjorseth, A., Lunde, G., 1978. "Formation of Chlorinated Hydrocarbon During Combustion of Polyvinyl Chloride," Chemosphere, 1(10): 799-806.

Air Resources Board (ARB), 1980. "Response to Petition Pursuant to California Health and Safety Code Section 40451 to Review Adoption of Rule 1005.1, Control of Vinyl Chloride Emissions by the South Coast Air Quality Management District," Sacramento, California.

ARB, 1982. "Suggested Control Measure to Reduce Organic Compound Emissions Associated with Volatile Organic Waste Disposal," Stationary Source Division, Sacramento, California.

ARB, 1982. "An Assessment of the Volatile and Toxic Organic Emissions from Hazardous Waste Disposal in California," Stationary Source Division, Sacramento, California.

ARB, 1985. Memorandum from Ken Jones to Dean Simeroth on "Source Tests for Vinyl Chloride and other VOC at Sewage Treatment Plants," October 1985, Engineering Evaluation Branch, Stationary Source Division, Sacramento, California.

ARB, 1986. "Testing Guidelines for Active Solid Waste Disposal Sites Prepared Pursuant to California Health and Safety Code Section 41805.5, Stationary Source Division, December 1986.

ARB, 1987. "Hazardous Waste Disposal Testing Guidelines," Prepared Pursuant to California Health and Safety Code Section 41805.5, Stationary Source Division, January 1987.

ARB, 1988a. Memorandum from Andrew Ranzieri to Joan Denton concerning "Updated Vinyl Chloride Exposure Results for BKK and OII Landfills," Modeling Support Section, May 1988.

ARB, 1988b. "Survey of California PVC Producers," January 1988.

Ayala, P., 1985a. Personal communication, telephone conversation between Pacita Ayala of ARB and PVC producer A, September 1985.

Ayala, P., 1985b. Personal communication, telephone conversation between Pacita Ayala of ARB and PVC producer B, September 4, 1985.

Ayala, P., 1985c. Personal communication, telephone conversation between Pacita Ayala of ARB and PVC producer C, August 28, 1985.

Ayala, P., 1985d. Personal communication, telephone conversation between Pacita Ayala of ARB and Karen Haack of SCAQMD, October 1, 1985.

Beeman, C.P. et al., 1978. "Survey of Trihalomethane Distribution in Various Potable Water Supply Sources in the State of Florida," Final Report to the State of Florida, Department of Environmental Regulation, Tallahassee, Florida.

Boettner, E.A., Ball, G.L., Weiss, B., 1973. "Combustion products from the Incineration of Plastics," U.S. EPA, Report No. 67-12-73-049, Cincinnati, Ohio.

BSK & Associates, 1987. "Solid Waste Assessment - Air: City of Clovis Landfill," Job No. 87147. Fresno, California.

Chang, D.P.Y., Schroeder, E.D., Corsi, R.L., 1987. "Emissions of Volatile Potentially Toxic Organic Compounds from Sewage Treatment Plants and Collection Systems," U.C. Davis, Department of Civil Engineering, Davis, California.

Chemical and Engineering News, 1984. "Additives Sales Buoyed by PVC Recovery," June 18,1984.

Chemical and Engineering News, 1985a. "Production by the U.S. Chemical Industry," June 10, 1985.

Chemical and Engineering News, 1985b. "Product Report," June 3, 1985.

Chemical and Engineering News, 1987. "Facts and Figures for the Chemical Industry," June 8, 1987.

California Highway Patrol, Operational Planning Section, Sacramento, California.

Chemical Marketing Reporter, June 24, 1985, pp. 3, 5, 24, and 27.

Cline, P.V., and Viste, D.R., 1984. "Mitigation and Degradation Patterns of Volatile Organic Compounds," Municipal and Industrial Waste, Annual Madison Waste Conference, 102(26): 14-29.

Coy, C., 1985. Attachments of the letter from Carol Coy of the South Coast Air Quality Management District (SCAQMD) to Ralph Propper of the ARB on September 25, 1985. SCAQMD, El Monte, California.

Eljumaily & Butter Associates (EBA), 1987. "Air Quality Solid Waste Assessment Test Report for Willits Solid Waste Disposal Site," Santa Rosa, California.

Hartley, G.S., 1969. Evaporation of Pesticides - Formulation Research, Physical, and Colloidal Chemical Aspects, Advance Chemical Series, 86, pp. 115-134.

Hwang, S.T., 1982. Toxic Emissions from Land Disposal Facilities, Environmental Progress, Vol. 1, pp. 46-52.

Kleopfer, R.D., Easley, D.M., Hass Jr., B.B., Deihl, T.G. 1985. "Anaerobic Degradation of Trichloroethylene in Soil." Environmental Science and Technology, 19(3), pp. 277-280.

Lamorte, M., 1978. "National Emissions Standards for Hazardous Air Pollutants - Inspection Manual for Vinyl Chloride," prepared for U.S. Environmental Protection Agency by Research Triangle Institute, PB 289778, Research Triangle Park, North Carolina.

McPherson, W., et al., 1979. Hydrocarbon Processing, "Vinyl Chloride Monomer - What You Should Know," March 1979.

Molita, D., 1989. Telephone conversation between Richard Cory of ARB and Dave Molita of SCAQMD, April 1989.

Molton, P.M., Hallen, R.T., Pyne, J.W., 1987. "Study of Vinyl Chloride Formation at Landfill Sites in California," Prepared for the ARB under contract #A4-154-32 and 2311206978. Battelle, Pacific Northwest Laboratory. Richland, Washington.

Office of Emergency Services, Planning Division, Sacramento, California.

Parsons, F., Wood, P.R., DeMarco, J., "Transformations of Tetrachloroethene and Trichloroethene in Microcosms and Groundwater," Journal of the American Water Association, February 1984.

Sanitation Districts of Los Angeles County, 1984. "SPADRA Landfill and Resource Conservation Project," State Clearing House #84053011, Whittier, California.

Sarokin, et al., 1985. "Cutting Chemical Waste - An INFORM Report," INFORM, Inc., New York, New York.

Shen, T.T., 1981. "Estimating Hazardous Air Emissions from Disposal Sites," Pollution Engineering, August 1981, pp. 31-34.

Sittig, M., 1981. "Vinyl Chloride and PVC Manufacture," Noyes Data Corporation, Park Ridge, New Jersey.

Thidobeaux, J.J., 1981. "Estimating the Air Emissions of Chemicals from Hazardous Waste Landfills," Journal of Hazardous Materials, 1981(4), pp. 235-244.

Todd, D. and Propper, R., 1985. "Method to Determine Emissions and Possible Health Effects of Organic Compounds from California Landfills," California Air Resources Board, Sacramento, California.

U.S. Department of Commerce (U.S. Doc), Bureau of Census, U.S. Exports FT410 and FT446, Annual 1974-1984.

U.S. Doc, Bureau of Census, U.S. Imports for Consumption and General Imports FT246, Annual 1974-1984.

U.S. Doc, International Trace Commission, Construction Review, Bimonthly Industrial Report, Washington, D.C.

U.S. Department of Health and Human Services, 1978. "Vinyl Chloride: An Information Resource," DHEW Publication No. (NIH) 79-1599.

U.S. Environmental Protection Agency (U.S.EPA), 1980. "Fate of Priority Pollutants in the Publicly Owned Treatment Works - Final Report, Volume I and II," EPA 440/1.82/303, PB 83-122/88, Washington, D.C.

U.S.EPA, 1982. "Vinyl Chloride - Review of National Emission Standards," Prepared by TRW, Inc. for the U.S.EPA, EPA 450/3-82-003, NTIS no. PB-114-354, Research Triangle Park, North Carolina.

Water Resources Quality Control Board, 1990. Data retrieved from computer database consists of information as required by the Calderon Bill (AB2535), Jonathan Mulder, Sacramento, California.

Wood, P.R., Jackson, D.F., Gervers, J.A., Waddell, D.H., Kaplan, L., 1980. "Removing Potential Organic Carcinogens and Precursors from Drinking Water," EPA Report, EPA 600/2-80-130a, U.S.EPA, MERL, Cincinnati, Ohio.

Zwiacher, W., Yuhas, L.D., Fakhoury, J.S., Whittacker, J.L., Grisinger, J., 1983. "Emissions of Potentially Toxic/Hazardous Air Contaminants in the South Coast Air Basin," Engineering Division, South Coast Air Quality Management District, Los Angeles, California.

III.

EXPOSURE TO VINYL CHLORIDE

A. AMBIENT MONITORING IN CALIFORNIA

To date, vinyl chloride has not been detected in California's ambient air except near known emission sources. However, in order to assure that vinyl chloride continues to pose no significant health risk in the background atmosphere of the state, a vinyl chloride screening procedure is routinely performed by the ARB's laboratory on samples collected from the state's 20-station ambient toxic air contaminant network. Bimonthly through-the-probe audits by the ARB Quality Assurance Section using known concentrations of vinyl chloride confirm that the screening procedure detects the presence of the compound. The screening procedure has not detected vinyl chloride in samples collected at the monitoring stations of the toxic air contaminant ambient monitoring network since the implementation of the procedure in 1988. Should vinyl chloride be detected, the ARB's Monitoring and Laboratory Division would begin immediate monitoring and investigation of the cause. Appendix VII describes the method for calculating the limit of detection (LOD) used by the ARB's Monitoring and Laboratory Division.

California Health and Safety Code Section 41805.5 required hazardous and municipal landfills throughout the state to conduct monitoring for several contaminants including vinyl chloride. 24-hour averaged ambient vinyl chloride concentrations ranging from the detection limit of 2 ppbv (the Testing Guidelines for Active Solid Waste Disposal Sites example method for calculating the LOD is discussed in Section C of Chapter II under Landfill Emissions Estimates) to 15 ppbv were detected at 24 out of the 251 landfills tested for ambient concentrations (see Appendix VI).

In recent years, the South Coast Air Quality Management District (SCAQMD) frequently measured 24-hour average ambient vinyl chloride concentrations above the SCAQMD's LOD of 2 ppbv at two South Coast Area Basin (SCAB) landfills: BKK Landfill and Operating Industries Incorporated (OII) Landfill. The SCAQMD used the following method for determining the vinyl chloride LOD: 1) a 10 ppbv standard was analyzed a minimum of 10

times, 2) response was calculated as peak height (in millimeters) times the attenuation of the signal, 3) the precision of the measurement at 10 ppbv was 0.5 millimeters, 3) the minimum observable peak was taken to be four times 0.5 millimeters or 2 millimeters which corresponds to the reported LOD of 2 ppbv (Barbosa, 1990). The analysis in this report estimates ambient concentrations and population exposure to vinyl chloride near BKK and OII because they are the only landfills in the state where vinyl chloride has been routinely monitored on a long-term basis.

The SCAQMD's monitoring program for vinyl chloride at BKK and OII consisted of six monitoring stations. Three stations were located on the southern borders of each landfill. Previous monitoring around both landfills indicated that the southern borders were generally where the highest concentrations were detected. All samples were collected in Tedlar bags over 24-hour periods and subsequently analyzed by gas chromatography employing a flame ionization detector. Details of the SCAQMD's sampling and analysis procedures are provided in Appendix I.

BKK Landfill is located near West Covina while OII Landfill is located near Monterey Park. Figure III-1 shows the locations of the two landfills in relation to major freeways. In addition, topographical maps of the BKK and OII landfills are provided respectively in Figures III-2 and III-3. These figures show the approximate perimeter of the landfills, the approximate locations of the monitoring sites, and the proximity of streets to the landfills. As indicated by the maps, the southern borders of BKK and OII are adjacent to a network of streets. However, the maps do not show that the area served by these streets consists of single-family residential housing.

FIGURE III-1

THE LOCATION OF BKK AND OII LANDFILLS IN RELATION TO MAJOR FREEWAYS

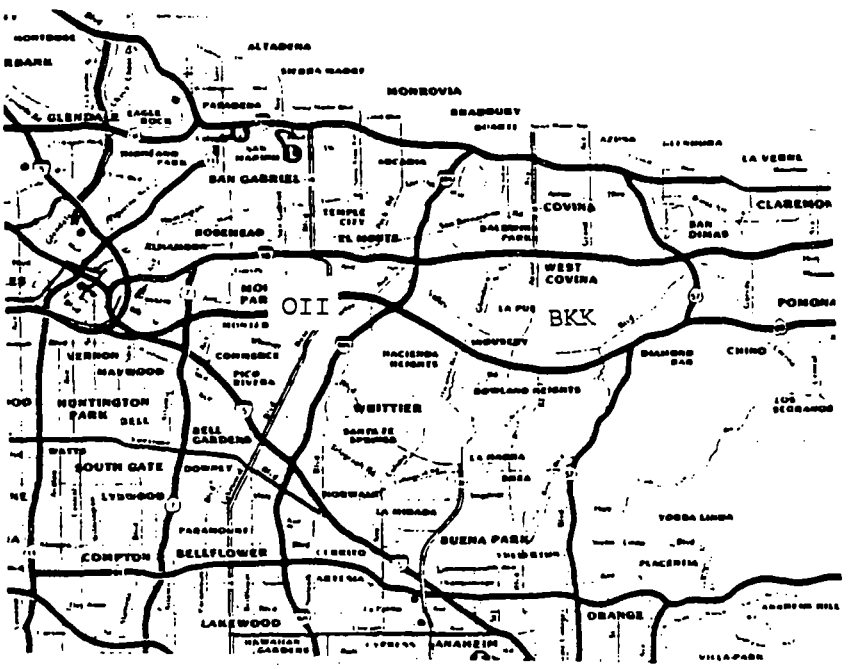


FIGURE III-2

BKK LANDFILL AND THE SURROUNDING AREA

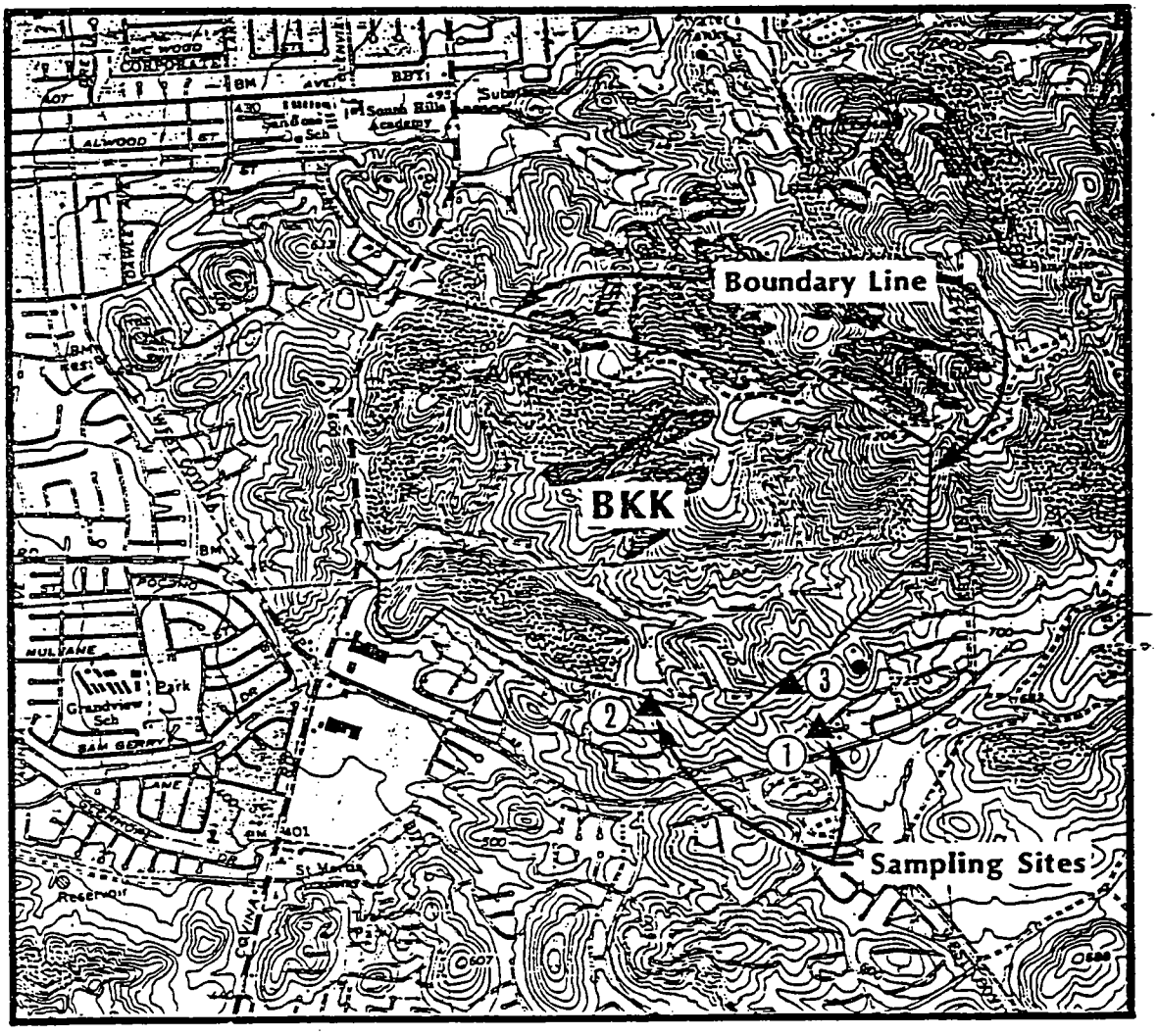
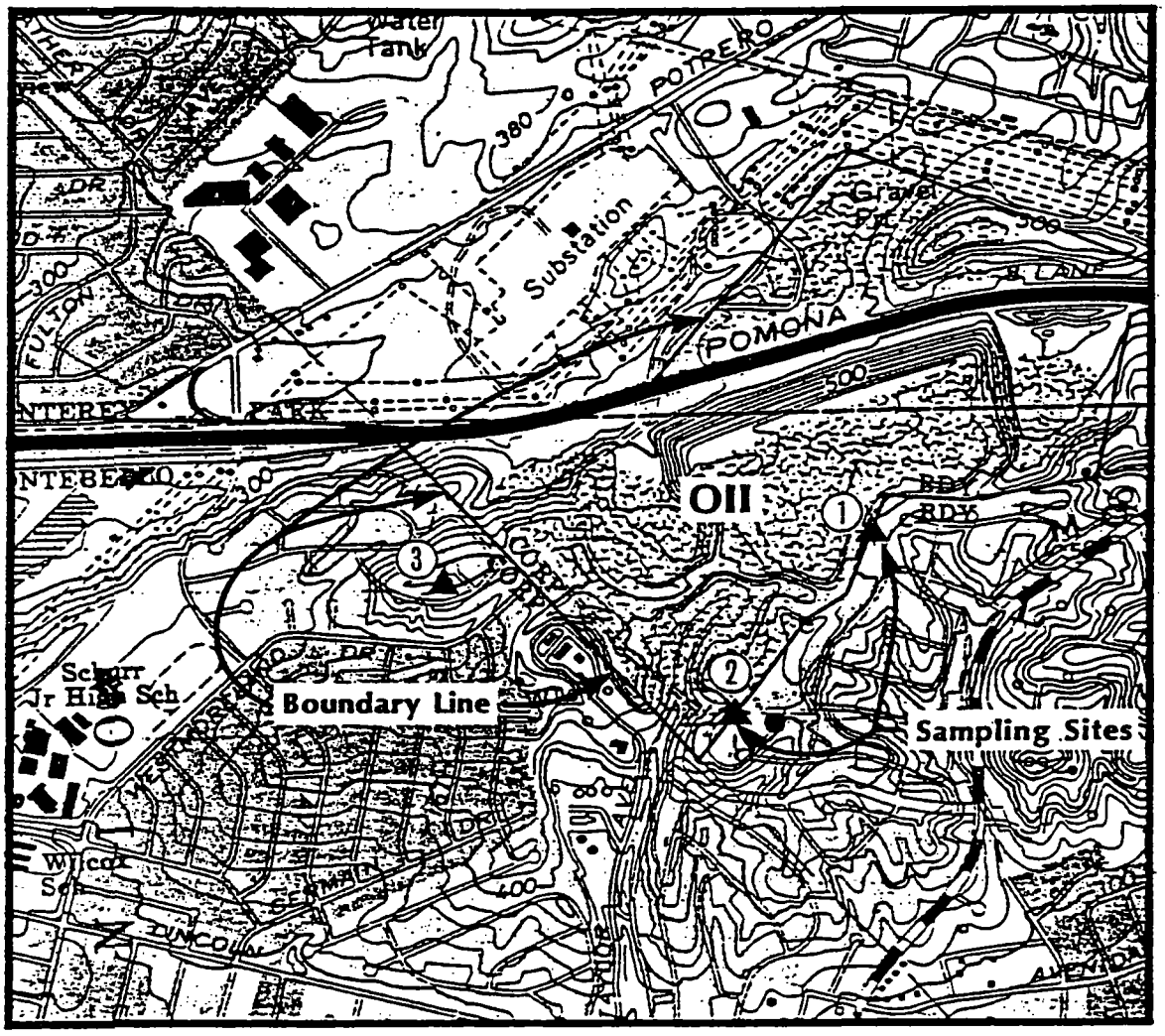


FIGURE III-3

OII LANDFILL AND THE SURROUNDING AREA



Boundary Line

① ▲ Sampling Sites

1 Kilometer

The 24-hour average ambient air samples used to estimate population exposure near BKK were collected from January through December of 1987. 24-hour ambient air samples used to estimate population exposure near OII were collected from January through December of 1986. When the exposure analysis was performed, these sampling periods represented the most recent calendar years of monitoring data that were available. For BKK, 337 to 345 samples were collected in 24-hour periods at each of the monitoring sites; of those sites, a range of 55 to 90 percent of the samples were below the LOD of 2 ppbv. For OII, 128 to 264 samples were taken at each of the monitoring sites; of those sites, 32 to 100 percent of the samples were below the LOD.

The ambient vinyl chloride monitoring data for BKK and OII are summarized in Tables III-1 and III-2, respectively. Each table provides the number of samples taken at each site, the percentage of samples below the LOD, an estimate for the values below the LOD, the estimated mean concentration, and the maximum 24-hour concentration that was measured.

Calculation of mean concentrations for stations was complicated by the presence of concentrations below the LOD. The concentrations below the LOD must be included in the calculation although their exact values were not known.

ARB staff has used a method proposed by Gleit (1985) to calculate the means. Gleit's method assumes that the sample of concentrations is a random sample from a normal distribution. Data that are judged not to be normally distributed may be transformed to approximate normality. Inspection of the vinyl chloride data suggested that they were lognormally distributed, and Gleit's method was applied to the logarithms of these data. The calculated means were then transformed back to the original units.

Gleit's method accounts for the concentrations below the LOD by setting them equal to the "below-LOD mean," the mean of the portion of the normal distribution below the LOD. Setting the unknown concentrations to their average value seems intuitively reasonable, and the simulations reported in Gleit's paper show that his method is more accurate than other commonly used approximations. A detailed description of the method used to estimate the concentration of data below the LOD is provided in Appendix II.

The estimated values for 24-hour averaged samples below the LOD ranged from 1.0 ppbv to 1.1 ppbv for BKK and from 1.0 ppbv to 1.2 ppbv for OII. As previously indicated, the specific value for each station is shown in Table III-1 for BKK and Table III-2 for OII. Because all samples for site 1 of OII were below the LOD, Gleit's method could not be used to estimate their concentration. A value of one-half the LOD (1.0 ppbv) was assumed for samples below the LOD based on the possibility that many contained between zero and 2 ppbv vinyl chloride.

TABLE III-1

SUMMARY STATISTICS FOR THE JANUARY 1987 THROUGH DECEMBER 1987 MONITORING DATA FOR VINYL CHLORIDE NEAR BKK LANDFILL
(Concentrations are reported in parts per billion by volume (ppbv) and are based on measurements averaged over a 24-hour sample collection period.)

	Station 1	Station 2	Station 3
Number of samples	337	337	345
Percent of Samples Below the LOD[a]	73	90	55
Estimated Concentration for[b] Samples Below the LOD	1.0	1.0	1.1
Estimated Mean[b] Concentration	1.7	1.2	2.6
Maximum 24-Hour Concentration[c]	7	8	15

a - The SCAQMD's limit of detection (LOD) for vinyl chloride is 2 ppbv.
b - Gleit's method was used to estimate the concentration of samples below the LOD.
c - California's Ambient Air Quality Standard for vinyl chloride is 10 ppbv for a 24-hour averaging period.

TABLE III-2

SUMMARY STATISTICS FOR THE JANUARY 1986 THROUGH DECEMBER 1986 MONITORING DATA FOR VINYL CHLORIDE NEAR OII LANDFILL
(Concentrations are reported in parts per billion by volume (ppbv) and are based on measurements averaged over a 24-hour sample collection period)

	Station 1	Station 2	Station 3
Number of Samples	264	220	128
Percent of Samples Below the LOD[a]	100	41	32
Estimated Concentration for[b] Samples Below the LOD	1.0	1.1	1.2
Estimated Mean[b] Concentration	1.0	2.0	2.0
Maximum 24-Hour Concentration[c]	d	8.3	9.8

a - The SCAQMD's limit of detection (LOD) for vinyl chloride is 2 ppbv.
b - Gleit's method was used to estimate the concentration of samples below the LOD, except for station 1.
c - California's Ambient Air Quality Standard for vinyl chloride is 10 ppbv for a 24-hour averaging period.
d - All samples are below 2 ppbv.

The estimated mean vinyl chloride concentrations using 24-hour averaged ambient measurements ranged from 1.2 ppbv to 2.6 ppbv for the monitoring stations at BKK and 1.0 ppbv to 2.0 ppbv for the monitoring stations at OII. The estimated mean vinyl chloride concentrations are shown in Tables III-1 and III-2. For all stations, except station 3 of BKK, the estimated annual mean concentration is equal to or less than the SCAQMD's LOD for vinyl chloride.

Tables III-1 and III-2 also list the maximum 24-hour average concentration of vinyl chloride for each monitoring station at BKK and OII, respectively. For BKK, the maximum 24-hour average concentration was 15 ppbv (measured at station 3); for OII the maximum 24-hour average concentration was 9.8 ppbv (measured at station 3). These concentrations can be compared to ARB's ambient air quality standard for vinyl chloride of 10 ppbv for a 24-hour averaging period. The standard was adopted in 1978 in response to information which associated vinyl chloride with the development

of cancer in humans. However, the standard is not necessarily health protective; it simply represented the LOD for vinyl chloride testing at the time it was adopted. According to the procedure specified in the standard, the LOD is based on 3 standard deviations of the method detection limit (within 10 standard deviations of the method detection limit). This method of calculating the LOD is the same as that used by the ARB Monitoring and Laboratory Division (see Appendix VII). For the monitoring periods presented in this report, BKK exceeded the state standard for vinyl chloride 11 times (all exceedances occurred at site 3) while OII did not exceed the standard. Based on previous years of monitoring data, the number of exceedances at BKK and OII has decreased substantially. In fact, due to the lack of exceedances of the standard, the SCAQMD discontinued routine monitoring for vinyl chloride at BKK in 1989 and at OII in early 1987. The reduction in ambient concentrations of vinyl chloride near BKK and OII landfills has been attributed to the installation of gas collection and flare systems.

In an effort to represent the uncertainties associated with the estimated mean concentrations of vinyl chloride, the staff developed a statistical treatment for calculating upper and lower bound estimates of the mean concentration at each monitoring station. This method takes into account factors such as sample size, variance of the data, and an estimate of the uncertainty associated with the sampling and analysis method. Table III-3 shows the estimated mean concentration as well as the upper and lower bound estimate of the mean concentration for each monitoring station at BKK and OII.

The following text discusses the statistical treatment that was used:

a) After reviewing the ambient vinyl chloride monitoring data for BKK and OII, the staff observed that the data appeared to be lognormally distributed. Because available software only analyze data that are normally distributed, vinyl chloride monitoring data were first converted from a lognormal distribution to a normal distribution. This was done by using the logarithms of the data for the analysis. The statistical analysis system (SAS, 1982) was used to calculate the standard error about the mean. The standard error calculated from the logarithms of the data is then converted back into concentration units by taking the antilogarithms.

b) The upper and lower bound estimates reported for the mean represented two standard errors. For the error associated with sampling and analysis, ARB staff used an overall uncertainty factor of $\pm$ 20 percent to calculate the upper and lower bound estimates of the mean. This was in agreement with the actual error which was estimated to be $\pm$ 1 ppbv in the range of 1 ppbv to 50 ppbv. The lower bound estimate represented two standard errors for the data with each sample concentration reduced by 20 percent. The upper bound estimate represented two standard errors for the data with each sample concentration increased by 20 percent. Upper and lower bound estimates for each station are shown in Table III-3. Because

all values for station 1 of OII are below the LOD, the upper and lower bound estimates represented ± 20 percent of one-half the LOD.

B. ESTIMATING AMBIENT CONCENTRATIONS

Annual average vinyl chloride concentrations were estimated for a 41 x 41 grid of one square kilometer cells surrounding each landfill with the use of the Industrial Source Complex Short Term (ISCST) Gaussian model. In order to predict the annual average concentration of vinyl chloride in each of the 1681 square kilometer cells, the ISCST model required the emission rates for each landfill as input. Emission rates were estimated for BKK and OII using the range of estimated annual mean concentrations at each of the monitoring stations.

The estimated emission rates were derived by ratioing estimated annual mean concentrations over modeled concentrations for each station.

TABLE III-3

UPPER AND LOWER BOUND ESTIMATES OF THE ANNUAL MEAN CONCENTRATIONS OF VINYL CHLORIDE AT BKK AND OII LANDFILLS

	Lower-bound Estimate	Annual Mean Concentration	Upper-bound Estimate
BKK Landfill			
Station 1	1.2	1.7	2.1
Station 2	0.9	1.2	1.4
Station 3	1.9	2.6	3.4
OII Landfill			
Station 1*	0.8	1.0	1.2
Station 2	1.4	2.0	2.8
Station 3	1.4	2.0	2.6

* - All samples were below the LOD of 2 ppbv.

The modeled concentrations were determined by assuming a landfill emission rate of 1 gram per square meter per second (gram meter^{-2} second^{-1}) in conjunction with historical meteorological data. Each landfill was represented as an area source. Based on review of topographical maps as well as information concerning the landfills disposal history, BKK was assumed to emit vinyl chloride from an area of approximately 1,700,000 meters^2 while OII was assumed to emit vinyl chloride from an area of approximately 330,000 meters^2. These assumed areas approximated the

area where wastes had been disposed. Meteorological data for 1981 at the SCAQMD's Walnut and Upland stations were used for BKK and OII, respectively. Meteorological data from these stations were used for this study because Walnut was considered the most representative station for BKK where processed data were avai$ble while Upland was considered the most representative station for OII where processed data were available. These data were entered into the ISCST model to calculate the annual average modeled concentration at each monitoring station. Because one year of meteorological data was used, one modeled concentration was obtained for each monitoring station at BKK and OII. For each site at BKK and OII the modeled concentration was divided into the estimated mean concentration (from Table III-3) of its respective monitoring station. The resulting factors or ratios were then multiplied by the assumed emission rate (1 gram $meter^{-2}$ $second^{-1}$) to estimate a landfill emission rate for each monitoring station that will result in an exact match between estimated and modeled concentrations. Equation (1) illustrates the procedure that was used:

$$\text{Estimated Emission Rate} = \text{Assumed Emission Rate} \times (\text{Estimated Concentration} / \text{Modeled Concentration}) \quad (1)$$

The estimated landfill emission rates for each monitoring station at BKK and OII are given in Table III-4. The emission rate derived from the estimated mean concentration for each monitoring station and the emission rates derived from the upper and lower bound estimates of the mean concentration for each monitoring station are listed. The greatest range of estimated emission rates for BKK was from 0.75 micrograms $meter^{-2}$ $second^{-1}$ (lower-bound at station 2) to 3.32 micrograms $meter^{-2}$ $second^{-1}$ (upper-bound at station 3). For OII, the estimated emission rates ranged from 0.31 micrograms $meter^{-2}$ $second^{-1}$ (lower-bound at station 1) to 4.42 micrograms $meter^{-2}$ $second^{-1}$ (upper-bound at station 3).

Using the full range of emission rate estimates (0.75 to 3.32 micrograms $meter^{-2}$ $second^{-1}$ for BKK and 0.31 to 4.42 micrograms $meter^{-2}$ $second^{-1}$ for OII), a range of estimated annual average vinyl chloride concentrations was derived for the 41 by 41 grid of one square kilometer cells. Each landfill was located in the center of the grid and was represented as an area source. As previously stated, BKK was assumed to emit vinyl chloride from an area of approximately 1,700,000 $meters^2$ while OII was assumed to emit vinyl chloride from an area of approximately 330,000 $meters^2$. These areas approximate the area where wastes were disposed at each landfill. However, because subsurface migration of landfill gases has been observed at BKK and OII, it is possible that emissions of vinyl chloride occur over an area substantially greater than where wastes were actually disposed. The ISCST model used the range of estimated emission rates assuming no plume rise in conjunction with historical meteorological data to predict a range of annual average concentrations for each of the 1681 one-square-kilometer-cells. The annual average concentrations of

TABLE III-4

ESTIMATED EMISSION RATES OF VINYL CHLORIDE FROM BKK AND OII LANDFILLS
(micrograms meters^{-2} second^{-1})

	Lower-bound[a]	Average[b]	Upper-bound[c]
BKK Landfill			
Station 1	1.36	1.80	2.30
Station 2	0.75	0.97	1.20
Station 3	1.88	2.55	3.32
OII Landfill			
Station 1	0.31	0.38	0.46
Station 2	0.52	0.74	1.04
Station 3	2.69	3.46	4.42

a - These emission rates were derived from the lower-bound annual mean concentration.
b - These emission rates were derived from the annual mean concentration.
c - These emission rates were derived from the upper-bound annual mean concentration.

vinyl chloride predicted for the one-square-kilometer cells within the grid centered on BKK, ranged from less than 0.1 ppbv to approximately 22 ppbv. For OII, the range was from less than 0.1 ppbv to approximately 3.8 ppbv.

In order to obtain these modeling results, several assumptions were made. These assumptions may act to elevate or reduce the estimated annual average concentrations of vinyl chloride predicted for the cells surrounding BKK and OII. The primary assumptions were as follows:

1) Vinyl chloride was assumed to be emitted from an area of approximately 1,700,000 meters^2 for BKK and 330,000 meters^2 for OII. Although these areas approximate the area where wastes were disposed, data were not available to demonstrate that these

areas actually represented where vinyl chloride emissions occurred. Emissions of vinyl chloride might have occurred over an area which is either larger or smaller than that assumed.

2) Emissions of vinyl chloride were assumed to occur continuously and uniformly over a given area of each landfill. In reality, vinyl chloride was not likely to emanate uniformly over the surface of the landfills. However, the data required by the model to take this into consideration were not available. If emissions of vinyl chloride vary over the surface of the landfills, the annual concentrations estimated for some cells would be expected to be underestimated while others would be overestimated.

3) This study did not use meteorology for the same year as the vinyl chloride measurements. Because there was not a great deal of variation in meteorological data from year to year, the degree of error from using a meteorological year different than the vinyl chloride measurement year was estimated to be less than ± 50 percent.

Because the emission rates were derived by model calibration to known vinyl chloride concentrations, the uncertainty was at a minimum near the monitoring sites. Alternatively, as the distance from each monitoring station increased, the uncertainty associated with the estimated concentration increased.

C. POPULATION EXPOSURE

The population exposure to vinyl chloride near BKK and OII was estimated by using the grid cell concentrations estimated from the ISCST model in conjunction with 1985 updated census data. Estimates of the cumulative population exposed to various concentration levels of vinyl chloride near BKK and OII landfills are shown in Tables III-5 and III-6. The 1985 residential population estimates were determined for each one kilometer grid cell with the concentration determined at the center of each cell by the ISCST model. The 1681 grid cells, with their associated populations, were sorted from high to low by concentration. The grid cell populations were then summed to determine the cumulative population exposed at or above certain levels of vinyl chloride. For Tables III-5 and III-6, a lower bound of exposure was estimated. This range of exposure is based on upper and lower bound estimates of the vinyl chloride emission rate from each of the two landfills. Table III-5 shows that approximately 730,000 to 2,000,000 people were exposed to an annual average concentration of at least 0.05 ppbv of vinyl chloride from the BKK landfill. Approximately 17,000 to 130,000 of these people were exposed to an annual average concentration of at least 1.0 ppbv from this facility. Table III-6 shows that approximately 33,000 to 1,100,000 people were exposed to an annual average concentration of at least 0.05 ppbv of vinyl chloride from the OII landfill. Approximately 0 to 22,000 of these people were exposed to an annual average concentration of at least 1.0 ppbv vinyl chloride from OII.

TABLE III-5

RANGE OF CUMULATIVE POPULATION EXPOSED
TO VINYL CHLORIDE NEAR BKK

Range of Cumulative Population			Exposed to Vinyl Chloride Concentrations (ppbv) at or above:
Lower-bound Estimate[a]		Upper-bound Estimate[b]	
2,154,000	-	2,154,000	>0 but <0.01[c]
2,026,000	-	2,154,000	0.01
732,000	-	1,970,000	0.05
374,000	-	1,431,000	0.1
17,000	-	131,000	1.0
0	-	54,000	2.0
0	-	28,000	3.0
0	-	20,000	4.0
0	-	14,000	5.0
0	-	7,000	6.0
0	-	2,500	7.0

a - The exposure estimate is based on an emission rate of 0.75 ug/m^2s^{-1}.

b - The exposure estimate is based on an emission rate of 3.32 ug/m^2s^{-1}.

c - According to the model, the entire population was at least exposed to vinyl chloride concentrations between 0 and 0.01 ppbv. In addition, the calculated population-weighted exposure for this population was estimated to range from an annual average of 0.08 to 0.34 ppbv vinyl chloride.

In addition to estimating the cumulative population exposure to vinyl chloride for people living near BKK and OII, the population-weighted exposure results were calculated. The population-weighted exposure was calculated by multiplying the estimated annual average concentration for each cell by the population represented by the cell. The exposure results for the 1681 cells were subsequently summed and divided by the total population represented by the 1681 cells. For BKK, the population-weighted

TABLE III-6

RANGE OF CUMULATIVE POPULATION EXPOSED TO VINYL CHLORIDE NEAR OII

Range of Cumulative Population Exposed to Vinyl Chloride			
Lower-bound Estimate[a]		Upper-bound Estimate[b]	Concentrations (ppbv) at or above:
4,287,300	-	4,287,300	>0 but <0.01[c]
272,000	-	3,111,000	0.01
33,000	-	1,073,000	0.05
12,000	-	445,000	0.10
0	-	22,000	1.0
0	-	12,000	1.5
0	-	6,000	2.0
0	-	6,000	3.0

a - The exposure estimate is based on an emission rate of 0.31 ug/m^2s^{-1}.

b - The exposure estimate is based on an emission rate of 4.42 ug/m^2s^{-1}.

c - According to the model, the entire cumulative population studied was at least exposed to vinyl chloride concentrations between 0 and less than 0.01 ppbv. In addition, calculated population-weighted exposure for this population was estimated to range from an annual average of 0.004 to 0.06 ppbv vinyl chloride.

exposure estimates showed that approximately 2,000,000 people were exposed to an annual average vinyl chloride concentration ranging from 0.08 ppbv to 0.34 ppbv. For OII the population-weighted exposure estimates showed that approximately 4,000,000 people were exposed to an annual average vinyl chloride concentration ranging from 0.004 ppbv to 0.06 ppbv.

The model was also used to estimate the annual average concentrations for the maximum exposed individual at each landfill. For BKK, the maximum exposed individual was estimated to be exposed to an annual average concentration ranging from 2.3 ppbv to 10.3 ppbv. For OII, the maximum exposed individual was estimated to be exposed to an annual average concentration ranging from 0.6 to 8.7 ppbv.

The population exposure estimates for BKK and OII suggest that other landfills in California that emit vinyl chloride may expose the nearby population to elevated concentrations. Chapter II of this report discusses other vinyl chloride monitoring data that are available as well as preliminary data on the Landfill Gas Testing Program (see Appendix VI).

D. INDOOR EXPOSURE TO VINYL CHLORIDE

With the exception of some homes located near landfills, indoor concentrations of vinyl chloride are not expected to be substantially greater than outdoor concentrations. Although data are limited, the above statement is supported by the following facts: 1) few indoor sources of vinyl chloride have been identified; and 2) most studies that have monitored for indoor concentrations of vinyl chloride fail to detect it. However, landfills have been identified as a source of emissions that contributes to elevated indoor levels of vinyl chloride in nearby residences. Grab samples from some houses located near landfills have shown vinyl chloride at concentrations up to 100 ppbv.

We estimate that people living near landfills may be inhaling up to 2600 micrograms of vinyl chloride a day (see Appendix III for assumptions). For these individuals, inhalation of vinyl chloride indoors is expected to represent the most significant source of exposure. A more detailed discussion of indoor exposure to air contaminants is presented in Appendix III.

1. Potential Sources of Indoor Vinyl Chloride

There are several potential sources that can contribute to indoor concentrations of vinyl chloride. These sources include landfills, polyvinyl chloride (PVC) products containing residues of vinyl chloride, water that contains residues of vinyl chloride and cigarette smoke. For most homes, these sources are not expected to result in substantially elevated indoor levels of vinyl chloride. However, for some homes located near landfills, staff believe that landfills may represent the most significant contribution to indoor levels of vinyl chloride.

Vinyl Chloride From Landfill Gas. There are at least two ways that vinyl chloride emissions from landfills may contribute to indoor concentrations of vinyl chloride in nearby residences: 1) homes that are located downwind from landfills can receive vinyl chloride through direct outdoor air influx into indoor environments; and 2) landfill gases containing vinyl chloride can migrate underground and enter homes through substructures. The rate of accumulation of vinyl chloride indoors depends on several factors including soil permeability, source strength, air exchange rate and structure of the home. In addition, higher indoor concentrations may occur because vinyl chloride is more rapidly destroyed in outdoor air than indoor air. Outdoor destruction proceeds more quickly because vinyl chloride's reaction with hydroxyl radicals is the compound's dominant atmospheric removal mechanism and because hydroxyl radicals are formed in the presence of direct sunlight.

Plastic Materials and Consumer Products. Plastic products made of PVC and other vinyl chloride polymers are ubiquitous in most homes. Because vinyl chloride monomer can remain in the PVC resin for an extended period of time, an indirect source of indoor vinyl chloride emissions may come from the release of unreacted vinyl chloride monomer from these plastic products.

Emissions of unreacted vinyl chloride monomer have been substantially reduced due to improvements in monomer stripping technology (Wheeler, 1981). In the past, residual vinyl chloride concentrations in PVC resins at the time of shipment, were as high as 2000 ppm. Currently, PVC resins contain about 10 ppm residual vinyl chloride at the time of shipment and may lose vinyl chloride at a rate of 20 to 50 percent per month during storage. In addition, most of the vinyl chloride will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products. Thus, consumer products made of PVC resins no longer contain elevated residual levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride.

Vaporization from Water Sources. Because activities such as using water for cooking, heating and showering can promote rapid vaporization of vinyl chloride from water, contaminated surface or ground water may increase indoor vinyl chloride levels.

In California, surface water is generally free of vinyl chloride (Sharrp, 1987). In assessing ground water quality, the California Department of Health Services reported, based on a limit of detection of 0.5 micrograms/liter, that one out of the 2,947 wells for large public water systems that were sampled had detectable levels of vinyl chloride (DHS, 1986). The maximum concentration found in that well was 23 micrograms/liter with a median value of 20 micrograms/liter. Vinyl chloride has not been detected in wells used for small public water systems (DHS, 1987). Therefore, vinyl chloride in the water supply is not believed to significantly impact indoor air concentrations of vinyl chloride.

Cigarette Smoke. Vinyl chloride has been identified in the smoke of cigarettes (1.3 to 16 nanograms/cigarette) and of little cigars (14 to 27 nanograms/cigar). (IARC, 1985; Hoffmann, Patrianakos and Brunnemann, 1976). The vinyl chloride level in the mainstream smoke may be estimated by the total inorganic chloride content of the tobacco. However, the contribution from tobacco smoke does not appear to have a significant impact on the indoor concentration of vinyl chloride.

2. Indoor Monitoring Data

Indoor air data can be obtained either by personal air sampling or by fixed-site air sampling. In personal sampling, the sampling equipment is carried by an individual and air samples are taken wherever the individual

may be. In contrast, fixed-site air sampling refers to air samples taken at fixed locations. Personal air sampling data generally provide a more realistic estimate of individual exposure. Because most people spend 80 to 90 percent of their time in indoor environments, personal air sampling data are strongly weighted by indoor air exposure data.

Personal Sampling Data. Based on limited personal sampling data, it appears that indoor air exposure to vinyl chloride is low. Nine subjects in New Jersey and three subjects in North Carolina were monitored for 5 to 10 hours on three separate occasions for several days over a 6-month period. All of the 138 air samples taken were below the LOD which was reported to be 20 ppbv (Wallace et al., 1984). The procedure for calculating the LOD was not described in the paper and the subcontractor who conducted the monitoring could not be located for his definition of LOD.

Fixed-site Sampling Data. For a study conducted in California, fixed-site monitoring stations were installed to monitor indoor and outdoor air concentrations of vinyl chloride. Based on the analysis of 32 indoor samples taken in eight homes during the summer season for two twelve-hour sampling periods (daytime and nighttime), concentrations of vinyl chloride were all below the LOD. The samples were analyzed by two analytical methods with LODs ranging from about 0.2 ppbv to 58 ppbv (0.55 and 148 micrograms meter^{-3})(Pellizzari et al., 1989). The LOD as defined by Pellizari et al. is a value where the measured signal of the analyte is three times that of the noise of the instrument. Therefore, values below the LOD are not reported.

A similar study was conducted in Baltimore where indoor air concentrations of vinyl chloride in about 160 homes were monitored by fixed-site sampling stations. Based on partially analyzed results, vinyl chloride was not detected in indoor air environments. The LOD was reported to range from 10.2 ppbv to 15.7 ppbv (26 to 40 micrograms meter^{-3}) (Pellizzari, 1987).

Special Situation Air Monitoring. In 1981, the SCAQMD collected 24-hour bag samples in the vicinity of BKK landfill. Over 500 air samples were taken at two outdoor sites and at four indoor sites downwind of the landfill (SCAQMD, 1982). All of the samples (approximately 120 samples) that equaled or exceeded the state vinyl chloride standard of 10 ppbv (26 micrograms meter^{-3}) were taken inside the residences. The highest recorded indoor vinyl chloride concentration was 50 ppbv (130 micrograms/meter^{-3}). The LOD was reported to be 2 ppbv (5.2 micrograms meter^{-3}) (see section A, Chpater III for the SCAQMD method for calculating the LOD).

In 1984, the South Coast Air Quality Management District (SCAQMD) sampled water meter boxes at the property lines of a few homes adjacent to OII Landfill as a screen for landfill gas migration. Water meter boxes are below-ground enclosed boxes containing an apparatus which measures the amount of water used by a household. The 10 grab samples taken from inside water meter boxes of homes adjacent to OII Landfill showed vinyl chloride levels ranging from 13 to 36000 ppbv. This finding prompted a 1985 South

Coast Air Quality Management District indoor air grab-sample study which showed vinyl chloride concentrations ranging from 8 to 100 ppbv (20.8 - 260 micrograms meter^{-3}) in some homes near the landfill (SCAQMD, 1985). Presently, indoor concentrations of vinyl chloride in these residences are believed to be substantially lower because of the installation of gas collectors and flares (Coy, 1987). OII is now a federal superfund site managed by the EPA.

E. EXPOSURE THROUGH OTHER ROUTES

While the main objective of this report is to estimate exposure through the air, exposure to vinyl chloride may also occur from the ingestion of food and water that contain residues of vinyl chloride. The Health and Safety Code specifies that the ARB shall identify the relative contribution to total exposure to the contaminant from indoor concentrations, taking into account both ambient and indoor environments (California Health and Safety Code, 1989). The inclusion of these data provide a useful perspective of the overall exposure to vinyl chloride through environmental media. The estimated daily dose of vinyl chloride from different environmental media are presented in Table III-7. From the table, exposure to vinyl chloride from the indoor air of homes not located near landfills, food, and water appears to be minor. However, for people living in houses located near landfills, indoor exposure to vinyl chloride may represent the major source of total vinyl chloride exposure. The need for total exposure assessment and some of the issues and concepts involved in total exposure estimates are discussed in Appendix III.

1. Water Ingestion

The major source of drinking water for California is surface water which is not expected to have detectable levels of the highly volatile vinyl chloride. Ground water used for public water systems is also relatively free of vinyl chloride with concentrations typically below 0.5 ug liter^{-1} (DHS, 1987, 1986). Based on this information, staff believe that exposure to vinyl chloride through drinking water is not important under ordinary situations.

2. Food Ingestion

Vinyl chloride is not routinely monitored for in U.S. food products. However, before 1973 vinyl chloride was found in food and beverages packaged in vinyl chloride polymer materials (IARC, 1979). At that time, levels as high as 20 mg^{-1} kg^{-1} (ppm) of vinyl chloride monomer were present in alcoholic beverages packaged in this material. Vinyl chloride was also found in edible oils, butter, and margarine at concentrations ranging from 0.05 - 14.8 mg kg^{-1}. In 1986, the Food and Drug Administration (FDA) proposed to limit the maximum amount of residual vinyl chloride monomer in rigid and semi-rigid food containers to 10 ppbw and the maximum amount of vinyl chloride monomer allowed in polymeric coatings and films which contact food to 5 ppbw. The regulation was not promulgated because the FDA believed that monomer stripping processes leave no residue of vinyl chloride monomer. In 1986, the Food and Drug Administration (FDA) estimated that the lifetime-averaged individual exposure to vinyl chloride

from food and beverages packaged with vinyl chloride polymer materials would not exceed 25 nanograms per day (FDA, 1986). An estimate of today's potential for vinyl chloride exposure from food ingestion is not possible because, to the ARB's knowledge, current information on the levels in food and food packaging are not available.

TABLE III-7

ESTIMATED VINYL CHLORIDE EXPOSURE THROUGH DIFFERENT MEDIA[a]

Media	Daily Dose	Reference
AIR		
Ambient Air		
not near landfills	b	
near landfills	<104 to 780 ug	Table III-1, 1990
Indoor Air		
homes not near landfills	<11 ug	Pellizari et al., 1989
homes near landfills	up to 2600 ug	SCAQMD, 1982
INGESTION		
Drinking water: Surface/Ground Water	<1 ug	DHS, 1986; 1987
Food including beverages	< 0.025 ug	FDA, 1986

a - The assumptions that were used for Table II-7 are provided in Appendix III.

b - The dose from exposure to ambient air not near landfills was not calculated because the ARB's ambient monitoring network has not detected vinyl chloride.

REFERENCES TO CHAPTER III

Barbosa, S., 1990. Personal communication between Steve Barbosa of the South Coast Air Quality Management District and Barbara Cook, September 1990.

California Health and Safety Code, 1989., Section 39660.5 (d).

Coy, C., 1987. Personal communication between Richard Corey of ARB staff and Carol Coy of SCAQMD. February, 1987.

DHS, 1986. California Department of Health Services. Final report on a monitoring program for organic chemical contamination of large public water systems in California.

DHS, 1987. California Department of Health Services. Status report- AB 1803 small system program: Summary of results.

FDA, 1986. Proposed uses of vinyl chloride polymers by the Food and Drug Administration-proposed rule, Federal Register 51(22):4177-4188.

Gleit, A., 1985. "Estimation for Small Normal Data Sets with Detection Limits," Environmental Science and Technology, 19:1201-1206.

Hoffmann D., Patrianakos C., and Brunnemann K.D., 1976. "Chromatographic determination of vinyl chloride in tobacco smoke." Analytical Chemistry, 48(1): 47-50.

IARC, 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans-some monomers, plastics and synthetic elastomers and acrolein. Volume 19, International Agency for Research on Cancer, World Health Organization.

IARC, 1985. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans-tobacco smoking. Volume 38, International Agency for Research on Cancer, World Health Organization.

Pellizzari, E., 1987. Personal communication between Steve Hui of ARB staff and Dr. E. D. Pellizzari of Research Triangle Institute on December, 1987.

Pellizzari, E.D., et al., 1989. Development and implementation of exposure assessment procedures for toxic air pollutants in several Los Angeles County, CA. communities, Research Triangle Park.

SAS, 1982. SAS Institute, Inc. "SAS User's Guide: Statistics 1982 Editor", Box 800, Cary, North Carolina.

SCAQMD, 1982. "Vinyl chloride in the South Coast Air Basin," Report by the South Coast Air Quality Management District.

SCAQMD, 1985. Internal memorandum between S. Levy and Edward Camarena of the South Coast Air Ouality Management District on September, 1985.

Sharrp, C., 1987. Personal communication between Steve Hui of ARB staff and Chris Sharrp, staff of California Department of Health Services on December, 1987.

Wallace, L.A. et al., 1984. "Personal exposures to volatile organic compounds - 1. Direct measurements in breath-zone air, drinking water, food, and exhaled breath. Environmental Research, 35(10):293-319.

Wheeler, R.N., 1981. "Poly(vinyl chloride) processes and products," Environmental Health Perspective, 41: 123-128.

IV.

PERSISTENCE IN THE ATMOSPHERE

A. PHYSICAL PROPERTIES

The chemical structure of vinyl chloride (chloroethene, chloroethylene) is CH_2= CHCl. Vinyl chloride is a sweet smelling, colorless gas at ambient temperature and pressure. It polymerizes in light or in the presence of a catalyst. Vinyl chloride is readily flammable and forms explosive mixtures in air. Upon combustion, it is degraded mainly to hydrogen chloride gas (HCl), carbon monoxide (CO), carbon dioxide (CO_2) and traces of phosgene (Cl_2C=O). Vinyl chloride is expected to volatilize rapidly from water (H_2O) systems. Experimental data indicate that for an initial concentration of 1 ppm at a solution depth of 6.5 cm and a stirring rate of 200 rpm, the average evaporative half-life of vinyl chloride at a temperature of approximately 25°C is 27.6 minutes (Dilling, 1977). Another study determined that distilled water spiked with 16 ppm vinyl chloride lost 96 percent of the vinyl chloride within two hours (U.S. EPA, 1974). Although it is soluble in ethanol (CH_3CH_2OH), industrial solvents, and a number of organic liquids, vinyl chloride is only slightly soluble in water. Vinyl chloride's physical properties are shown in Table IV-1.

B. ATMOSPHERIC PERSISTENCE

Reaction with hydroxyl radicals (OH) is the dominant mechanism removing vinyl chloride from the troposphere (Cupitt, 1980; Atkinson, 1986a). Estimates of vinyl chloride's tropospheric lifetime range from 0.5 to 5.8 days. However, for reasons provided later in this section, ARB staff believe that a tropospheric lifetime ranging from 1.6 to 3.9 days is representative of typical atmospheric conditions. The rate at which this reaction proceeds depends on the temperature and the tropospheric concentration of both vinyl chloride and hydroxyl radicals. The temperature dependence of the reaction rate is incorporated in the rate constant for the reaction of vinyl chloride with hydroxyl radicals. The product of the rate constant and both species concentrations gives the rate at which vinyl chloride is being degraded (Finlayson-Pitts and Pitts, 1986).

TABLE IV-1

PHYSICAL PROPERTIES OF VINYL CHLORIDE

Properties	Value	Reference
Boiling point, 1 Atm	-13.37 °C	Merck Index, 1983
Molecular weight	62.5	Merck Index, 1983
Vapor Pressure, 20 °C	2530 mm Hg	Merck Index, 1983
Sol. in water, 25°C	0.11g/100g H_2O	Kirk-Othmer, 1980
Partition Coeff. H_2O/Air 10°C	0.02	McConnell, G., et al., 1975
Octanol/H_2O Partition Coeff.	20.7	Withey, 1976
Specific gravity, 20/4 °C	0.912	Kirk-Othmer, 1980
Flash pt. open cup	-77.8°C	Kirk-Othmer, 1980
Liq. Dens. -14.2 Cg/cm^3	0.969	CRC Handbook, 1985
Heat capacity, 27°C	16.1	CRC Handbook, 1985

The tropospheric lifetime of a compound is an estimate of the time required for a given amount of the compound to decrease to 1/e (0.368) of its original concentration (at time zero). The tropospheric lifetime (τ) of vinyl chloride is related to the rate constant (k) and the hydroxyl radical concentration ([OH]) by the equation (1):

$$\tau = (k[OH])^{-1} \qquad (1)$$

In deriving the above equation, it is assumed that hydroxyl radicals are at a constant steady state concentration in the troposphere.

Estimates have been made for the rate constant resulting from vinyl chloride's reaction with hydroxyl radicals. Perry et al. (1977) estimated the absolute rate constants over the temperature range of 299 Kelvin (°K) to 426°K. The limiting high pressure rate constant for a temperature of 299°K is estimated to be $6.60 \pm 0.66 \times 10^{-12}$ cm^3 $molecule^{-1}$ $second^{-1}$. Howard determined rate constants for the reaction of vinyl chloride with hydroxyl radicals at 296°K over a range of pressure where the highest pressure employed had not reached the limiting high pressure regime (Howard et al., 1976). However, when data obtained by Howard are extrapolated to the high pressure limit, the resulting rate constant of

approximately 7 x 10^{-12} cm^3 $molecules^{-1}$ $second^{-1}$ is in good agreement with the value reported by Perry (Perry et al., 1976). Using a different technique, a study by Liu, et al. over the temperature range of 313 to 423°K was also in good agreement with Perry, et al. (Perry, et al.,1976; Liu, et al., 1989). Table IV-2 summarizes the rate constant estimates, atmospheric lifetime estimates, average temperature assumed, and the method used to estimate the rate constant for the reaction of vinyl chloride with hydroxyl radicals and ozone (O_3).

The 24-hour average hydroxyl radical concentration in the troposphere has been estimated to range from 3 x 10^5 to 3 x 10^6 molecules cm^{-3} (Hewitt & Harrison, 1985). Because hydroxyl radicals are only present during daylight, the actual range for daytime concentrations is twice the 24-hour averages given above while nighttime concentrations are essentially zero. Prinn, et al. derived the most reliable average hydroxyl radical concentration of 7.7 X 10^5 molecules cm^{-3} using the ambient tropospheric concentration and emission inventory of methyl chloroform (CH_3CCl_3) (Prinn, et al., 1987). Daytime hydroxyl radical concentrations vary depending on many factors including photolytic activity and the concentration of ozone as well as other pollutants in the troposphere.

Using the rate constant determined by Perry et al. for an average tropospheric temperature of 299°K and a range of hydroxyl radical concentrations ranging from 3 x 10^5 to 3 x 10^6 molecules cm^{-3}, the estimated tropospheric lifetime for vinyl chloride ranges from:

0.6 days for [OH] = 3 x 10^6 molecules cm^{-3}

to

5.8 days for [OH] = 3 x 10^5 molecules cm^{-3}

As previously indicated, the concentration of hydroxyl radicals in the troposphere can vary considerably. However, several researchers recommend 24-hour average hydroxyl radical concentrations which are between 0.5 x 10^6 and 1 x 10^6 molecules cm^{-3} (Prinn et al., 1987; Winer, 1978; Singh et al., 1983; Cupitt, 1980; Cox et al., 1976; Davis et al., 1976). By using this range of 24-hour average hydroxyl radical concentrations (0.5 x 10^6 to 1 x 10^6 molecules cm^{-3}) in conjunction with the rate constants determined from Perry's rate constant at 299°K, the resulting range in atmospheric lifetimes is from 1.6 days to 3.9 days. Using Howard's adjusted rate constant derived by extrapolating to the high pressure limit, and the same range of hydroxyl radical concentrations (0.5 x 10^6 to to 1 x 10^6 molecules cm^{-3}), the atmospheric lifetime estimates for vinyl chloride ranges from 1.6 to 3.3 days.

TABLE IV-2

ATMOSPHERIC LIFETIME AND REACTION
RATE CONSTANT ESTIMATES FOR VINYL CHLORIDE

Reactant	Rate[a] Constant	Temperature (Kelvin)	Method	Atmospheric[b] Lifetime (days)	References
OH	$6.6 \pm 0.66 \times 10^{-12}$	299	FP-RF[c]	1.6 - 3.9[d]	Perry et al., 1977
O_3	$2.45 \pm 0.45 \times 10^{-19}$	298	S-FTIR[e]	47[f]	Zhang et al., 1983
O_3	2.3×10^{-19}	NR	S-FTIR[e]	50	Gay et al., 1976
O_3	6.5×10^{-21}	295	S-UV[g]	4.9 years	Sanhueza et al. 1976

a - Rate constant units are cm^3 $molecule^{-1}$ $second^{-1}$.

b - The atmospheric lifetime is defined as the time required for a given amount of the compound to decrease to 1/e (0.368) of its original concentration (at time zero).

c - FP-RF = Flash photolysis, resonance fluorescence.

d - Assumes a 24-hour average hydroxyl radical concentration ranging from 0.5×10^5 to 1×10^6 molecules cm^{-3} (Cupitt, 1980).

e - S-FTIR = Static system, Fourier transform infrared absorption spectroscopy.

f - Assumes a 24-hour average O_3 concentration of 1×10^{12} molecules cm^{-3} (Singh et al., 1978).

g - S-UV = Static system, ultraviolet absorption.

NR- Not Reported

The initial step in the reaction of vinyl chloride with hydroxyl radicals proceeds by the addition of hydroxyl radical to the carbon-carbon double bond. Although subsequent steps in the reaction mechanism are unknown, reaction products have been identified (Atkinson, 1986b). The major product resulting from hydroxyl radical attack on vinyl chloride is formyl chloride (HCOCl). Within the experimental error of two independent studies, the reaction of one molecule of vinyl chloride with hydroxyl radicals was demonstrated to yield one molecule of formyl chloride (Pitts et al., 1984, Tuazon et al., 1988). An ARB sponsored study demonstrated that the yield of formyl chloride from the reaction of hydroxyl radicals with vinyl chloride is unity (one molecule of formyl chloride for each molecule of vinyl chloride) within the experimental error of the study (Pitts et al., 1984). The

observed unit yield of formyl chloride implies a corresponding unit yield of formaldehyde (HCHO) and shows that the reaction of vinyl chloride with hydroxyl radicals proceeds by essentially 100 percent cleavage of the double bond. Equations (2) through (6) summarize the overall reaction scheme which seems most likely (Pitts et al., 1984).

$$OH + CH_2{=}CHCl \longrightarrow HOCH_2CHCl \quad (2)$$

$$HOCH_2CHCl \xrightarrow{O_2} HOCH_2\underset{\displaystyle O\text{-}O^{\cdot}}{\underset{|}{C}}HCl \quad (3)$$

$$HOCH_2\underset{\displaystyle O\text{-}O^{\cdot}}{\underset{|}{C}}HCl + NO \longrightarrow HOCH_2\underset{\displaystyle O\text{-}O^{\cdot}}{\underset{|}{C}}HCl + NO_2 \quad 4)$$

$$HOCH_2\underset{\displaystyle O^{\cdot}}{\underset{|}{C}}HCl \longrightarrow CH_2OH + HCOCl \quad (5)$$

$$CH_2OH + O_2 \longrightarrow HCHO + HO_2 \quad (6)$$

This reaction was confirmed in a study by Tuazon, et al. (Tuazon, et al., 1988).

Under atmospheric conditions, the reaction of vinyl chloride with ozone is not expected to be important compared to its reaction with hydroxyl radicals (Atkinson, 1986a; Atkinson and Carter, 1984). Several rate constant estimates have been made for the reaction of vinyl chloride with ozone. Based on these rate constants, atmospheric lifetime estimates range from about 47 days to approximately 5 years (Zhang et al., 1983; Sanhueza et al., 1976). Table IV-2 summarizes the atmospheric lifetime and rate constant estimates along with other pertinent information for vinyl chloride's reaction with ozone. Due to the variability among the estimated rate constants, a review publication made no recommendations as to the rate constant for the reaction of vinyl chloride with ozone (Atkinson and Carter, 1984). Furthermore, because the reaction of ozone with vinyl chloride can be complicated by secondary reactions, the rate constants provided in Table IV-2 should be considered to be upper bound limits.

Products resulting from the reaction of ozone with vinyl chloride in the absence of scavengers are formyl chloride and formic acid (HCOOH) (Zhang et. al., 1983). Other products resulting from the reaction of ozone with vinyl chloride include carbon monoxide, carbon dioxide, formaldehyde, and hydrochloric acid (Gay et al., 1976; Zhang et al., 1983).

A relative rate technique was recently employed to obtain a rate constant for the gas-phase reaction of vinyl chloride and the nitrate (NO_3) radical (Atkinson, et al., 1987). The rate constant ratio of k(NO_3+ vinyl chloride)/ k(NO_3+ ethene) at 298 $\pm$ 2°K is 2.08 $\pm$ 0.09 with the room temperature rate constant for the reaction of the nitrate radical with ethene

($CH_2=CH_2$) is 2.1 X 10^{-16} cm^3 $molecule^{-1}$ $second^{-1}$. Combining the two measured rates leads to a rate constant of 4.4 X 10^{-16} cm^3 $molecule^{-1}$ $second^{-1}$ at 298 ± 2°K for k(NO_3+ vinyl chloride). The measured average lower tropospheric nitrate radical concentration over continental areas ranges from less than 1 ppt to 430 ppt (Atkinson, et al., 1986). Assuming an average value of 10 ppt (2.4 X 10^8 molecule cm^{-3}) ± 10 would give a vinyl chloride lifetime of 220 days with respect to reactions with the nitrate radical.

As stated, the most important atmospheric removal mechanism for vinyl chloride is its daytime reaction with hydroxyl radicals. Vinyl chloride does not absorb in the actinic ultraviolet region, hence photolysis need not be considered.

Little is known about the formation of vinyl chloride in the atmosphere. However, under experimental conditions, vinyl chloride has been shown to be a photodissociation product of 1,2-dichloroethane (CH_2ClCH_2Cl) (Yano and Tschulkaw-Roux, 1980). In the study, 1,2-dichloroethane photodissociated when irradiated with ultraviolet light at 147 nanometers (nm) under pressure and in the presence of nitrous oxide (NO) and carbon tetrafluoride (CF_4) additives. Although it was not the purpose of the study to identify vinyl chloride formation pathways, vinyl chloride was one of the photodissociation products. Since wavelengths of ultraviolet light below 290 nm do not reach the troposphere, this formation pathway is not important for vinyl chloride in the atmosphere.

REFERENCES TO CHAPTER IV

Atkinson, R., 1986. Personal communication between Richard Corey of ARB Staff and Dr. Roger Atkinson of UCR. May, 1986.

Atkinson, R., 1986. "Kinetics and Mechanisms of the Gas-Phase Reactions of the Hydroxyl Radical with Organic Compounds under Atmospheric Conditions." Chemical Reviews., 86:69-201.

Atkinson, R., Aschmann, S.M., and Goodman, M.A., 1987. "Kinetics of the Gas-phase Reactions of NO_3 Radicals with a Series of Alkynes, Haloalkenes, and alpha, beta-Unsaturated Aldehydes," International Journal of Chemical Kinetics, Vol.19, 299-307.

Atkinson, R. and Carter, W.P.L., 1984. "Kinetics and Mechanisms of the Gas-Phase Reactions of Ozone with Organic Compounds under Atmospheric Conditions," Chemical Reviews., 84:437-470.

Cox, R.A.; Derwent, R.G.; Eggleton, A.E.J.; Lovelock, J.E., 1976. "Photochemical Oxidation of Halocarbons in the Troposphere," Atmospheric Environment, 10: 305-308.

CRC Handbook of Chemistry and Physics, 1985. 66th Edition.

Cupitt, L.T., 1980. "Fate of Toxic and Hazardous Materials in the Air Environment," Environmental Protection Agency, EPA-600/3-80-084, Research Triangle Park, North Carolina, August 1980.

Davis, D.D., Machado, G., Conaway, B., Oh, Y., Watson, R., 1976. "A Temperature Dependent Kinetics Study of the Reaction of OH with CH_3Cl, CH_2Cl_2.$CHCl_3$, and CH_3Br," Journal of Chemical Physics, 65(4): 1268-1269.

Dilling, W.L., 1977. "Interphase Transfer Processes. II. Evaporation Rates of Chloromethanes, Ethanes, Ethylene Propenes, Propylenes from Dilute Aqueous Solutions, Comparisons with Theoretical Prediction," Environmental Science and Technology, 11(4): 405-409.

Finlayson-Pitts, B.J. and Pitts, Jr., J.N., 1986 "Atmospheric Chemistry: Fundamentals and Experimental Techniques," John Wiley & Sons Inc., 1986.

Gay Jr., B.W., Hanst, P.L., Bufalini, J.J., and Noonan, R.C., 1976. "Atmospheric Oxidation of Chlorinated Ethylenes," Environmental Science and Technology, 10(1):58-67.

Hewitt, C.N. and Harrison, R.M., 1985. "Tropospheric Concentrations of the Hydroxyl Radical - A Review," Atmospheric Environment, 19(4): 545-554.

Howard, C.J., 1976. "Rate Constants for the Gas-Phase Reaction of OH Radicals with Ethylene and Halogenated Ethylene Compounds," Journal of Chemical Physics, 65(11):4771-4777.

IARC,. 1979. Vinyl Chloride, Polyvinyl Chloride and Vinyl Chloride-Vinyl Acetate Copolymers. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 19:377-438.

Kirk-Othmer, 1980. Encyclopedia of Chemical Technology. 3rd Edition, Volume 23. John Wiley and Sons, Inc., New York.

Lillian, D., Singh, H.B., Appleby, A., Lobban, L., Arnts, R., Gumpert, R., Hague, R., Toomey, J., Kazazis, J., Anteil, M., Hansen, D., Scott, B., 1975. "Atmospheric Fates of Halogenated Compounds," Environmental Science and Technology, 9(12): 1042-1048.

Liu, A., Mulac, W.A., and Jonah, C.D., 1989. "Pulse Radiolysis Study of the Gas-phase Reaction of OH Radicals with Vinyl Chloride at 1 Atm. and over the Temperature Range 313-1173°K," Journal of Physical Chemistry, Vol. 93, 4092-4094.

McConnell, G.; Ferguson, D.M.; Pearson, C.R., 1975. "Chlorinated Hydrocarbons and the Environment," Endeavour, 34 (121): 13-18.

Merck Index, 1983. An Encyclopedia of Chemical Drugs, and Biologicals, Tenth Edition, Merck & Co., Inc.

Perry, R.A., Atkinson, R., Pitts, J.N., Jr., 1977. "Rate Constants for the Reaction of OH Radicals with CH_2=CHF, CH_2=CHCl, and CH_2=CHBr over the Temperature Range 299 - 426°K," Journal of Chemical Physics, 67(2): 458-462.

Pitts, J.N., Jr., Atkinson, R., Winer, A., 1984. "Formation and Fate of Toxic Chemicals in California Atmosphere," Final Report to California Air Resources Board Contract No. A2-115-32.

Prinn, R., Cunnold, D., Rasmussen, R., Simmonds, P., Alyea, F., Crawford, A., Fraser, P., Rosen, R., 1987. "Atmospheric Trends in Methylchloroform and the Global Average for the Hydroxyl Radical" Science, 238(13): 945-950.

Sanhueza, E., Hisatsune, I.C., Heicklen, J., 1976. "Oxidation of Haloethylenes," Chemical Reviews, 76(6): 801-826.

Singh, H.B., Ludwig, F.L., Johnson, W.B., 1978. "Tropospheric Ozone: Concentrations and Variabilities in Clean, Remote Atmospheres," Atmospheric Environment, 12: 2185.

Singh, H.B.; Salas, L.J.; Stiles, R.E., 1983. "Selected Man-made Halogenated Chemicals in the Air and Oceanic Environment," Journal of Geophysical Research, 88(C6): 3675-3683.

Tuazon, E.C., Atkinson, R., Aschmann, S.M., Goodman, M.A., and Winer, A.M., 1988. "Atmospheric Reactions of Chloroethene with the OH Radical," International Journal of Chemical Kinetics, Vol.20, 241-265.

U.S. EPA,1 1974, "Preliminary Assessment of the Environmental Problem Associated with Vinyl Chloride and Polyvinyl Chloride," Office of Toxic Substances, Washington, D.C., EPA/560/4-74-001.

Winer, A., 1987. Personal communication between Richard Corey of ARB staff and Arthur Winer of UCR. October, 1987.

Withey, J.R., 1976. "Pharmacodynamics and Update of Vinyl Chloride Monomer Administered by Various Routes to Rates," Journal of Toxicology and Environmental Health, 1: 381-394.

Yano, T. and Tschulkaw-Roux, E., 1980. "A Reexamination of the Photodissociation of CH_2ClCH_2Cl at 147 nm. Test for Chlorine Atom Reactions," Journal of Physical Chemistry, 84(25):3372-3377.

Zhang, J.; Hatakeyama, S.; Akimoto, H., 1983. "Rate Constants of the Reaction of Ozone with Trans-1, 2-Dichloroethene and Vinyl Chloride in Air," International Journal of Chemical Kinetics, 15:655-668.

C. DRINKING WATER

The relative contribution of drinking water to daily exposures of vinyl chloride appears to be insignificant. The average concentration of vinyl chloride in drinking water is estimated to be below the limit of detection (0.5 ppb or 0.5 ug/l).

D. ASSUMPTIONS

Some of the assumptions used for making the daily dose estimates from different environmental media are:

1. The average person ingests 2 liters of drinking water per day;

2. The average person inhales an average of 20 cubic meters of air daily;

3. Dermal exposure is negligible; and

4. 100% of the pollutant ingested or inhaled is absorbed.

Table 1: Estimated Doses Of Vinyl Chloride Exposure Through Different Media

Media	Daily Dose	Refs.
AIR		
Indoor Air		
Homes not near landfills	less than 11 ug	Pellizzari et al., 1989
Homes near landfills	up to 2600 ug	SCAQMD, 1982
FOOD		
Including beverages	less than 0.025 ug	FDA, 1986
WATER-DRINKING PURPOSES		
Surface/Ground Water	less than 1 ug	CDHS, 1986; 1987

APPENDIX A - INDOOR AIR EXPOSURE

Prediction of health risk from pollutants depends upon knowledge of total personal exposure to the pollutants. For direct exposure to air pollutants, the dose of pollutant received through the respiratory system is the basic quantity needed for risk assessment. In general, that dose depends on: a) the pollutant concentration in the environment occupied by an individual (exposure concentration); b) the length of time spent in that environment (exposure duration); c) the rate of breathing in that environment; and d) other physiological factors. Exposure through air can be estimated by using only the first two parameters, exposure concentration and exposure duration.

Historically, outdoor air concentrations of an air pollutant have been used as a surrogate for estimating personal air exposure. However, studies of indoor environments and of personal exposures to pollutants have revealed that indoor concentrations of some pollutants are regularly higher than outdoor concentrations of those pollutants. In addition, human time-activity pattern studies show that people spend most of their time in non-outdoor microenvironments such as in their homes, work places, transportation vehicles and public buildings. On the average, people spend 80-90 percent of their time indoors.

The California Legislature recognizes the importance to risk assessment of considering both indoor air exposure and outdoor air exposure. The current statute requires the Board, when identifying toxic air contaminants, to assess exposures in indoor, as well as outdoor, environments (H&SC Sec. 39660.5). This combined indoor plus outdoor, or total air, exposure assessment permits more accurate public health risk estimates for airborne toxics. Indoor air exposure information can also provide direction for the control of many toxic air contaminants.

An even more realistic estimate of total air exposure would be the sum of the products of the pollutant concentration in each microenvironment and the fraction of time people spend in that microenvironment. However, time-activity and indoor/personal monitoring data are limited and insufficient at this time for quantifying the concentration of most air pollutants in each microenvironment. Based on this limited database, indoor air exposure assessment of most of the toxic air contaminants will be crude estimates.

Risk assessments, based only on outdoor air concentrations, may greatly underestimate health risk to the public. For some pollutants present in high concentrations indoors, ventilation with clean air is the only feasible method of reducing exposure. The Board must, therefore, manage outdoor concentrations of toxic air contaminants, not only to reduce significant outdoor exposures where they occur, but also to preserve a clean air supply for controlling indoor exposure to these substances.

APPENDIX B - TOTAL EXPOSURE FROM ALL MEDIA

The concentrations of some pollutants have been measured in different environmental media such as air, water, food, pesticides and drugs. Ideally, these measurements can be integrated to estimate the total exposure to those pollutants through all the environmental media. Total exposure data are critical for setting priorities and formulating regulatory actions that can best achieve overall personal risk reduction.

While one of the main objectives of this report is to define exposure through the air medium, personal exposure data through other media are also included. Exposure data are presented according to three basic routes of exposure which are inhalation, ingestion, and skin absorption.

The combination of exposure data from all media will allow the determination of the total human exposure to a toxic air contaminant through the environment. To determine the added risk caused by a particular exposure, both the shape of the dose-response curve and the previously existing exposure level must be known. Although the exposure through a particular medium may be small, its addition to exposures through other media could provide a total dose in excess of a postulated "safe level".

In addition, the pathway of pollutants in the environment is dynamic and complex. Pollutants emitted into the environment in one medium can remain in that medium, transfer to another medium, and/or disperse into a number of media. This results in different routes of exposure. For example, solvents emitted as water pollutants can become airborne and cause exposure through inhalation. Airborne lead particles can be deposit onto food and result in exposure through ingestion. Thus, inclusion of exposure through all media will provide a more accurate exposure estimate for each route of exposure, including inhalation, which is the Board's primary concern.

Documenting exposure to toxic substances through different media can serve as a stimulus for coordinated risk reduction efforts among different regulatory agencies. Other regulatory agencies are more likely to increase their efforts in reducing the overall exposure through other media if they are made aware of such exposure data.

REFERENCES:

ARB (Air Resources Board) 1989. Staff report on reducing exposures to indoor air pollutants in California: existing authorities and recommended actions.

ARB (1987). Staff report on indoor air quality and personal exposure--briefing paper.

CDHS (Calif. Dept. of Health Services) 1987. Status report- AB1803 small system program: Summary of results.

CDHS (1986). Final report on a monitoring program for organic chemical contamination of large public water systems in California.

Coy (1987). Personal communication between Richard Corey of ARB staff and Carol Coy of SCAQMD. February 10, 1987.

FDA (Food and Drug Administration) 1986. Proposed uses of vinyl chloride polymers by the Food and Drug Administration-Proposed rule. Federal Register 51(22):4177-4188.

Girman, JR, J Wesolowski and P Jenkins (1987). The role of total exposure in air pollution control strategies. In: Indoor Air '87 Volume 3--Developing countries, guaranteeing adequate indoor air quality, control measures, ventilation effectiveness, thermal control and comfort, policy and strategies. West Berlin, Germany, pp.515-520.

Hoffmann D, C Patrianakos and KD Brunnemann (1976). Chromatographic determination of vinyl chloride in tobacco smoke. Analytical Chem. 48(1):47-50.

IARC (International Agency for Research on Cancer) 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans-some monomers, plastics and synthetic elastomers and acrolein. Volume 19. IARC, World Health Organization.

IARC 1985. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans-tobacco smoking. Volume 38. IARC, World Health Organization.

Molton, PM, RT Hallen and JW Pyne (1987). Study of vinyl chloride formation at landfill sites in California. Battelle, Pacific Northwest Laboratories report prepared for the California Air Resources Board, Contract No. A4-154-32.

Pellizzari, ED (1987). Personal communication between Steve Hui of ARB staff and Dr. E. D. Pellizzari of Research Triangle Institute on 12/28/1987.

Pellizzari, ED et al. (1986). Comparison of indoor and outdoor residential levels of volatile organic chemicals in five U.S. geographical areas. Environ. International 12:619-623.

Pellizzari, ED et al. (1989) Development and implementation of exposure assessment procedures for toxic air pollutants in several Los Angeles county, CA community. Research Triangle Institute.

SCAQMD (South Coast Air Quality Management District) 1982. Vinyl chloride in the South Coast Air Basin. Report by the South Coast Air Quality Management district.

SCAQMD (1985a). Letter from Edward Camarena of the South Coast Air Quality Management district to Angelo Bellomo of the California Department of Health Services on 1/5/1985.

SCAQMD (1985b). Internal Memorandum between S. Levy and Edward Camarena of the South Coast Air Quality Management district on 9/18/1985.

Sharrp (1987). Personal communication between Steve Hui of ARB staff and Chris Sharrp, staff of California Department of Health Services on 12/12/1987.

Wallace, LA (1987). The total exposure assessment methodology (TEAM) study: Summary and Analysis: Vol. I Final Report. (EPA/600/6-87/002a)

Wallace, LA and CA Clayton (1987). Volatile organic compounds in 600 US Homes: Major sources of personal exposure. In: Indoor Air '87, Volume 1--Volatile organic compounds, combustion gases, particles and fibers, microbiological agents. Berlin, West Germany, pp.183-187.

Wallace, LA et al. (1984). Personal exposures to volatile organic compounds-1. Direct measurements in breath-zone air, drinking water, food, and exhaled breath. Environ. Research 35(10):293-319.

Wallace, LA et al. (1986). TEAM study: Personal exposures, indoor-outdoor relationships, and breath levels of volatile compounds in New Jersey. Environ. International 12:369-387.

Wheeler, RN (1981). Poly(vinyl chloride) processes and products. Environ. Health Perspective 41:123-128.

Wood, JA and ML Porter (1987). Hazardous pollutants in class II landfills. JAPCA 37(5):609-615.

U.S. EPA (Environmental Protection Agency) 1976. Sampling of automobile interiors for vinyl chloride monomer. EPA-600/2-76-124.

U.S. EPA (1977). Organic emissions from automobile interiors. EPA-600/7-77-149.

U.S. EPA (1987a). The total exposure assessment methodology (TEAM) study: Elizabeth and Bayonne,New Jersey, Devils Lake, North Dakota and Greensboro, North Carolina: Vol. II Part 1&2, Final Report. (EPA/600/6-87/002b)

U.S. EPA (1987b). The total exposure assessment methodology (TEAM) study: Selected communities in northern and southern California: Vol. III, Final Report. (EPA/600/6-87/002c)

APPENDIX IV

INFORMATION REQUEST LETTER WITH ATTACHMENTS AND RESPONSES

ATE OF CALIFORNIA
IR RESOURCES BOARD
02 Q STREET
). BOX 2815
CRAMENTO, CA 95812

GEORGE DEUKMEJIAN, Governor

April 4, 1985

Dear Sir or Madam:

Subject: Request for Information Regarding Vinyl Chloride

I am writing to request information on the health effects of vinyl chloride as part of our toxic air contaminant program. This program is based on Health and Safety Code Sections 39650, et seq. which require the ARB to identify compounds as toxic air contaminants and once identified to develop and adopt control measures for such compounds. After consultation with the staff of the Department of Health Services (DHS), we have selected vinyl chloride as a candidate toxic air contaminant to be evaluated in accordance with the provisions of Health and Safety Code Sections 39650, et seq. During our evaluation of vinyl chloride, we will consider all available health information regarding this compound. Additionally, we are soliciting information regarding possible biological production of vinyl chloride.

Before the ARB can formally identify a compound as a toxic air contaminant, several steps must be taken. First, the ARB must request the Department of Health Services to evaluate the health effects of candidate compounds. Second, the ARB staff must prepare a report which includes the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted in response to this request will be considered in the ARB report to the Panel. Although any person may also submit information directly to the Panel for its consideration, I urge you to submit all information at this time for our consideration in the development of the report for the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Last, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the Air Resources Board and will be the basis for any regulatory action by the Board officially to identify a compound as a toxic air contaminant.

Prior to formally requesting the DHS to prepare a health effects evaluation of vinyl chloride, we are providing, pursuant to the provisions of

Section 39660(e) of the Health and Safety Code, an opportunity to interested parties to submit information on the health effects of vinyl chloride which he or she believes would be important in DHS's evaluation of vinyl chloride as a candidate toxic air contaminant.

In March 1985, we received a reference search on vinyl chloride health effects using the MEDLINE and TOXLINE Information Services. These information services include material available to the public in late 1984. The attached bibliography lists the references from this information search. We are requesting pertinent information on vinyl chloride health effects, including any material that may not be available to the public, that is not included in the attached bibliography.

Pursuant to the provisions of the Public Records Act (Government Code Sections 6280 et seq.), the information you provide will be a public record and subject to public disclosure, except for trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law. The information may also be released to the Environmental Protection Agency, which protects trade secrets and confidential information in accordance with federal law, and to other public agencies, which are also required to protect such information.

To expedite the review process, we ask that any information which you believe should be regarded as "trade secret" be clearly marked and separated from other information. You may identify portions of the information you submit as "trade secret" in accordance with Health and Safety Code Section 39660(e). The claim of trade secrecy must be supported upon the request of the Air Resources Board. Other information claimed to be trade secret and information otherwise claimed to be exempt from disclosure may be identified as confidential in accordance with Section 91011, Title 17, California Administrative Code. Section 91011 requires that the claim of confidentiality be accompanied by specified supporting information.

I would appreciate receiving any relevant information you wish to submit by May 19, 1985. Your help in expediting our review will be greatly appreciated. Please send the information to the attention of:

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Vinyl Chloride
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have any further questions regarding health effects information, please contact Mr. John Batchelder at (916) 323-1505. For any other questions, please contact Mr. Don Ames at (916) 322-8285.

If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate compounds, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

for Peter D. Venturini, Chief
Stationary Source Division

cc: Alex Kelter, DHS
Lori Johnston, DFA
Wayne Morgan, President, CAPCOA
Jan Bush, Executive Secretary, CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Sally Tanner, Chairwoman, Committee on Toxic Materials
Senator Ralph Dills, Chairman, Committee on Governmental Organization
Senator Art Torres, Chairman, Committee on Toxics and Public Safety Management
Emil Mrak, Chairman and Scientific Review Panel Members
APCOs

Attachment

Vinyl Chloride Refs. (3/1/85)

1. Anderson, D. (1982) The predictability of bioassays.. Prog Clin Biol Res. 109:149-68.

2. Anderson, D. and Richardson, C. R. (1981) Issues relevant to the assessment of chemically induced chromosome damage in vivo and their relationship to chemical mutagenesis.. Mutat Res. 90(3):261-72.

3. Anderson, D., Richardson, C. R., Purchase, I. F., Evans, H. J. and O'Riordan, M. L. (1981) Chromosomal analysis in vinyl chloride exposed workers: comparison of the standard technique with the sister-chromatid exchange technique.. Mutat Res. 83(1):137-44.

4. Anderson, M. W., Hoel, D. G. and Kaplan, N. L. (1980) A general scheme for the incorporation of pharmacokinetics in low-dose risk estimation for chemical carcinogenesis: example--vinyl chloride.. Toxicol Appl Pharmacol. 55(1):154-61.

5. Anon (1980) The Carcinogenicity of Vinyl Chloride and Related Compounds (NTIS/PB80-922904). Govt Reports Announcements & Index (GRA&I),. 11.

6. Anonymous (1976) Editorial: Vinyl chloride: the carcinogenic risk.. Br Med J . 2 (6028) :p134-5.

7. Antweiler, H. (1976) Studies on the metabolism of vinyl chloride.. Environ Health Perspect . 17:p217-9.

8. Apfeldorf, R. and Infante, P. F. (1981) Review of epidemiologic study results of vinyl chloride-related compounds.. Environ Health Perspect. 41:221-6.

9. Bahlman, L. J., Alexander, V., Infante, P. F., Wagoner, J. K., Lane, J. M. and Bingham, E. (1979) Vinyl halides: carcinogenicity. Vinyl bromide, vinyl chloride, and vinylidene chloride.. Am Ind Hyg Assoc J. 40(4):A30,32,34.

10. Barbin, A., Bartsch, H., Leconte, P. and Radman, M. (1981) Studies on the miscoding properties of 1,N6-ethenoadenine and 3,N4-ethenocytosine, DNA reaction products of vinyl chloride metabolites, during in vitro DNA synthesis.. Nucleic Acids Res. 9(2):375-87.

11. BARTSCH, H. (1976) MUTAGENICITY TESTS IN CHEMICAL CARCINOGENESIS. IARC(INT AGENCY RES CANCER)SCI PUBL. 13:229-240.

12. BARTSCH, H., MALAVEILLE, C., BARBIN, A., PLANCHE, G. and MONTESANO, R. (1976) ALKYLATING AND MUTAGENIC METABOLITES OF HALOGENATED OLEFINS PRODUCED BY HUMAN AND ANIMAL TISSUES. PROC AM ASSOC CANCER RES. 17:17.

13. Bartsch, H., Malaveille, C., Camus, A. M., Martel-Planche, G., Brun, G., Hautefeuille, A., Sabadie, N., Barbin, A., Kuroki, T., Drevon, C., Piccoli, C. and Montesano, R. (1980) Validation and comparative studies on 180 chemicals with S. typhimurium strains and V79 Chinese hamster cells in the presence of various metabolizing systems.. Mutat Res. 76(1):1-50.

14. Bartsch, H. and Montesano, R. (1975) Mutagenic and carcinogenic effects of vinyl chloride.. Mutat Res . 32 (2):p93-114.

15. BARTSCH, H., TOMATIS, L. and MALAVEILLE, C. (1982) QUALITATIVE AND QUANTITATIVE COMPARISONS BETWEEN MUTAGENIC AND CARCINOGENIC ACTIVITIES OF CHEMICALS. MUTAGEN:NEW

16. Basler, A. and R:ohrborn, G. (1980) Vinyl chloride: an example for evaluating mutagenic effects in mammals in vivo after exposure to inhalation.. Arch Toxicol. 45(1):1-7.

17. Becker, C. E. and Coye, M. J. (1984) Recent advances in occupational cancer.. J Toxicol Clin Toxicol. 22(3):195-208.

18. Bingham, E. and Lane, J. M. (1980) Vinyl halides -- carcinogenicity.. Vet Hum Toxicol. 22(1):31-3.

19. Bolt, H. M. (1978) Pharmacokinetics of vinyl chloride.. Gen Pharmacol . 9 (2):p91-5.

20. Bolt, H. M., Filser, J. G. and Buchter, A. (1981) Inhalation pharmacokinetics based on gas uptake studies. III. A pharmacokinetic assessment in man of "peak concentrations: of vinyl chloride.. Arch Toxicol. 48(4):213-28.

21. BOLT, H. M., FILSER, J. G., LAIB, R. J. and OTTENWAELDER, H. (1980) BINDING KINETICS OF VINYL CHLORIDE AND VINYL BROMIDE AT VERY LOW DOSES, IN: QUANTITATIVE ASPECTS OF RISK ASSESSMENT IN CHEMICAL CARCINOGENESIS. ARCH TOXICOL SUPPL. 3:129-142.

22. Bolt, H. M., Laib, R. J., Kappus, H. and Buchter, A. (1977) Pharmacokinetics of vinyl chloride in the rat.. Toxicology . 7 (2):p179-88.

23. Brand, K. G., Buoen, L. C. and Brand, I. (1975) Foreign-body tumorigenesis by vinyl chloride vinyl acetate copolymer: no evidence for chemical cocarcinogenesis.. J Natl Cancer Inst . 54 (5) :p1259-62.

24. BRAUN, R., SCHOENEICH, J., LEGATOR, M. S., MCGREGOR, D. B. and MOHN, G. R. (1981) MUTAGENICITY OF SELECTED CHEMICALS IN THE HOST-MEDIATED ASSAY, IN: COMPARATIVE CHEMICAL MUTAGENESIS. ENVIRON SCI RES. 24:353-392.

25. Buchter, A., Filser, J. G., Peter, H. and Bolt, H. M. (1980) Pharmacokinetics of vinyl chloride in the Rhesus monkey.. Toxicol Lett . 6 (1):p33-6.

26. Byczkowska, Z. (1982) [Carcinogenicity of vinyl chloride]. Pol Tyg Lek (POLAND) 37 (3) :p95-7.

27. California Air Resources Board (1977) Effects of airborne vinyl chloride. ARB Staff Report# 78-1-1. 127pp.

28. Chu, K. C. and Milman, H. A. (1981) Review of experimental carcinogenesis by compounds related to vinyl chloride.. Environ Health Perspect. 41:211-20.

29. Clemmesen, J. (1982) International Commission for Protection against Environmental Mutagens and Carcinogens. ICPEMC working paper TG1/2/79. Mutagenicity and teratogenicity of vinyl chloride monomer (VCM): epidemiological evidence.. Mutat Res. 98(1):97-100.

30. Collins, B. (1982) Models for the pharmacokinetics of vinyl chloride [letter]. Toxicol Appl Pharmacol (UNITED STATES) . 64 (2) :p362-3.

31. Coustou, F. (1979) Carcinogenic risk of products used in the pharmaceutical and related industries.. IARC Sci Publ . (25) :p129-49.

32. Crump, K. S., Guess, H. A. and Deal, K. L. (1977) Confidence intervals and test of hypotheses concerning dose response relations inferred from animal carcinogenicity data.. Biometrics . 33 (3):p437-51.

33. Dannaher, C. L., Tamburro, C. H. and Yam, L. T. (1981) Occupational carcinogenesis: the Louisville experience with vinyl chloride-associated hepatic angiosarcoma.. Am J Med. 70(2):279-87.

34. DEAN, B. J., ANDERSON, D. and SRAM, R. J. (1981) MUTAGENICITY OF SELECTED CHEMICALS IN THE MAMMALIAN DOMINANT LETHAL ASSAY, IN: COMPARATIVE CHEMICAL MUTAGENESIS. ENVIRON SCI RES. 24:487-538.

35. Delorme, F. (1978) [Association of angiosarcoma of the liver and hepatoma in vinyl chloride worker]. Ann Anat Pathol (Paris) . 23 (2) :p105-14.

36. de Meester, C., Duverger-van Bogaert, M., Lambotte-Vandepaer, M., Roberfroid, M., Poncelet, F. and Mercier, M. (1980) Mutagenicity of vinyl chloride in the Ames test: possible artifacts related to experimental conditions.. Mutat Res. 77(2):175-9.

37. de Meester, C., Poncelet, F., Roberfroid, M. and Mercier, M. (1979) Vinyl chloride: direct or indirect mutagen [proceedings]. Arch Int Physiol Biochim . 87 (3) :p620-1.

38. Dietz, F. K., Ramsey, J. C. and Watanabe, P. G. (1983) Relevance of experimental studies to human risk.. Environ Health Perspect. 52:9-14.

39. Dietz, F. K., Reitz, R. H., Watanabe, P. G. and Gehring, P. J. (1981) Translation of pharmacokinetic/biochemical data into risk assessment.. Adv Exp Med Biol. 136 Pt B:1399-424.

40. Doss, M., Lange, C. E. and Veltman, G. (1984) Vinyl chloride-induced hepatic coproporphyrinuria with transition to chronic hepatic porphyria.. Klin Wochenschr. 62(4):175-8.

41. Drew, R. T., Boorman, G. A., Haseman, J. K., McConnell, E. E., Busey, W. M. and Moore, J. A. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters.. Toxicol Appl Pharmacol. 68(1):120-30.

42. Duverger, M., Lambotte, M., Malvoisin, E., de Meester, C., Poncelet, F. and Mercier, M. (1981) Metabolic activation and mutagenicity of 4 vinylic monomers (vinyl chloride, styrene, acrylonitrile, butadiene).. Toxicol Eur Res. 3(3):131-40.

43. Duverger-Van Bogaert, M., Lambotte-Vandepaer, M., De Meester, C., Mercier, M. and Poncelet, F. (1982) Vinyl chloride and acrylonitrile: activation mechanism and mutagenicity.. Toxicol Eur Res. 4(1):35-7.

44. ECKARDT, F., DE, R. U. I. T. E. R. N. and OTTENWAELDER, H. (1980) MUTAGENICITY OF VINYL CHLORIDE IN VITRO AND IN VIVO WITH YEAST AS INDICATOR ORGANISM. NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL. 311(SUPPL):R23.

45. Elmore, J. D., Wong, J. L., Laumbach, A. D. and Streips, U. N. (1976) Vinyl chloride mutagenicity via the metabolites chlorooxirane and chloroacetaldehyde monomer hydrate.. Biochim Biophys Acta . 442 (3) :p405-19.

46. Evans, D. M., Williams, W. J. and Kung, I. T. (1983) Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers.. Histopathology. 7(3):377-88.

47. Exon, J. H. (1984) The immunotoxicity of selected environmental chemicals, pesticides and heavy metals.. Prog Clin Biol Res. 161:355-68.

48. Fabricant, J. D. and Legator, M. S. (1981) Mutagenicity studies of vinyl chloride.. Environ Health Perspect. 41:189-93.

49. Fishbein, L. (1979) Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons.. Sci Total Environ . 11 (2) :p111-61.

50. Fishbein, L. (1976) Industrial mutagens and potential mutagens I. Halogenated aliphatic derivatives.. Mutat Res. 32(3-4):267-307.

51. FLEIG, I. and THIESS, A. M. (1978) MUTAGENICITY OF VINYL CHLORIDE. EXTERNAL CHROMOSOME STUDIES ON PERSONS WITH AND WITHOUT VC ILLNESS AND ON VC EXPOSED ANIMALS. JOM,J OCCUP MED. 20:557-561.

52. Garro, A. J., Guttenplan, J. B. and Milvy, P. (1976) Vinyl chloride dependent mutagensis: effects of liver extracts and free radicals.. Mutat Res . 38 (2) :p81-8.

53. Greenberg, R. A. and Tamburro, C. H. (1981) Exposure indices for epidemiological surveillance of carcinogenic agents in an industrial chemical environment.. J Occup Med. 23(5):353-8.

54. Griciute, L. (1978) The carcinogenicity of vinyl chloride.. IARC Sci Publ . (22):p3-11.

55. Gwinner, L. M., Laib, R. J., Filser, J. G. and Bolt, H. M. (1983) Evidence of chloroethylene oxide being the reactive metabolite of vinyl chloride towards DNA: comparative studies with 2,2'-dichlorodiethylether.. Carcinogenesis. 4(11):1483-6.

56. Haas, J. F. and Schottenfeld, D. (1979) Risks to the offspring from parental occupational exposures.. JOM . 21 (9):p607-13.

57. Hallstrom, I., Sundvall, A., Rannug, U., Grafstrom, R. and Ramel, C. (1981) The metabolism of drugs and carcinogens in isolated subcellular fractions of Drosophila melanogaster. I.Activation of vinyl chloride, 2-aminoanthracene and benzo[a]pyrene as measured by mutagenic effects in Salmonella typhimurium.. Chem Biol Interact . 34 (2) :p129-43.

58. Haseman, J. K., Hoel, D. G. and Jennrich, R. I. (1981) Some practical problems arising from use of the gamma multihit model for risk estimation.. J Toxicol Environ Health. 8(3):379-86.

59. Hathaway, D. E. (1981) Mechanisms of vinyl chloride carcinogenicity/mutagenicity [letter]. Br J Cancer. 44(4):597-600.

60. Hattis, D. (1981) Needs for public health intervention and needs for new research on vinyl halides and their polymers: a public policy perspective.. Environ Health Perspect. 41:227-31.

61. Heath, C. W. J. (1978) Environmental pollutants and the epidemiology of cancer.. Environ Health Perspect . 27 :p7-10.

62. Hehir, R. M., McNamara, B. P., McLaughlin, J. J., Willigan, D. A., Bierbower, G. and Hardisty, J. F. (1981) Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer.. Environ Health Perspect. 41:63-72.

63. Heldaas, S. S., Langard, S. L. and Andersen, A. (1984) Incidence of cancer among vinyl chloride and polyvinyl chloride workers.. Br J Ind Med. 41(1):25-30.

64. Hemminki, K., Lindbohm, M. L., Hemminki, T. and Vainio, H. (1984) Reproductive hazards and plastics industry.. Prog Clin Biol Res. 141:79-87.

65. Hens, L., Verschaeve, L. and Susanne, C. (1978) Mutagenicity of vinyl chloride monomer.. Arch Belg Med Soc. 9(2):91-95.

66. Henschler, D. and Bonse, G. (1977) Metabolic activation of chlorinated ethylenes: dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides.. Arch Toxicol (Berl). 39(1-2):7-12.

67. Henschler, D., Bonse, G. and Dekant, W. (1983) Mechanisms of formation and reactions of electrophilic intermediates of halogenated olefins.. Prog Clin Biol Res. 132B:175-83.

68. Henschler, D., Bonse, G. and Greim, H. (1976) Carcinogenic potential of chlorinated ethylenes tentative molecular rules.. IARC Sci Publ . (13):p171-5.

69. Hernandez Bronchud, M. (1984) Toxic oil syndrome and vinyl chloride disease [letter]. Lancet. 2(8408):931.

70. Himeno, S., Okuda, H. and Suzuki, T. (1983) Lack of dominant lethal effects in male CD-1 mice after short-term and long-term exposures to vinyl chloride monomer.. Toxicol Lett. 16(1-2):47-53.

71. Holmberg, B. (1984) The toxicology of monomers of the polyvinyl plastic series.. Prog Clin Biol Res. 141:99-112.

72. Hong, C. B., Winston, J. M., Thornburg, L. P., Lee, C. C. and WSoods, J. S. (1981) Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent to exposure.. J Toxicol Environ Health. 7(6):909-24.

73. Hopkins, J. (1980) Vinyl chloride--part 5: mutagenicity in man.. Food Cosmet Toxicol. 18(2):200-1.

74. HOPKINS, J. (1979) VINYL CHLORIDE. 2.MUTAGENICITY. FOOD COSMET TOXICOL. 17:542-544.

75. Huberman, E., Bartsch, H. and Sachs, L. (1975) Mutation induction in Chinese hamster V79 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloroacetaldehyde.. Int J Cancer . 16 (4):p639-44.

76. IARC (1974) Some anti-thyroid and related substances, nitrofuran and industrial chemical--vinyl chloride. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 7:291-318.

77. IARC (1979) Some monomers, plastics and synthetic elastomers and acrolein--vinyl chloride, polyvinyl chloride and vinyl chloride-vinyl acetate copolymers. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 19:377-438.

78. Infante, P. F. (1977) Mutagenic and carcinogenic risks associated with halogenated olefins.. Environ Health Perspect . 21 :p251-4.

79. Infante, P. F. (1981) Observations of the site-specific carcinogenicity of vinyl chloride to humans.. Environ Health Perspect. 41:89-94.

80. Infante, P. F., McMichael, A. J., Wagoner, J. K., Waxweiler, R. J. and Falk, H. (1980) Genetic risks of vinyl chloride. Lancet. 1:734-735.

81. Infante, P. F., Wagoner, J. K. and Waxweiler, R. J. (1976) Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride.. Mutat Res . 41 (1 spel. no) :p131-41.

82. J:edrychowski, R. A., Sokal, J. A. and Chmielnicka, J. (1984) Influence of exposure mode on vinyl chloride action. Arch Toxicol. 55(3)p1:195-198.

83. John, J. A., Smith, F. A. and Schwetz, B. A. (1981) Vinyl chloride: inhalation teratology study in mice, rats and rabbits.. Environ Health Perspect. 41:171-7.

84. Kalmaz, E. E. and Kalmaz, G. D. (1984) Carcinogenicity and epidemiological profile analysis of vinyl chloride and polyvinyl chloride.. Regul Toxicol Pharmacol. 4(1):13-27.

85. KILBEY, B. J. (1981) COMPARATIVE MUTAGENICITY OF AFLATOXIN B1 AND VINYL CHLORIDE, IN: COMPARATIVE CHEMICAL MUTAGENESIS. ENVIRON SCI RES. 24:857-882.

86. Koller, L. D. (1980) Public health risks of environmental contaminants: heavy metals and industrial chemicals.. J Am Vet Med Assoc. 176(6):525-9.

87. KUROKI, T., ABBONDANDOLO, A., DREVON, C., HUBERMAN, E. and LAVAL, F. (1980) MUTAGENESIS ASSAYS WITH MAMMALIAN CELLS, IN: LONG-TERM AND SHORT-TERM SCREENING ASSAYS FOR CARCINOGENS: A CRITICAL APPRAISAL. IARC MONOGR SUPPL. 2:107-133.

88. Langauer-Lewowicka, H., Kurzbauer, H., Byczkowska, Z. and Wocka-Marek, T. (1983) Vinyl chloride disease-neurological disturbances.. Int Arch Occup Environ Health. 52(2):151-7.

89. Lassiter, D. V. (1976) Recent approaches to the control of carcinogenic exposures. Case study 3: vinyl chloride--best available technology.. Ann NY Acad Sci . 271:p176-8.

90. Lee, C. C., Bhandari, J. C., Winston, J. M., House, W. B., Dixon, R. L. and Woods, J. S. (1978) Carcinogenicity of vinyl chloride and vinylidene chloride.. J Toxicol Environ Health . 4 (1) :p15-30.

91. Li, F. P. (1977) Clinical studies of cancer etiology.. Cancer . 40 (1 Suppl) :p445-7.

92. Lilis, R. (1981) Review of pulmonary effects of poly(vinyl chloride) and vinyl chloride exposure.. Environ Health Perspect. 41:167-9.

93. Lloyd, M. H., Gauld, S., Copland, L. and Soutar, C. A. (1984) Epidemiological study of the lung function of workers at a factory manufacturing polyvinylchloride.. Br J Ind Med. 41(3):328-33.

94. Loew, G. H., Kurkjian, E. and Rebagliati, M. (1983) Metabolism and relative carcinogenic potency of chloroethylenes: a quantum chemical structure-activity study.. Chem Biol Interact. 43(1):33-66.

95. Loprieno, N., Barale, R., Baroncelli, S., Bauer, C., , Bronzetti G, , Cammellini A, Cercignani, G., Corsi, C., Gervasi, G., Leporini, C., Nieri, R., Rossi, A. M., Stretti, G. and Turchi, G. (1976) Evaluation of the genetic effects induced by vinyl chloride monomer (VCM) under mammalian metabolic activation: studies in vitro and in vivo.. Mutat Res . 40 (2) :p85-96.

96. Louagie, Y. A., Gianello, P., Kestens, P. J., Bonbled, F. and Haot, J. G. (1984) Vinyl chloride-induced hepatic angiosacroma. Br J Surg. 71(4):322-323.

97. Magnusson, J., Hallstrom, I. and Ramel, C. (1979) Studies on metabolic activation of vinyl chloride in Drosophila melanogaster after pretreatment with phenobarbital and polychlorinated biphenyls.. Chem Biol Interact . 24 (3) :p287-98.

98. Makarov, I. A. and Fedotova, I. V. (1983) [Mechanisms of the carcinogenic effects of vinyl chloride (literature review)]. Gig Tr Prof Zabol (USSR) . (6) :p42-5.

99. Maltoni, C. (1977) Recent findings on the carcinogenicity of chlorinated olefins.. Environ Health Perspect . 21:p1-5.

100. Maltoni, C. (1978) Predictive carcinogenicity bioassays in industrial oncogenesis.. Prog Biochem Pharmacol . 14:p47-56.

101. Maltoni, C. (1976) Occupational chemical carcinogenesis: new facts, priorities and perspectives.. IARC Sci Publ (FRANCE) . (13):p127-49.

102. MALTONI, C. (1977) VINYL CHLORIDE CARCINOGENICITY:EXPERIMENTAL MODEL FOR CARCINOGENESIS STUDIES. COLD SPRING HARBOR CONF CELL PROLIFERATION. 4:119-146.

103. MALTONI, C. (1976) CARCINOGENICITY OF VINYL CHLORIDE:CURRENT RESULTS.EXPERIMENTAL EVIDENCE. ADV TUMOR PREV DETECT CHARACT. 3:216-237.

104. Maltoni, C., Ciliberti, A. and Carretti, D. (1982) Experimental contributions in identifying brain potential carcinogens in the petrochemical industry.. Ann NY Acad Sci. 381:216-49.

105. Maltoni, C. and Lefemine, G. (1975) Carcinogenicity bioassays of vinyl chloride: current results.. Ann NY Acad Sci . 246:p195-218.

106. Maltoni, C., Lefemine, G., Ciliberti, A., Cotti, G. and Carretti, D. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis.. Environ Health Perspect. 41:3-29.

107. MOHN, G. R. (1981) MUTAGENICITY OF SELECTED CHEMICALS IN ESCHERICHIA COLI TEST SYSTEMS, IN: COMPARATIVE CHEMICAL MUTAGENESIS. ENVIRON SCI RES. 24:

108. MONTESANO, R. and BARTSCH, H. (1976) MUTAGENICITY AND METABOLISM OF VINYL CHLORIDE. ADV TUMOUR PREV,DETECT CHARACT PROC INT SYMP 5TH(1973). 3:342-245.

109. Nicholson, W. J. (1984) Research issues in occupational and environmental cancer.. Arch Environ Health. 39(3):190-202.

110. Nicholson, W. J. (1977) Cancer following occupational exposure to asbestos-and vinyl chloride.. Cancer . 39 (4 Suppl) :p1792-801.

111. Nicholson, W. J., Henneberger, P. K. and Seidman, H. (1984) Occupational hazards in the VC-PVC industry.. Prog Clin Biol Res. 141:155-75.

112. Nicholson, W. J., Henneberger, P. K. and Tarr, D. (1984) Trends in cancer mortality among workers in the synthetic polymers industry.. Prog Clin Biol Res. 141:65-78.

113. Oesch, F. and Doerjer, G. (1982) Detection of N2,3-ethanoguanine in DNA after treatment with chloroacetaldehyde in vitro.. Carcinogenesis. 3(6):663-5.

114. Oser, J. L. (1980) Extent of industrial exposure to epichlorohydrin, vinyl fluoride, vinyl bromide and ethylene dibromide.. Am Ind Hyg Assoc J. 41(7):463-8.

115. Ottenw:alder, H., Kappus, H. and Bolt, H. M. (1983) Covalent protein binding of vinyl chloride metabolites during co-incubation of freshly isolated hepatocytes and hepatic sinusoidal cells of rats.. Arch Toxicol [Suppl]. 6:266-70.

116. Peter, S. and Ungvary, G. (1980) Lack of mutagenic effect of vinyl chloride monomer in the mammalian spot test.. Mutat Res. 77(2):193-6.

117. Peto, R. (1978) Carcinogenic effects of chronic exposure to very low levels of toxic substances.. Environ Health Perspect . 22 :p155-9.

118. PRESTON, R. J., ADLER I-D, , LEONARD, A. and LYON, M. F. (1981) MUTAGENICITY OF SELECTED CHEMICALS IN IN VIVO CYTOGENETIC ASSAYS, IN: COMPARATIVE CHEMICAL MUTAGENESIS. ENVIRON SCI RES. 24:549-632.

119. Preussmann, R. (1978) Toxicological aspects of food safety - carcinogenicity and mutagenicity.. Arch Toxicol [Suppl] . (1):p69-84.

120. Preussmann, R. (1976) Chemical carcinogens in the human environment; problems and quantitative aspects.. Oncology (Switzerland) . 33 (2):p51-7.

121. Purchase, I. F. (1980) Appraisal of the merits and short comings of tests of mutagenic potential.. Dev Toxicol Environ Sci. 8:105-19. .

122. Radike, M. J., Stemmer, K. L. and Bingham, E. (1981) Effect of ethanol on vinyl chloride carcinogenesis.. Environ Health Perspect. 41:59-62.

123. RANNUG, U. (1978) SHORT-TERM MUTAGENICITY TESTS ON SALMONELLA TYPHIMURIUM. STUDIES ON VINYL CHLORIDE, ETHYLENE DICHLORIDE AND OTHER COMPOUNDS RELATED TO THE VINYL CHLORIDE INDUSTRY. ACTA UNIV UPS ABSTR UPPSALA DISS FAC SCI. 467:38 PP.

124. Rannug, U., Gothe, R. and Wachtmeister, C. A. (1976) The mutagenicity of chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride.. Chem Biol Interact. 12(3-4):251-63.

125. Rice, J. M. (1981) Prenatal susceptibility to carcinogenesis by xenobiotic substances including vinyl chloride.. Environ Health Perspect. 41:179-88.

126. Richardson, C. R., Styles, J. A. and Bennett, I. P. (1983) Activity of vinyl chloride monomer in the mouse micronucleus assay.. Mutat Res. 122(2):139-42.

127. Rinkus, S. J. and Legator, M. S. (1979) Chemical characterization of 465 known or suspected carcinogens and their correlation with mutagenic activity in the Salmonella typhimurium system.. Cancer Res . 39 (9) :p3289-318.

128. Robinson, J. S., Thompson, J. M., Belcher, R. and Stephen, W. I. (1976) Vinyl chloride: the carcinogenic risk [letter].. Br Med J (England) . 2 (6039) :p815.

129. Rowan, C. A., Connolly, W. M. and Brown, H. S. (1984) Evaluating the use of occupational standards for controlling toxic air pollutants.. J Environ Sci Health [B]. 19(7):611-48.

130. Sabadie, N., Malaveille, C., Camus, A. M. and Bartsch, H. (1980) Comparison of the hydroxylation of benzo(a)pyrene with the metabolism of vinyl chloride, N-nitrosomorpholine, and N-nitroso-N'-methylpiperazine to mutagens by human and rat liver microsomal fractions.. Cancer Res. 40(1):119-26.

131. Shubik, P. (1975) Potential carcinogenicity of food additives and contaminants.. Cancer Res . 35 (11 Pt. 2) :p3475-80.

132. Sims, P. (1980) The metabolic activation of chemical carcinogens.. Br Med Bull. 36(1):11-8.

133. Smith, A. H. (1983) Problems in dose response interpretation in occupational epidemiology.. Sangyo Ika Daigaku Zasshi. 5 Suppl:189-95.

134. Smith, A. H., Waxweiler, R. J. and Tyroler, H. A. (1980) Epidemiologic investigation of occupational carcinogenesis using a serially additive expected dose model.. Am J Epidemiol. 112(6):787-97.

135. Spirtas, R., Beebe, G., Baxter, P., Dacey, E., Faber, M., Falk, H., van Kaick, G. and Stafford, J. (1983) Angiosarcoma as a model for comparative carcinogenesis [letter]. Lancet. 2(8347):456.

136. Storetvedt Heldaas, S., Lang~ard, S. L. and Andersen, A. (1984) Incidence of cancer among vinyl chloride and polyvinyl chloride workers.. British Journal of Industrial Medicine . 41(1):25-30.

137. Styles, J. A. (1977) A method for detecting carcinogenic organic chemicals using mammalian cells in culture.. Br J Cancer . 36 (5) :p558-63.

138. Suzuki, Y. (1983) Neoplastic effect of vinyl chloride in mouse lung--lower doses and short-term exposure.. Environ Res. 32(1):91-103.

139. Tamburro, C. H. (1978) Health effects of vinyl chloride.. Tex Rep Biol Med . 37:p126-44.

140. TAMBURRO, C. H. (1978) HEPATIC ROLE IN CARCINOGENESIS AND ITS EARLY DETECTION-THE VINYL CHLORIDE MODEL. YALE J BIOL MED. 51:67-80.

141. Tamburro, C. H. (1984 May) Relationship of vinyl monomers and liver cancers: angiosarcoma and hepatocellular carcinoma.. Semin Liver Dis. 4(2):158-69.

142. Tamburro, C. H. and Greenberg, R. A. (1980) Identification of human toxicity and carcinogenicity by ethylene derivatives.. Dev Toxicol Environ Sci. 8:319-33.

143. Tamburro, C. H., Makk, L. and Popper, H. (1984) Early hepatic histologic alterations among chemical (vinyl monomer) workers.. Hepatology. 4(3):413-8.

144. Th:eriault, G., Iturra, H. and Gingras, S. (1983) Evaluation of the association between birth defects and exposure to ambient vinyl chloride.. Teratology. 27(3):359-70.

145. U.S.E.P.A. (1984) Draft Criteria Document for Vinyl Chloride.(NTIS/PB84-199538). EPA Report. 109pp.

146. U.S.E.P.A. (1981) Ambient Water Quality Criteria for Vinyl Chloride (NTIS/PB81-117889). EPA report. EPA 400/5-80-78:99pp.

147. Ungvary, G., Hudak, A., Tatrai, E., Lorincz, M. and Folly, G. (1978) Effects of vinyl chloride exposure alone and in combination with trypan blue--applied systematically during all thirds of pregnancy on the fetuses of CFY rats.. Toxicology . 11 (1):p45-54.

148. Vainio, H. (1978) Vinyl chloride and vinyl benzene (styrene)--metabolism, mutagenicity and carcinogenicity.. Chem Biol Interact . 22 (1) :p117-24.

149. Van Duuren, B. L. (1975) On the possible mechanism of carcinogenic action of vinyl chloride.. Ann NY Acad Sci . 246:p258-67.

150. Wagoner, J. K. (1983) Toxicity of vinyl chloride and poly(vinyl chloride): a critical review.. Environ Health Perspect. 52:61-6.

151. WAGONER, J. K. and INFANTE, P. F. (1978) QUALITATIVE EXTRAPOLATION FROM LABORATORY ASSAY TO HUMANS AS SEEN THROUGH THE CARCINOGENICITY, MUTAGENICITY OR TERATOGENICITY OF VINYL CHLORIDE AND ANESTHETIC GASES. ENVIRON HEALTH PERSPECT .

152. Wagoner, J. K., Infante, P. F. and Apfeldorf, R. B. (1980) Toxicity of vinyl chloride and polyvinyl chloride as seen through epidemiologic observations.. J Toxicol Environ Health. 6(5-6):1101-7.

153. Watanabe, P. G., Young, J. D. and Gehring, P. J. (1977) The importance of non-linear (dose-dependent) pharmacokinetics in hazard assessment.. J Environ Patho Toxicol. 1(2):147-59.

154. Waters, M. D., Garrett, N. E., Covone-DeSerres, C. M., Howard, B. E. and Stack, H. (1983) Genetic toxicology of some known or suspected human carcinogens. Chem Mutagens:Prin methods their detection. 8:261-341.

155. Withey, J. R. and Collins, B. T. (1976) A statistical assessment of the quantitative uptake of vinyl chloride monomer from aqueous solution.. J Toxicol Environ Health . 2 (2) :p311-21.

156. Zajdela, F., Croisy, A., Barbin, A., Malaveille, C., Tomatis, L. and Bartsch, H. (1980) Carcinogenicity of chloroethylene oxide, an ultimate reactive metabolite of vinyl chloride, and bis(chloromethyl)ether after subcutaneous administration and in initiation-promotion experiments in mice.. Cancer Res. 40(2):352-6.

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The Law and Policy of Toxic Substances Control

A Case Study of Vinyl Chloride

DAVID D. DONIGER

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Natural Resources Defense Council, Inc.
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202-783-7800

To: William V. Loscutoff

From: David D. Doniger

Date: April 10, 1985

Subject: Vinyl Chloride

The attached is in answer to your recent inquiry.

DDD

dards, however, give virtually no guidance on the relative weight to be accorded health and environmental interests in comparison to economic ones, and to date, the agencies' actions reflect Congress's lack of consensus on the issue of acceptable risk.

A measure of guidance to decision makers in the face of uncertainty and lack of consensus is provided by the observation that regulatory decisions involve moral as well as economic values. We may begin with the observation that the sacrifice of an individual for the benefit of a group is acceptable if the benefit served is the group's survival or the fulfillment of some other basic need. The sacrifice is morally unacceptable, however, if it is for no more important benefit than the provision of the luxuries of our consuming society. That some must die so that all can eat is one thing; that some must die so that all can have see-through food packaging is another.[80b] Particularly where non-essential products are concerned, the long-term goal of toxic substances control and the long-term effect of each regulation should be to channel economic growth away from industries hazardous to health and towards safer products and forms of employment.

As the case study in Part II shows, the problems of deciding under uncertainty and of balancing incommensurable interests have pervaded the regulation of VC. Reluctance to face these difficult problems accounts in part for the fact that in more than four years the agencies have set standards for only two of the major sources of exposure to VC. While the standards that have been set and the proposals that have been put forward are by no means totally deficient, there have been significant instances in which the agencies have made factually or logically insupportable conclusions, or in which they have ignored evidence and failed to draw conclusions the evidence virtually demands. In all instances, the agencies have held back from imposing standards that would require any significant economic change in the regulated industries. The industries' profits, volume of production of the regulated substances, and future growth prospects have been virtually unaffected. One may question whether the benefits of VC production and use are substantial enough to justify such extreme deference to the

80b. Many value judgments are not so easily made as the distinction between food and food packaging. Typically, economists take the position that neutrality is required at all times in this regard, because of the difficulty of making so many of these value judgments. *See, e.g.*, *Evaluation of Life and Limb*, *supra* note 74, at 695-96, 703. But the difficulty of making the hard decisions does not require us to avoid making the clearcut ones. And one need not accept the view that the values of a society must be regarded as inviolate. They change in a manner not fully understood, but certainly not free from the influences of groups, such as the business community, with strong financial interests in promoting the materialistic, consuming behavior of the public. As Professor Tribe puts it: "[W]e cannot simply assume that we must stand mute when confronting the ultimate question of whether we want our children, and their children's children, to live in--and *enjoy*--a plastic world." Tribe, *Ways Not to Think About Plastic Trees* in When Values Conflict 61, 70 (L. Tribe, C. Schelling, & J. Voss eds. 1976) (emphasis in original). *See also* Dorfman, *An Afterword: Humane Values and Environmental Decisions*, in *id.* at 153-73.

industries' market position. This question is pursued in the sections that follow, each detailing the regulatory situation with regard to one or more of the many sources of human exposure to VC.

II

VINYL CHLORIDE: CASE STUDY

A. *An Introduction to Vinyl Chloride*

In the previous section the problems of deciding under uncertainty and determining socially acceptable risks were discussed as they apply to toxic substances regulation generally. In this case study, these problems are considered as they have affected agency decision making with respect to the regulation of vinyl chloride. The case study begins with essential background material on the applications of VC, on the industries which create, transform, and use it, and on its deadly properties. Subsection 1 surveys the chemical's uses and the industries associated with them. Subsection 2 surveys VC's toxicity and the sources of human exposure to it.

1. *Vinyl Chloride's Uses and the Associated Industries*

The carcinogen vinyl chloride is the basis of the second most widely used plastic in the United States.[81] VC, a gas, is made from petrochemicals and chlorine. When polymerized into polyvinyl chloride, a solid, it is fabricated into a phenomenal array of products. VC was first manufactured commercially in the United States in 1939;[82] by 1976, VC production exceeded 5.5 billion pounds.[83]

The wide variety of uses of PVC is testimony to its adaptability. The major use of PVC is in construction products; other important uses are packaging and consumer products of all kinds. Figure 1 summarizes the applications of PVC in 1974. Woods, metals, glass, other plastics, and other materials can substitute for nearly all of PVC's uses, but PVC is preferred because of better performance or lower cost.[84] However, there are only a few uses for which no direct substitutes exist.[85]

Several direct uses of VC gas itself once existed, but these have been discontinued. In the late 1940s, VC was tested for use as an anaesthetic, but

81. *See Thermoplastics Poised For a Good Five Years*, Chem. & Eng'g News, Nov. 8, 1976, at 15. Polyethylene is the highest volume plastic. *Id.*

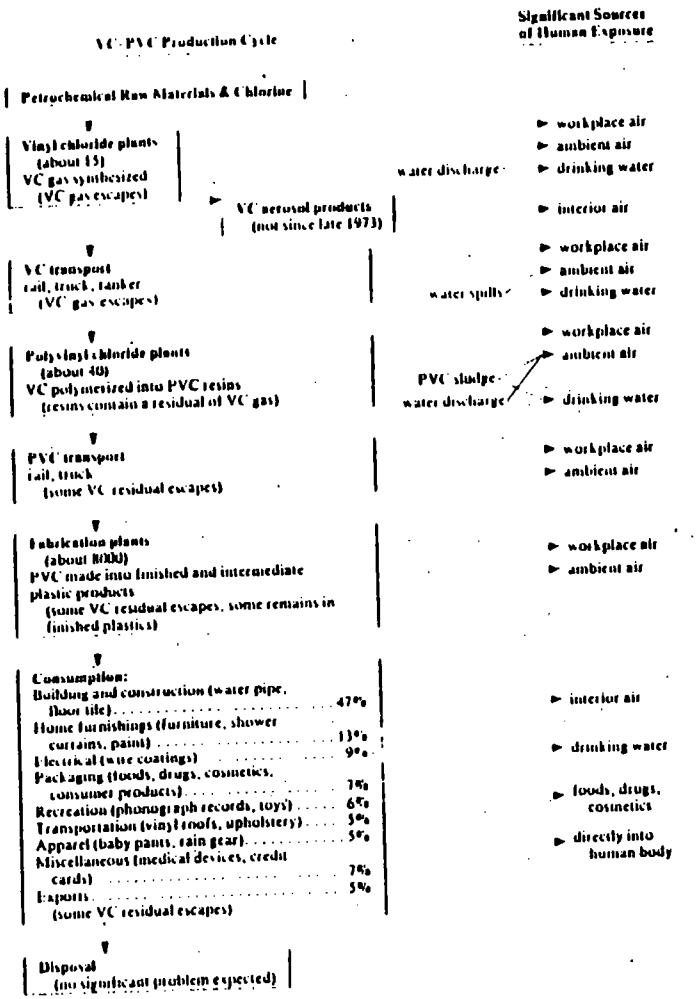
82. *OSHA Permanent Standard for VC*, *supra* note 1, at 35,890.

83. *Key Chemicals: Vinyl Chloride*, Chem. & Eng'g News, Aug. 23, 1976, at 13.

84. *Second Thoughts On Using PVC*, Chemical Week, July 31, 1974, at 19.

85. U.S. Environmental Protection Agency, Standard Support and Environmental Impact Statement: Emission Standard for Vinyl Chloride 7-4 (Oct. 1975) [hereinafter cited as EPA EIS]; U.S. Environmental Protection Agency, Preliminary Assessment of the Environmental Problems Associated With Vinyl Chloride and Polyvinyl Chloride, Report on the Activities and Findings of the Vinyl Chloride Task Force at app. I, table 2 (Sept. 1974) [hereinafter cited as EPA Task Force Report].

FIGURE I
THE LIFE CYCLE OF VINYL CHLORIDE-POLYVINYL CHLORIDE



it was rejected because it upset cardiac function.[86] There are also indications that VC was once used as a refrigerant in cooling equipment.[87] Until late 1973, a small percentage of the VC produced was used as an aerosol propellant in some cosmetics, drugs, pesticides, and other consumer products. In 1974, when VC's carcinogenicity became generally known, millions of VC-propelled aerosols were still on the market or in consumer hands. The use of VC in aerosols has since been prohibited.[88]

Figure I illustrates the cycle of VC's creation, transformation, use, and disposal, and the routes of human exposure. There are three industries of central importance. The VC industry produces VC from petrochemicals. The PVC industry polymerizes the gas into the solid plastic, known in its raw form as resin. The fabrication industry converts PVC resins into finished products ready for consumer use or for incorporation into products of other industries. It is in these three industries that the workers are most heavily exposed to VC, and that the known human cancers have occurred.

Outside of these plants, additional people are exposed to VC in two major ways. First, VC emissions escape from factories to the surrounding air.[89] Second, since the polymerization process is imperfect, some VC remains a gas trapped in PVC materials. This residual escapes from the plastic in later production in fabrication plants and beyond, and in subsequent use and disposal.

As one moves through the production cycle of VC and PVC, the number of plants and companies increases, and plants become smaller and more labor intensive. The VC industry is composed of 10 companies operating 15 plants; in 1973, Shell, Dow, and Goodrich together held 56 percent of capacity.[90] In 1975, 23 companies operating 37 plants comprised the PVC industry. Goodrich is the major PVC producer with 15 percent; Firestone, Conoco, Union Carbide, Borden, Diamond Shamrock, and Tenneco each produce between five and nine percent.[91] There are about 8,000 fabrication companies of all sizes.[92] Beyond this point industries cease to be identified primarily by their use of VC.

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86 Osico, Carl, Krantz, & Saueweld, *Anesthesia XXVII. Narcosis with Vinyl Chloride*, 8 ANESTHESIOLOGY 359, 361 (1947)

87 2 I. PATTY, INDUSTRIAL HYGIENE AND TOXICOLOGY 811 (1963)

88 The fate of these aerosols is discussed in the text accompanying notes 551-556 *infra*.

89 Most VC escapes directly into the air. Some leaves the plants in effluent water, most of this VC evaporates into the air. Some, however, enters drinking water. *See* EPA Task Force Report, *supra* note 85, at 5, 10. Appendices at IV, ENVIRONMENTAL PROTECTION AGENCY, PRELIMINARY ASSESSMENT OF SUSPECTED CARCINOGENS IN DRINKING WATER (REPORT TO CONGRESS) I, 26-30, 33-39 (1975) [hereinafter cited as EPA PRELIMINARY REPORT ON DRINKING WATER CARCINOGENS].

90 OFFICE OF RESEARCH AND DEVELOPMENT, U.S. ENVIRONMENTAL PROTECTION AGENCY, SCIENTIFIC AND TECHNICAL ASSESSMENT REPORT ON VINYL CHLORIDE AND POLYVINYL CHLORIDE 20 (June 1975) [hereinafter cited as EPA SCIENTIFIC AND TECHNICAL REPORT].

91 *Id.* at 21-23.

92 EPA TIS, *supra* note 85, at I-23.

As the above figures indicate, the VC and PVC industries are substantially concentrated. They are also vertically integrated. In 1972, 34 percent of VC produced was sold to PVC plants owned by VC companies, although this figure had dropped from 61 percent in 1962 as the industries grew.[93]

The fact that the VC and PVC industries contain only a small number of relatively concentrated and integrated firms has made it easy for the industries to speak with one voice in regulatory proceedings regarding the limits of their technological and economic capabilities to control VC exposures. The industrial market structure also makes it difficult to analyze the true costs of control measures and to determine the incidence of those costs on product prices, profits, wages, and other inputs.

Most VC plants are open-air, resembling oil refineries. They are located in populated areas in warm states—principally Louisiana, Texas, Kentucky, and California.[94] PVC plants are enclosed, but still emit VC, and they too are located mostly in populated areas. In addition to the above states, New Jersey, Ohio, and Massachusetts are major PVC-producing states.[95]

Only about one-third of total VC production is polymerized at the site at which it is produced. Most VC must be transported between VC and PVC plants, mainly by rail tank car, and also by tank truck and barge. In addition, PVC resin must be transported between the PVC and fabrication plants; this is done primarily by train and truck.[96]

VC and PVC plants are highly mechanized and employ a relatively small number of workers. At any one time, there are only about 1,000 employees in the VC industry, and only about 5,500 in the PVC industry.[97] Taking into account the normal turnover of workers, about 30,000 employees are estimated to have worked in these industries since 1939.[98] Fabrication plants are more labor intensive. The number of fabrication workers is estimated at 350,000.[99] These workers are subject to much lower exposures of VC than the workers in VC and PVC plants, as the exposure of the fabrication workers comes only from escaping VC residual.[100] The size of the group, however, gives rise to fears that even a low incidence of cancers may claim a large number of lives.

93 Foster D. Snell, Inc., Draft Final Report: Economic Impact Studies of the Effects of Proposed OSHA Standards for Vinyl Chloride, at III-3 (Sept. 13, 1974) [hereinafter cited as Snell Economic Impact Study].

94 *Id.* at III-2; EPA EIS, *supra* note 85, at 3-31, -39.

95 EPA Scientific and Technical Report, *supra* note 90, at 21-23.

96 EPA Task Force Report, *supra* note 85, at 7.

97 Snell Economic Impact Study, *supra* note 93, at III-4, -8.

98 K. Ashford *et al.*, *supra* note 5, at 9-41, -45 (appendix concerning VC regulation in the workplace). The number of cancers found in these workers, while not large in absolute terms, represents an extremely high incidence in the small population.

99 EPA Task Force Report, *supra* note 85, at 11.

100 OSHA Permanent Standard for VC, *supra* note 1, at 35 892-93.

The VC and PVC workers are represented primarily by three unions: the United Rubber Workers, the United Steelworkers, and the Oil, Chemical and Atomic Workers. On their own and through the Industrial Union Department of the AFL-CIO, these unions were major participants in setting the VC occupational exposure standard. The fabrication workers are represented by a variety of unions, and some are not unionized at all.

The technological and economic capabilities of the VC, PVC, and fabrication industries to lower the release of VC—in plants, to the surrounding air, and through later-escaping residual in PVC—have been constantly at issue in the regulatory actions described in subsequent sections. The difficulty of predicting the future technological and economic limits to changes in these industries is discussed elsewhere,[101] but here it is useful to give some indication of their clearly demonstrated past and present capabilities.

Without need for any significant technological breakthroughs, in the four years since VC's carcinogenicity became clear, the VC, PVC, and fabrication industries have significantly reduced their releases of VC. In response the regulations or the threat of regulations, the VC and PVC industries have been shown to be able to reduce workplace airborne concentrations of VC from about 250 parts per million (ppm) to about one ppm,[102] to reduce VC emissions to the outside by about 95 percent,[103] and to reduce the VC residual content of food packaging by several orders of magnitude.[104] New plants face no difficulties meeting these lowered levels.[105] Furthermore, there is no sign that the limits of current technologies have been reached and the possibility remains that fundamental technological breakthroughs could occur.

These reductions have been achieved without any significant economic strain on the companies or damage to PVC's market position and future growth prospects. Throughout the 1960s and early 1970s, PVC consumption grew at a staggering rate as prices declined and the number of uses increased.[106] In 1973, the business analysts forecast uninterrupted growth; the major problem experienced at that time was the tight supply of petrochemical raw materials.[107]

101 See notes 61-72 *supra*.

102 See text accompanying notes 227, 325-383 *infra*.

103 EPA EIS, *supra* note 85, at 1-4; EPA Scientific and Technical Report, *supra* note 90, at 113-14.

104 See text accompanying note 535 *infra*.

105 *PVC Rolls Out of Jeopardy, Into Jubilation*, Chemical Week, Sept. 15, 1976, at 34, 36.

106 *See* Snell Economic Impact Study, *supra* note 93, at III-3, exhibit III-2; EPA EIS, *supra* note 85, at 2-1.

107 *Tight Monomer Supply Plagues PVC Producers*, Chem. & Eng'g News, May 28, 1973, at 6.

In 1974 and 1975, VC and PVC consumption dropped sharply, marking the first break in the trend of phenomenal growth. The slump, however, was not caused by a consumer response to the revelation of VC's carcinogenicity and to the costs of complying with subsequently imposed standards. Rather, the slump had two extrinsic causes: (1) attempts in the early 1970s to pass on to consumers the rising costs of petrochemical feedstocks; and (2) the general economic recession in 1974 and 1975, which was particularly severe in the building construction industry, a major user of plastics.[108] The slump was shared equally by all the major plastics.

With the end of the recession and the revival of the housing industry, plastics generally and PVC in particular returned to the prior trend of profitable growth. Presently, new plants are being built to meet anticipated demand, without any apparent hindrance from current and proposed regulations.[109] Hence, it appears that somewhat greater reductions in VC exposure could be demanded of the industries without rendering either current operations or expansion unprofitable.

As the following survey of VC's toxicity will show, there is no basis for thinking the VC hazard has been eliminated by the measures already taken, or that it will be eliminated by the additional measures conceded by the industries to be both technologically and economically within their reach. Further reductions are justified by the medical evidence. The point at which the industries would be seriously burdened economically is, however, impossible to predict reliably.

2 *Health Risks and Sources of Exposure to Vinyl Chloride*

The toxic effects of VC are now known better than those of nearly any other industrial chemical. VC's carcinogenicity has been well established by human experience, animal experiments, and other laboratory tests. The bitter experience of occupational exposure has confirmed VC's ability to cause cancers and a host of lesser effects in humans. The risks extend beyond the workers; millions of other people are exposed to VC. This subsection surveys the evidence of VC's toxicity and the extent of human exposure to the chemical.

a. *Acute and chronic human toxicity*

Before 1974, when VC had not yet been connected to human cancer, other dangers of the chemical were well known. VC is extremely flammable, and concentrations in air exceeding 40,000 ppm are explosive.[110]

108. Lagneau, *1976 Outlook Brighter in U.S. and European Chemical Industries*, Chem. Eng. & Eng. News, Apr. 1976, at 14; Greek, *Vinyl Chloride May Face Shortages By 1977*, Chem. & Eng. News, Aug. 11, 1975, at 8.

109. *PVC Rolls Out of Icepinds, Into Inhalation*, *supra* note 100, at 31.

110. Haley, *Vinyl Chloride: How Many Unknown Problems?*, 14 Environment & Env't 16 at 16–17, 49 (1975) (hereinafter cited as *VC: How Many Unknown Problems?*).

Several workers have died from inhaling extremely high concentrations.[111] Exposure to concentrations greater than 8,000 ppm VC causes one to become dizzy, drowsy, disoriented, and eventually unconscious.[112] Lower doses inhaled over a period of a work shift make one prone to deep, dreamless sleep.[113]

Before 1974, VC concentrations of 250 to 300 ppm were common for many job categories in the VC and PVC industries.[114] Among workers exposed to these concentrations for periods of months or years, a number of effects had been identified. Many workers suffered enlargement and fibrosis of the liver and spleen.[115] Many exhibited Reynaud's syndrome, characterized by circulatory degeneration in the extremities and by a cold feeling or a feeling of pins and needles in the hands and feet.[116] Many developed sclerdoma, a skin condition, and acroosteolysis, a rare disease characterized by the shrinking of the last bones in the fingers and toes.[117] Although workers who suffered one of these effects did not always suffer the others, the effects were grouped under the name "vinyl chloride disease."[118]

When VC's capacity to cause cancer in humans became clear in 1974, close medical examination of VC and PVC workers identified numerous acute and chronic effects of VC that previously had gone unnoticed. Impaired arterial circulation and fibrosis of the liver and spleen were found to occur at a microscopic level long before they were clinically observable.[119]

111. Spitas, McMichael, Gamble, & Van Eijl, *The Association of Vinyl Chloride Exposures With Morbidity Symptoms*, 36 Am. Indus. Hygiene Ass'n J. 779 (1975).

112. EPA Scientific and Technical Report, *supra* note 90, at 85; *VC: How Many Unknown Problems?*, *supra* note 110, at 61.

113. *VC Hearings*, *supra* note 1, at 30 (testimony of Dr. Marcus Key, Director, National Institute for Occupational Safety and Health).

114. Kramer & Mutchler, *The Correlation of Clinical and Environmental Measurements For Workers Exposed to Vinyl Chloride*, 33 Am. Indus. Hygiene Ass'n J. 19 (1972) (hereinafter cited as *Worker Exposure to VC*); EPA Scientific and Technical Report, *supra* note 90, at 91–94.

115. Lilis, Anderson, Nicholson, Daum, Fischbein, & Schkoff, *Prevalence of Disease Among Vinyl Chloride and Polyvinyl Chloride Workers*, 246 Annals N.Y. Acad. Sci. 22 (1975) (hereinafter cited as *Prevalence of Disease*); Lange, Infante, Stein, & Veltman, *Further Results in Polyvinyl Chloride Production Workers*, 246 Annals N.Y. Acad. Sci. 18 (1975) (hereinafter cited as *Further Results*).

116. *Prevalence of Disease*, *supra* note 115, at 22; *Further Results*, *supra* note 115, at 18.

117. *Prevalence of Disease*, *supra* note 115, at 22; *Further Results*, *supra* note 115, at 18; Sakabe, *Bone Lesions Among Polyvinyl Chloride Production Workers in Japan*, 246 Annals N.Y. Acad. Sci. 78 (1975); *VC: How Many Unknown Problems?*, *supra* note 110, at 62–63.

118. Veltman, Lange, Infante, Stein, & Bachner, *Clinical Manifestations and Course of Vinyl Chloride Disease*, 246 Annals N.Y. Acad. Sci. 6 (1975).

119. Marsh, Johnson, Whetstone, & LeRoy, *Capillary Abnormalities in Polyvinyl Chloride Production Workers: Examination By In Vivo Microscopy*, 246 J. Am. Med. Ass'n 1368 (1976); Popper & Thomas, *Alterations of Liver and Spleen Among Workers Exposed to Vinyl Chloride*, 246 Annals N.Y. Acad. Sci. 172 (1975); Thomas & Popper, *Pathology of Angiosarcoma of the Liver Among Vinyl Chloride-Polyvinyl Chloride Workers*, 246 Annals

Microscopic examination revealed other changes in liver cells.[120] Some workers displayed a wide variety of abnormal liver function and blood tests.[121] Some suffered impairment of lung function.[122]

The medical researchers had hoped that these observable effects could be used to indicate who is at increased risk of developing cancer and how VC produces its carcinogenic effect. To their disappointment, however, none of these effects correlated well enough with observed cases of liver angiosarcoma or of other cancers to indicate clearly which workers are at increased risk, nor has the knowledge of these effects enabled researchers to explain how VC causes cancer.[123]

b Human cancers

Throughout the spring of 1974, after the deaths of the four Goodrich workers became known, other companies reported additional angiosarcoma deaths among VC and PVC workers.[124] The toll has risen steadily since then. Thirteen cases of angiosarcoma of the liver had been counted among American workers by July 1974,[125] and a total of 25 cases were known

N.Y. Acad. Sci. 268 (1975); Gedigk, Muller, & Bechtelsheimer, *Morphology of Liver Damage Among Polyvinyl Chloride Production Workers: A Report on 31 Cases*, 246 Annals N.Y. Acad. Sci. 278 (1975).

120. *See* sources cited in note 119 *supra*.

121. Blood platelet count has been down in some, but not all, victims of liver angiosarcoma. Liver function tests show a wide variety of abnormalities. *Prevalence of Disease*, *supra* note 115; *Further Results*, *supra* note 115; Veltman, Lange, Jahe, Stein, & Bachner, *supra* note 118; Marsteller, Tulloch, Muller, & Gedigk, *Unusual Splenomegalic Liver Disease as Evidenced by Peritoneoscopy and Guided Liver Biopsy Among Polyvinyl Chloride Production Workers*, 246 Annals N.Y. Acad. Sci. 95 (1975).

122. Gamble, Liu, McMichael, & Waxweiler, *Effects of Occupational and Nonoccupational Factors on the Respiratory System of Vinyl Chloride and Other Workers*, 18 J. Occupational Med. 659 (1976).

123. In promulgating the permanent standard for workplaces, OSHA noted the failure to find in blood tests, liver function tests, and certain other examinations a reliable indication of increased cancer risk. *OSHA Permanent Standard For VC*, *supra* note 1, at 35,895. Since the fall of 1974, when OSHA's observation was made, there has been little change in the state of knowledge of VC's carcinogenesis. Some hope of identifying VC-induced changes at an early stage is promised by two recent techniques. The first is ultrasonography, a technique for "taking a picture" of internal organs such as the liver and spleen without surgery through a sort of "sonar." This technique can reveal fibrosis and other gross changes to these organs. Taylor, Barrett, Williams, Smith, & Duck, *Preliminary Results of Grey-scale Ultrasonography in the Detection of Vinyl Chloride Related Liver and Spleen Disease*, 69 Proc. Roy. Soc. Y. Med. 292 (1976). Another technique detects microscopic changes in the circulatory system in the fingers. It was reasoned that the Reynaud's syndrome and acroosteolysis would be preceded by subclinical changes, which, if they could be found, would be an indication of increased risk. Maricq, Johnson, Whetstone, LeRoy, *supra* note 119. Neither of these techniques, however, offers any assurance of detecting VC-induced changes before the changes at the cellular level which eventually lead to cancer have already occurred.

124. Occupational Safety and Health Administration, *Vinyl Chloride: Proposed Standard*, 39 Fed. Reg. 16,896 (1974) [hereinafter cited as *OSHA Proposed Standard for VC*].

125. *OSHA Permanent Standard for VC*, *supra* note 1, at 35,891.

worldwide one month later.[126] Although the majority of cases involved workers at PVC plants, other workers were also affected.[127] There were 38 cases worldwide by June 1975,[128] at least 51 cases by December 1976,[129] and at least 68 cases by the spring of 1978.[130]

Although in absolute terms these numbers are not large, the rate of liver angiosarcoma in various groups of PVC workers studied ranges from 400 to 3,000 times the expected incidence in the general population.[131] Since the latency period—the time between initial exposure to VC and the clinical appearance of liver cancer—has been averaging about 20 years, more cases can be expected as the result of high exposures in the 1950s, 1960s, and early 1970s.[132]

Many of the employees who have died of liver angiosarcoma worked as cleaners of the polymerization reactor (the chamber in which VC is converted to PVC) or worked in areas with similarly high VC exposures.[133] These workers probably were the most heavily exposed, in terms of both momentary peaks and sustained averages. The precise levels are not known but are estimated to have included peak exposures of several thousand ppm and an average of 250 to 300 ppm.[134] Other liver angiosarcoma victims presumably had lower, less sustained exposures to VC.[135]

126. *VC Hearings*, *supra* note 1, at 60-62 (statement of Dr. Joseph K. Wagoner).

127. Those affected included a worker at a VC plant, a worker who filled pesticide cans with VC propellant, and an accountant and a worker at PVC cloth fabricating plants. *Id.* These last two are assumed to have had very low exposures.

128. *Id.* at 60; EPA Statistical and Technical Report, *supra* note 90, at 72, 82.

129. Reported Cases of Angiosarcoma of the Liver Among Vinyl Chloride Polymerization Workers (Dec. 6, 1976) (typewritten tabular data enclosed with letter to the author from Rose Kaminski, Statistician (Health), Illness Effects Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health (Dec. 6, 1976)).

130. Personal communication with Rose M. Kaminski, Statistician (Health), Illness Effects Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Apr. 18, 1978.

131. The lower figure is from Heath, Falk, & Creech, *Characteristics of Cases of Angiosarcoma of the Liver Among Vinyl Chloride Workers in the United States*, 246 Annals N.Y. Acad. Sci. 231, 233 (1975). The higher figure is from EPA, EPA, *National Emission Standards for Hazardous Air Pollutants, Proposed Standard for Vinyl Chloride*, 40 Fed. Reg. 59,532 (1975) (hereinafter cited as *EPA Proposed Standard for VC*). These figures are the result of comparing the rates of angiosarcoma of the liver in workers with the rates in the general population, assuming that the general population cases are not caused by VC. But if, as the reminder of this section suggests, some of the cases in the general population may be caused by nonoccupational VC exposure, then these figures understate the potency of the chemical.

132. *VC Hearings*, *supra* note 1, at 25 (statement of Dr. Irving J. Selikoff); Heath, Falk, & Creech, *supra* note 131, at 231.

133. Nicholson, Hammond, Seidman, & Selikoff, *Mortality Experience of a Cohort of Vinyl Chloride-Polyvinyl Chloride Workers*, 246 Annals N.Y. Acad. Sci. 225, 226-27 (1975). *See also* Fox & Collier, *Mortality Experience of Workers Exposed to Vinyl Chloride Monomer in the Manufacture of Polyvinyl Chloride in Great Britain*, 34 Brit. J. Indus. Med. 1 (1977).

134. *Worker Exposure to VC*, *supra* note 114.

135. EPA Statistical and Technical Report, *supra* note 90, at 72, 82.

The long-term risks of VC exposure may not be limited to liver angiosarcoma. One study of PVC workers identified a statistically significant excess incidence of cancers of the brain and the respiratory system.[136] A study of the causes of death among fabrication workers identified no liver angiosarcomas, but it did suggest an increased incidence of cancers of the digestive system among both men and women and the breast and the urinary system in women.[137] Evidence of other effects has appeared in populations other than workers. One study has shown a statistically significant excess of birth defects and central nervous system tumors among the children of families in three Ohio communities that have hosted PVC plants for as long as 28 years.[138]

c. Animal bioassays and other tests for carcinogenicity

VC's carcinogenicity has been confirmed by the results of experiments on animals and by other laboratory tests. VC has been shown to cause cancer in animals both when inhaled and when ingested. The first hint that the chemical causes cancer came from the publication in 1971 of the results of Italian experiments sponsored by the European and American VC and PVC producers. In these tests rats inhaling high concentrations of VC (30,000 ppm) developed cancerous tumors of the skin, lung, and bone.[139] Further tests sponsored by the producers were concluded and reported to the Occupational Safety and Health Administration (OSHA) in early 1974. As shall be seen in the case study of OSHA's standard setting, the data arrived at a crucial time. On February 15, at OSHA's fact-finding hearing on VC, the Italian researchers reported their then-unpublished findings that VC had induced angiosarcoma of the liver in rats inhaling concentrations as low as 250 ppm.[140] On April 15, OSHA received reports from tests conducted in

136. Tabershaw & Gaffey, *Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers*, 16 J. OCCUPATIONAL MED. 509 (1974). *See also* Monson, Peters, & Johnson, *Proportional Mortality Among Vinyl Chloride Workers*, THE LANCET, Aug. 17, 1974, at 397.

137. Chairze, Nichols, & Wong, *Mortality Among Employees of PVC Fabricators*, 19 J. OCCUPATIONAL MED. 623, 628 (1977) [hereinafter cited as *Mortality Among Fabrication Employees*]. The authors noted a number of flaws in the design and data for their study that precluded drawing firm conclusions from it. In particular, it would be useful to follow the population of fabrication workers for some years into the future, as a sufficient latency period may not yet have elapsed for some effects to manifest themselves.

138. Infante, *Oncogenic and Mutagenic Risk in Communities with Polyvinyl Chloride Production Facilities*, 271 ANNALS N.Y. ACAD. SCI. 49, 50 (1976). *Cf.* Infante, McMichael, Wagoner, Waxweiler, & Falk, *Genetic Risks of Vinyl Chloride*, THE LANCET, Apr. 3, 1976, at 734 (finding increased fetal loss among wives of workers exposed to VC).

139. Viola, Bignotti, & Caputo, *Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride*, 31 CANCER RESEARCH 516 (1971) [hereinafter cited as *Oncogenic Response of Rats to VC*].

140. Occupational Safety and Health Administration, *Emergency Temporary Standard for Exposure to Vinyl Chloride*, 39 Fed. Reg. 12,342 (1974) [hereinafter cited as *OSHA Emergency Temporary Standard for VC*].

Illinois of similar results in mice at the lowest level of exposure then being tested, 50 ppm.[141]

Animal test results stood at this point until early 1975. It was reported then that *ingestion* by rats of as little as approximately 17 milligrams per kilogram of body weight produces liver angiosarcoma and other cancers.[142] Most recently, in September 1976, the results of another round of inhalation experiments demonstrated that VC causes liver angiosarcoma in rats at 25 ppm, and that it causes mammary tumors at one ppm, the lowest concentration yet tested.[143]

The animal experiments also support suspicions that VC causes human cancers other than angiosarcoma of the liver. The experiments have shown increased cancer incidence at many sites other than the liver, including the lungs, spleen, brain, and, as already noted, breast.[144] Experiments demonstrating the induction of cancer in two species other than rats—mice and hamsters—further confirm that VC is carcinogenic.[145] In the animal experiments the subjects were exposed to constant, prolonged doses of VC. The need was noted in mid-1974 for studies of the effects of single and sporadic doses, typical of many humans' exposure.[146] Such a study is now nearing completion, but the results are not yet available.[147]

d. Additional humans at risk

In addition to several hundred thousand workers in VC and PVC production and in PVC fabrication, millions of American have been, and continue to be, exposed to VC. First, about 4.6 million people live within

141. *OSHA Proposed Standard for VC*, *supra* note 124, at 16,896. The results of the Italian tests, also showing the induction of liver angiosarcoma at 50 ppm, were published in early 1975. Maltoni & Lefemine, *Carcinogenicity Bioassays of Vinyl Chloride: Current Results*, 246 ANNALS N.Y. ACAD. SCI. 195 (1975).

142. Maltoni, Ciliberti, Gianni, & Chieco, *Gli Effetti Oncogeni Del Cloruro Di Vinile Somministrato Per Via Orale Nel Ratto (Oncogenic Effects of VC Administered Orally to Rats: Preliminary Report)*, GLI OSPEDALI VITA, Dec., 1975 (unpaginated reprint on file in offices of the *Ecology Law Quarterly*).

143. Memorandum from Cesare Maltoni to the Members of the European Cooperative Group for the Experimental Bioassays on Vinyl Chloride Carcinogenicity (undated) [hereinafter cited as Maltoni Memorandum].

144. See sources cited in notes 140-143 *supra*.

145. EPA SCIENTIFIC AND TECHNICAL REPORT, *supra* note 90, at 36. In addition, metabolites of VC have been shown to mutate bacteria and yeasts in the "quick tests" for mutagenicity. *See, e.g.*, Lopriemo, Barale, Baroncelli, Barsch, Bourretti, Cannellini, Corsi, Frezza, Nieri, Leporini, Rosellini, & Rossi, *Induction of Gene Mutations and Gene Conversions by Vinyl Chloride Metabolites in Yeast*, 37 CANCER RESEARCH 253 (1977), and sources cited therein. Mutagenicity as revealed in these tests correlates well with carcinogenicity. *See* McCann & Ames, *supra* note 57; *From Microbes to Men*, *supra* note 57.

146. *VC Hearings*, *supra* note 1, at 80-81 (statement of Dr. Theodore R. Torkelson).

147. Telephone interview with Dr. Joseph McLaughlin, Director, Division of Toxicology and Medicine, Consumer Product Safety Commission, Feb. 27, 1978.

five miles of a VC or PVC plant.[148] In 1974, about 220 million pounds of VC escaped into the air surrounding such plants.[149] The plant neighbors appear to have been exposed to more than one ppm less than 10 percent of the time.[150] One air sample, however, measured 33 ppm near a plant,[151] suggesting that there may be short term, localized peak exposures.[152] In addition, VC is found in the sludge waste and water effluent of these plants. VC has been found in sludge at levels as high as 3,000 ppm,[153] and in water effluent as high as 20 ppm.[154] Most of this VC escapes into the air surrounding the plants;[155] some, however, makes its way into drinking water.[156] These VC emissions to the ambient air have been implicated as the cause of increased rates of cancer and birth defects in the surrounding communities.[157]

Another large group of persons is exposed to VC released in transportation. Only about one-third of VC production is polymerized at the site where it is produced. The rest must be shipped between VC and PVC factories under pressure as a liquified gas. About 95 percent of this is shipped in rail tank cars, and the rest in tank trucks, tank vessels, and barges.[158] These tanks may leak, puncture, or explode, sometimes in heavily populated areas.[159] Between 1971 and 1974, there were at least 24 accidental releases of VC from rail tank cars alone.[160] As VC diffuses from the site of a spill or an accident, transportation workers, nearby residents, travellers, and other bystanders can receive short-term exposures to VC concentrations ranging from a few parts per billion (ppb) to thousands of ppm. Transportation workers and emergency personnel such as firemen and police officers may

148. EPA, *National Emission Standard for Hazardous Air Pollutants, Standard for Vinyl Chloride*, 41 Fed. Reg. 46,560 (1976) [hereinafter cited as *EPA Standard for VC*].
149. EPA Scientific and Technical Report, *supra* note 90, at 18.
150. *Id.*
151. *Id.*
152. *See id.*
153. EPA Task Force Report, *supra* note 85, at 2.
154. *Id.*
155. *Id.*, apps., at 31-32.
156. See note 89 *supra*.
157. See sources cited in note 138 *supra*.
158. EPA Task Force Report, *supra* note 85, at 7.
159. See note 160 *infra*.
160. Most of these accidents occurred in Texas and Louisiana, the states with the highest concentrations of VC and PVC facilities. There were several other accidents involving no release. Data on accidents and releases is derived from a computer file of the Department of Transportation which records incidents of hazardous materials leakage or accidents during this period, and from the appendix to H.R. Rep. No. 1083, 93d Cong., 2d Sess. 30-34 (1974). One accident, in Fort Wayne, Indiana, necessitated the evacuation of 4,500 people. *Id.* at 32. When a rail tank car ruptures, as much as 30,000 gallons of VC escapes and returns to its gaseous state. The figure for the maximum tank size comes from an interview with Mary Williams, Chemical Engineer, Department of Transportation, Office of Hazardous Materials Operations, Oct. 28, 1976.

be subject to repeated exposures and, if accidents occur in the same places, so may residents and bystanders. These exposures are less sustained than those suffered by VC and PVC workers and plant neighbors, but peak concentrations may reach those experienced by PVC polymerization reactor cleaners, the most heavily exposed occupational group.

Third, people are exposed to VC through consumer products, food, and drinking water. Until late 1973 or early 1974, VC was used as an aerosol propellant in drug, cosmetic, pesticide, and other consumer products.[161] The user of a VC-propelled aerosol product such as a hair spray or a pesticide in a small, enclosed space such as a bathroom may have been exposed to short term concentrations approaching 400 ppm, and persons may have had an average exposure from all VC-propelled products in their homes equivalent to an average exposure of about 16 ppm in the factories.[162] VC has been detected in the air of rooms freshly painted with certain latex paints, but no VC emissions have been detected in a limited sampling of other new PVC products or from automobile interiors.[163] VC leaches into food and beverages from the more than 300 million pounds of PVC packaging and other PVC food-contact materials used annually.[164] VC also enters drinking water from raw water supplies and by leaching from increasingly common PVC pipe.[165] One study estimates average American daily human intake of VC through food, water, and air at 34 micrograms.[166]

The hazardousness of non-occupational exposures to VC is even less well understood than the risk to the workers. The danger from inhaling extremely low concentrations of VC, or from single or sporadic exposures to high VC concentrations, is unknown. Similarly, the relative risks of ingesting and inhaling VC are unknown.[167] Thus the urgency of reducing or eliminating these sources of exposure is impossible to assess.

161. See text accompanying notes 551-556 *infra*.
162. Gay, Lonneman, Bridbord, & Moran, *Measurement of Vinyl Chloride from Aerosol Sprays*, 246 Annals N.Y. Acad. Sci. 286, 294-95 (1975).
163. Environmental Protection Agency, Office of Toxic Substances, Sampling and Analysis of Selected Toxic Substances: Task III—Vinyl Chloride, Secondary Sources, table 6, at 21 (Apr. 1976).
164. Food and Drug Administration, *Vinyl Chloride Polymers in Contact with Food, Notice of Proposed Rulemaking*, 40 Fed. Reg. 40,529, 40,530 (1975) [hereinafter cited as *FDA Proposed Rules for Food-Contact PVC*].
165. EPA Scientific and Technical Report, *supra* note 90, at 38-39; EPA Preliminary Report on Drinking Water Carcinogens, *supra* note 89, at 40-44; EPA Task Force Report, *supra* note 85, at 7, 19.
166. EPA Scientific and Technical Report, *supra* note 90, at 43.
167. *See* Withey & Collins, *A Statistical Assessment of the Quantitative Uptake of Vinyl Chloride Monomer from Aqueous Solution*, 2 J. Toxicology & Env't Health 311 (1976); Withey, *The Pharmacodynamics and Uptake of Vinyl Chloride Monomer Administered by Various Routes to Rats*, 1 J. Toxicology & Env't Health 181 (1976). In the former article, the authors estimate that for rats, 0.9 micrograms of VC in the daily intake of water is approximately equal to inhaling 6 ppm for eight hours. They caution against any direct extrapolation to human equivalences. Withey & Collins, *supra*, at 319-20.

South Coast
AIR QUALITY MANAGEMENT DISTRICT
9150 FLAIR DRIVE, EL MONTE, CA 91731 (818) 572-6200

April 22, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Bill:

Vinyl Chloride

In response to Mr. Venturini's request for information on the health effects of vinyl chloride, we are submitting several references which could be of use in your toxic air contaminant program. These references were not included in your bibliography dated March 1, 1985. Also, information regarding possible biological production of vinyl chloride may be obtained from Dr. Freeman Allen of Pomona College.

We would like to continue to receive information inquiries for other candidate compounds and to be kept informed of your program's progress.

Very truly yours,

Jo Anne Aplet
Director of Planning

JAA:cas

Enclosure

PACIFIC GAS AND ELECTRIC COMPANY

77 BEALE STREET • SAN FRANCISCO, CALIFORNIA 94106 • (415) 781-4211 • TWX 910-372-6587

May 7, 1985

Mr. William V. Locustoff, Chief
Toxic Pollutants Branch
Re: Vinyl Chloride.
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

Request for Public Health
Information Regarding Vinyl Chloride

Pacific Gas and Electric Company received your April 4, 1985 request for additional public health information regarding Vinyl Chloride. We have reviewed the bibliography attached to your request and concluded that we are unaware of any additional information which would be of use to you.

Sincerely,

J. F. McKenzie

Chemicals

Chlor-Alkali Business Unit
PPG Chemicals
One PPG Place
Pittsburgh, Pennsylvania 15272

May 13, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Re: Vinyl Chloride

Dear Sirs:

Relative to your request for health information on vinyl chloride, we have no information which was not covered in the MEDLINE and TOXLINE information services.

We thank you for asking for our input.

Sincerely yours,

Clete M. Smith
Technical Service

CMS/rs

Additional References on Vinyl Chloride Health Effects

Albert, R.E. Letter to R.S. Naveen, EPA, "Comparison of Vinyl Chloride Carcinogenic Risks with Risk From Other Pollutants," Washington, D.C., June 16, 1978.

Edmonds, L. "Birth Defects and Vinyl Chloride," Proc. Conference on Women and the Workplace, Washington; D.C., 1976, also Teratology 17, 137 (1978).

Equitable Environmental Health, Inc. "Epidemiological Study of Vinyl Chloride Workers, Final Report." Prepared for Manufacturing Chemists Association, Washington, D.C., January, 1978.

Graniger, R.G., A.E. Walker, and A.M. Ward. "Vinyl Chloride Monomer-Induced Disease: Chemical, Radiological and Immunological Aspects," Chapter II in Induced Disease; Drug, Irradiation, Occupation, L. Preger, ed., Grune and Stratton, London, 1980.

Kuzmack, A.M. and R.E. McGaughy. "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride," U.S. EPA, Washington, D.C., December 5, 1975.

National Academy of Science. Principles of Toxicological Interactions Associated with Multiple Chemicals Exposures 1981, 207 p. AD-A093 809/2 PC A10/MF A01.

National Cancer Institute (1978). Vinyl Chloride - An Information Resource, 112 p. HRP-0028012/3 PC A06/MF A01.

National Institute of Occupational Safety and Health (1977). A Cross-Sectional Epidemiologic Survey of Vinyl Chloride Workers. 50 p. NIOSH Pub. No. 77-177, NTIS No. PB-274.

Ziskind, R.A., Smith, D.F., and Spivey, G.H. Health Effects in Children Exposed to Vinyl Chloride. Final Report to U.S. Environmental Protection Agency, SAI-068-81-569, January 1981.

Air Products and Chemicals, Inc.
Box 538
Allentown, PA 18105
Telephone (215) 481-4911

AIR PRODUCTS

16 April 1985

W. V. Loscutoff
Chief, Toxics Pollutant Branch
CARB
Box 2815
Sacramento, CA 95812

Re: Vinyl Chloride

Dear Mr. Loscutoff:

We are happy to provide some information relative to vinyl chloride in response to the April request of P. D. Venturini. This includes:

1. A paper by me given at the APCA, New Orleans meeting.

2. A paper presented at a CMA seminar in Washington, 9 December 1983.

3. An unpublished review by me on the safety and health aspects of vinyl chloride, which contains several references not in the bibliography with the Venturini letter.

4. A report from Br. J. Surg. 71 322 (1984) of an apparently successful liver resection on an ASL patient.

5. An article from EST 19 277 (1985) on biodegradation of TCE to VC. Note especially reference 10, Parsons, et. al., for corroborating evidence. You may want to get the Dade County report "An Investigation into the Source of Vinyl Chloride Detected at the Preston and Hialiah Water Treatment Plants" by J. C. Balter, 1983, for more details.

6. A summary of a report on a 1984 bioassay by CIVO.

I hope that these are useful to you in your evaluation of this substance.

Very truly yours,

John T. Barr, Manager
Regulatory Response

JTB:csb

Air Products

ASL
VC

3650

Date 21 August 1984

INTEROFFICE
MEMORANDUM

Subject Surgical Removal of Angiosarcoma

To L. B. Tepper — Corporate Medical Department
(Location, Organization, or Department)

From J. T. Barr — Regulatory Response
(Location, Organization, or Department)

cc: G. Bays
H. L. Watson

The attached article is a report of an apparently successful surgical removal of an angiosarcoma from the liver of a PVC worker. It appeared at Br. J. Surg. 71 322 (1984).

J. T. Barr

JTB:csb

Vinylchloride induced hepatic angiosarcoma

Y.A. Louagie, P. Gianello, P.J. Kestens, F. Bonbled and J.G. Haot

Department of Surgery of the Alimentary Tract, Louvain-en-Woluwe Medical School, and St. Luc Hospital, 1200 Brussels, Belgium

Correspondence to: Dr Y.A. Louagie, 20 Avenue d'Huart (bte 3), 1150 Brussels, Belgium

The relationship between vinylchloride exposure and human angiosarcoma of the liver (ASL) received attention in 1973 when a case of this rare tumour was diagnosed at autopsy[1].

Case report

A 39-year old man was first seen in July 1979 with pain in the right upper quadrant. The liver was palpated at the right costal margin. Oral cholecystography and barium swallow were normal and liver function tests were in normal limits. From 1965 to 1970 he had cleaned reactors used for the polymerization of the vinylchloride monomer in PVC and was thus exposed to high amounts.

He was admitted 3 months later with persisting right upper quadrant pain, loss of appetite and fatigue. The liver edge was by then hard and 4 cm below the costal margin. The ESR was accelerated (80 mm/h) and alkaline phosphatases and GGTP were elevated. Carcino-embryonic antigen (CEA) and α fetoglobulin were normal. Ultrasound showed a large dense tumour of the right hepatic lobe with areas of necrosis. The ^{99m}Tc hepatic scan confirmed the presence of an ill-defined filling defect in the inferior part of the right lobe with two small defects at the level of the hilum.

The liver computerized tomography confirmed the integrity of the left lobe.

A selective angiography of the celiac artery revealed a hypervascularized tumour of the right hepatic lobe (*Figure 1*).

At a right thoracophrenolaparotomy the tumour was found to be confined to the right lobe. An extended right lobectomy was then performed. The postoperative recovery was uneventful and the patient was sent home with a monthly administration of Vincristine (1 mg IV) and Adriamycin (150 mg/m² IV) which was discontinued in June 1981.

Repeated controls up to September 1981 by liver scan and computerized tomography remained normal. The patient is still in good health 38 months after the resection.

Pathology

The resected specimen was 2050 g. On macroscopical examination, the main tumour (13-5 × 8 cm) was yellowish and spongy and contained cystic and haemorrhagic zones. A second smaller haemorrhagic mass was found at the inferior aspect of the right lobe surrounded by numerous purple masses.

Macroscopically, the main tumour showed large areas of necrosis and haemorrhagic pseudocystic spaces (*Figure 2*). These spaces were surrounded by areas of dense vascular proliferation. The sinusoids were lined with variably sized irregular sarcomatous cells with hyperchromatic nuclei. Elsewhere, blood-filled spaces were surrounded by sarcomatous cells. The sarcoma cells encompassed adjacent liver cells and bile ductules and infiltrated the parenchyma. The pathological diagnosis of multicentric angiosarcoma was made. The rest of the liver was normal except for some moderately enlarged portal tracts. Progressive fibrosis separated hepatocytes at the margins of the portal tracts from adjacent hepatic

Figure 1 *Selective angiography of the coeliac artery. The hypervascularized tumour is supplied by an anterior branch (arrows) of the right hepatic artery*

Figure 2 *Photomicrography of the main tumour showing blood filled spaces surrounded by sarcomatous cells. Haematoxylin eosin. × 160*

cord cells. Anisocaryosis and anisocytosis were frequent. A cross-section biopsy of the left lobe showed normal tissue with slight hepatocytic anisocaryosis. The lymph nodes taken from the liver hilum were hyperplastic. The main features of this tumour were its multicentricity and the presence of mild fibrosis.

Discussion

The occurrence of liver angiosarcoma in vinylchloride polymerization workers was reported in 1974[1,2]. Prolonged exposure and long interval from initial exposure is required before liver disease becomes apparent. The average interval is 12 years (range 6–29)[3]. Our patient was exposed for 5 years and became symptomatic 14 years later.

It is a rapidly progressing fatal disease, especially in adults. The clinical features include rapid liver enlargement with haemorrhagic ascites, fast deterioration and cachexia usually with death within 6 months.

The treatment is disappointing and chemotherapy and radiation of palliative value only. If the diagnosis is made early, the disease is localized and there is no associated liver fibrosis or portal hypertension, resective operation might prove to be curative. However, there are few reported cases of successful operative removal of hepatic angiosarcoma and the longest survival has been 16 months[4].

In our case the tumour was confined to the right lobe and there was no sign of the extensive fibrosis. So far the patient is apparently free of disease after 38 months. This is, to our knowledge, the longest published survival.

References

1. Creech JL Jr, Johnson MN. Angiosarcoma of the liver in the manufacture of Polyvinyl Chloride. *J Occup Med* 1974; 16: 150–1.
2. Block JB. Angiosarcoma of the liver following vinyl chloride exposure. *JAMA* 1974: 229: 53–4.
3. Heath CW, Flak H, Creech JL Jr. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann NY Acad Sci* 1975: 246: 231–6.
4. Adam YG, Huvos AG, Hajdu SI. Malignant vascular tumours of the liver. *Ann Surg* 1972: 175: 375–83.

Paper accepted 27 July 1983

face morphology, there was no evidence that the surface nodules were composed of any special, unique element. These particles from these particular collections seem to be quite similar to the micrometer size particles emitted in the ash (2). It is not clear, therefore, why the collected ash shows a bimodal distribution of micrometer size particles centered around 5 μm and submicrometer size particles centered around 0.5 μm. X-ray photoelectron spectroscopy (XPS) and depth profile XPS have been applied to these samples to determine surface composition. Results of these analyses will be presented in the near future.

Literature Cited

(1) "Planning Studies for Measurements of Chemical Emissions in Stack Gases of Coal-Fired Power Plants". Report prepared for EPRI, Palo Alto, CA, by Southern Resear Institute, Birmingham, AL, Battelle Columbus Laborator Columbus, OH, and Roth Associates, Inc., Rockville, M (EA-2892, Research Project 1776-1), March 1983.
(2) Kaufherr, N.; Lichtman, D. *Environ. Sci. Technol.* 198 *18*, 544.
(3) Valković, V. "Trace Elements in Coal"; CRC Press: Boc Raton, FL 1983; Vol. I, pp 83–177.
(4) Diamond, S.; Lopez-Flores, F. *Proc. Symp. N. Mater. Res. Soc.* 1981, 34.
(5) Rahn, K. A.; Lowenthal, D. H. *Science (Washington, D.C.)* 1984, 223, 132.

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TCE Biodeg JC.

Anaerobic Degradation of Trichloroethylene in Soil

Robert D. Kleopfer,* Diane M. Easley, Bernard B. Haas, Jr., and Trudy G. Delhi

Region VII Laboratory, U.S. Environmental Protection Agency, Kansas City, Kansas 66115

David E. Jackson†

Ecology and Environment, Inc., Kansas City, Kansas 66101

Charles J. Wurrey

Department of Chemistry, University of Missouri, Kansas City, Missouri 64110

■ When trichloroethylene (TCE) isotopically labeled with one ^{13}C atom is used and gas chromatography/mass spectrometry is employed to monitor the production of 1,2-dichloroethylene-$^{13}C_1$ (DCE), it has been demonstrated that reductive dechlorination of TCE takes place in the soil. Microbial involvement in this process is indicated since unsterilized soil samples yielded up to 78 ppb of labeled DCE while sterilized soil samples produced none. Isomer specificity was also found; only 1,2-DCE was produced—no 1,1-DCE was observed.

Introduction

Since trichloroethylene (TCE) is a major industrial solvent (234 000 metric tons produced annually, worldwide (*1*)) used for degreasing and cleaning metal parts and electronic components, it is perhaps not surprising that TCE has found its way into the environment. In fact, TCE appears to be widely distributed in the aquatic environment (*1*).

However, the environmental fate of TCE has not been well documented, and considerable controversy still exists concerning its behavior in environmental matrices. Early literature references have concluded that C_1 and C_2 halogenated hydrocarbons are not metabolized by microorganisms (*2*, *3*). More recent studies, however, are split on the issue of whether TCE is biodegraded (*4*–*7*), with one research group reporting both "no appreciable anaerobic degradation" and 40% degradation of TCE in similar methanogenic cultures (*8*, *9*).

In a very recent publication, Parsons et al. have demonstrated that tetrachloroethylene (herein referred to as perchloroethylene, PCE) is reductively dechlorinated to TCE, dichloroethylene (DCE), and vinyl chloride in Florida muck/surface water microcosms (*10*). Whether TCE, which was present as a 1.6% impurity in the PCE study, was similarly biotransformed was not directly investigated but was implied by the results for PCE (*10*).

Therefore, in order to determine whether TCE itself undergoes biodegradation, we have undertaken a study using TCE with single atom ^{13}C isotopic labeling, soil from a TCE spill site in Des Moines (*11*), and very sensitive gas chromatography/mass spectrometry (GC/MS) analytical techniques. Since DCE-$^{13}C_1$ could only arise via a soil or soil–microbe-induced reductive dechlorination of TCE-$^{13}C_1$, this experimental method should provide concrete evidence in support of such a pathway. The results of our investigation of this problem are reported herein.

Experimental Section

Materials. Since any microbes present had probably adapted to TCE, soil samples were collected at the Des Moines site, at depths of 1–2 ("A" samples), 6–8 ("B" samples), and 15–17 ft ("C" samples), by using an 18 in. long by 2 in. o.d. split barrel sampler (*11*). These soil samples were analyzed by GC/MS for the presence of TCE and DCE. In spite of the TCE sludge application having been discontinued in 1979 (*11*), all soil samples contained 6 ppb of "native" (unlabeled) TCE. No DCE's were found in any soil sample. (An analysis of the Des Moines TCE sludge itself by this laboratory and by an independent testing laboratory showed very high levels of TCE (3000 ppm), but no DCE was detected.)

TCE-$^{13}C_1$ was purchased from Merck Sharp & Dohme Isotopes. Single ^{13}C labeling was used to produce molecular and fragment ion peaks which did not have the same m/z values as the $^{35}Cl/^{37}Cl$ natural isotopic GC/MS analysis sho

†Present address: Department of Civil Engineering, University Illinois, Urbana, IL 61801.

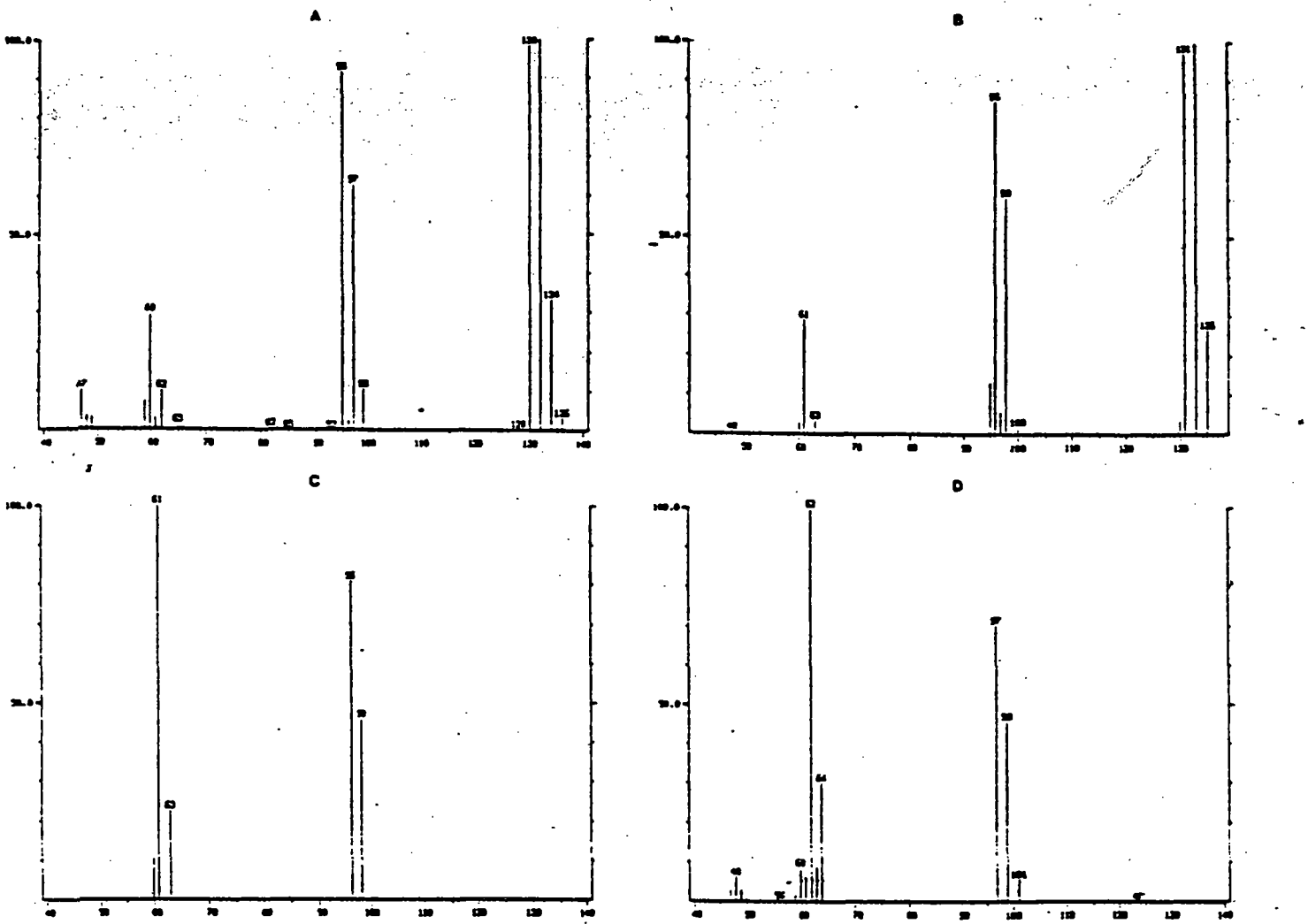

Figure 1. Representative mass spectra of trichloroethylene and 1,2-dichloroethylene: (A) trichloroethylene; (B) trichloroethylene-$^{13}C_1$; (C) 1,2-dichloroethylene; (D) 1,2-dichloroethylene-$^{13}C_1$.

contamination. Volatile organic standards were purchased from Supelco, Inc., and were diluted appropriately with methanol to contain 200 ppb of TCE and DCE. Soybean meal was obtained commercially.

Methods. Five grams of soil from each depth was placed in 5-mL amber vials which had been baked at 150 °C for 3 h to remove any adhering volatile organic compounds. One gram of soybean meal was added to each vial to ensure anaerobic conditions, and the vials were then filled with "organic-free" distilled water (which had been purged with nitrogen). (Organic-free water is distilled, passed through a carbon column, and checked for organics by using GC/MS methods.) The vials were sealed with Teflon septa. Samples to be sterilized were placed in an autoclave for 30 min at 15 psi. Each vial was then injected with 10 μg of TCE-$^{13}C_1$ (2000 ppb, or μg/kg). Duplicates of each sample were prepared. The sealed vials were transferred into CO_2/H_2 Anaerobic-Paks (BBL, Division of Bioquest), which were then placed in an incubator at 23 °C. As much as possible, the samples were kept in the dark to avoid photolytic degradation of the TCE. Subsets of the vials were removed for analyses at 6, 17, and 41 weeks.

Control and method blank samples were prepared as follows: (1) Vials containing only organic-free water, both with and without the TCE-$^{13}C_1$ spike, were prepared to monitor volatilization losses and to check for cross-contamination throughout the procedure. (2) Vials containing only soybean meal (both sterilized and unsterilized) and TCE to DCE by the soybean meal itself or any "foreign" microbes and to monitor adsorption of the TCE onto this organic matter. (3) For the 6-week samples only, vials containing soils A–C, soybean meal, and water without the TCE-$^{13}C_1$ spike were prepared as method blanks.

For the analyses, the contents of each vial were transferred to a 25-mL vial by using organic-free water to eliminate headspace again, sealed with a Teflon septum, mixed, and allowed to settle. Five milliliters of the supernatant liquid was then removed for volatile organics analysis using a Finnigan Model OWA GC/MS and standard purge and trap methodology (*12*, *13*). Detection limits for TCE and DCE by this method are estimated to be 1 ppb.

Results and Discussion

All compounds involved in this study were identified by their characteristic GC elution times and mass spectra. (Figure 1 shows the observed mass spectra of labeled and unlabeled TCE and DCE.) Both qualitative and quantitative identifications were effected from several selected ion mass chromatograms for each substance. For example, the ions at the listed m/z values were used for the analyses of the following compounds: TCE (m/z (95, 97, 130, 132, 134); TCE-$^{13}C_1$ (m/z 96, 98, 131, 133, 135); DCE (m/z 61, 63, 97, 99); DCE-$^{13}C_1$ (m/z 62, 64, 98, 100). No confusion resulted from peaks having the same m/z values for these substances since each compound (exclusive of its isoto-

Table I. Amounts (μg/kg) of 1,2-Dichloroethylene-$^{13}C_1$ Produced by Degradation of Trichloroethylene-$^{13}C_1$ in Unsterilized Soils

time, weeks	soil A[a]	soil B[a]	soil C[a]
6	8	7	11
17	28	31	8
41	78[b]	27	25

[a] See text for soil depth designations. Results are averages for duplicate samples; ranges were ±50%. [b] No duplicate value was obtained.

for the ^{12}C and ^{13}C compounds were identical. This assumption appears to be valid since we observed natural abundance ^{13}C peaks in the unlabeled TCE and DCE mass spectra having 2% of the intensity of the corresponding ^{12}C peaks (theoretical value 2.2%). The pertinent results of this study are discussed as follows:

(1) In the water-only samples, no cross-contamination was observed at any stage of the experiment. Therefore, no exogenous substances appear to have entered the sample vials.

(2) The vials containing the water with the TCE-$^{13}C_1$ spike showed considerable variability in their percent recoveries, indicating substantial and inconsistent volatilization losses of the TCE. We were thus unable to obtain reliable quantitative data measuring the conversion of TCE to DCE by following the rate of loss of TCE. Any experiment that measures only the loss of TCE appears to suffer from these volatilization problems and from adsorption problems (to be discussed next). No degradation products of TCE-$^{13}C_1$ were observed in these water and TCE-$^{13}C_1$ samples, so soil or microorganisms contained in the soil must be present to effect this conversion.

(3) In the samples containing water, soybean meal (whether sterilized or not), and the TCE-$^{13}C_1$ spike, no conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ was observed. Thus, these control samples eliminate the soybean meal as a potential source of TCE degradation. However, adsorption of the TCE on the soybean meal was significant. From 50 to 60% of the TCE spike was adsorbed after 6 weeks. As seen from the sterilized soil samples (where, except in one case of incomplete sterilization, *no* conversion of TCE to DCE occurred), another 10–15% of the TCE was adsorbed on the soil. Thus, adsorption losses pose another major problem in a study like this. Experiments that monitor the loss of, for example, TCE and attribute it solely to degradation are potentially suspect, particularly if care is not taken to account for volatilization and adsorption losses.

(4) The 6-week method blanks (containing water, soil, and soybean meal with no TCE-$^{13}C_1$ spike) showed no generation of any substance (TCE or DCE, labeled or unlabeled) not already present in the soil itself.

(5) Conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ was noted in *all* unsterilized soils. Table I summarizes the amounts of labeled DCE produced. As seen from Table I, a general and gradual increase in the amount of DCE-$^{13}C_1$ produced occurs with time. (Of course, due to adsorption and volatilization losses, the amounts of DCE-$^{13}C_1$ actually produced are no doubt larger than those reported here. Actual amounts of TCE → DCE conversion in "real" soils may be even larger than those reported here, since the soybean meal added to ensure anaerobiosis may well have been a more attractive energy source for the soil microbes than the TCE. Indeed, breakdown products of the soybean meal were also noted in the unsterilized soil samples.)

(6) With one exception, *no* sterilized soils demonstrated soil samples showed the presence of 2 ppb of DCE-$^{13}C_1$. This may, however, be the result of an incomplete sterilization since this was only observed for one of the longest time samples.

Since conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ occurred almost exclusively in unsterilized soils, microbial participation seems certain. Some caution should be exercised in drawing this conclusion, however, since Kaufman (*14*) has reported that autoclaving changes not only the biological properties of the soil but also its physical and chemical properties. Nevertheless, on the basis of our results for TCE and those of Parsons et al. (*10*) for PCE, it appears that the degradation of TCE to DCE in the soil is indeed of biological origin.

(7) Only 1,2-DCE-$^{13}C_1$ was produced whenever TCE-$^{13}C_1$ was degraded. No 1,1-DCE-$^{13}C_1$ (which elutes more rapidly than 1,2-DCE) was found in any sample. Under our experimental conditions, *cis*- and *trans*-1,2-DCE coeluted (and cannot be differentiated on the basis of their mass spectra). Thus, we could not identify which geometrical isomer was formed, or if a mixture of the two was produced. (In their study of PCE biodegradation, Parsons et al. (*10*) were able to separate the cis and trans isomers chromatographically. They found that *cis*-1,2-DCE is significantly favored over the trans isomer.)

Summary

By using TCE isotopically labeled with a single ^{13}C atom, we have shown that TCE is definitely dechlorinated in the soil to 1,2-DCE. Isomer specificity was also observed; no 1,1-DCE was detected. The TCE → DCE degradation appears to be biological in nature, since soil samples which had been sterilized exhibited no such conversion.

Since it has been shown that microbes that have adapted to degrade one member of a homologous series have also simultaneously adapted to degrade other members of the same series (*15*), the possibility exists that DCE can be further biotransformed into vinyl chloride in soils. Monitoring data at the Des Moines site (*11*) and elsewhere (*16*), this work and the work of Parsons et al. (*10*) all strongly support this DCE → vinyl chloride contention. Considering the well-known carcinogenicity of vinyl chloride, further research along these lines is definitely warranted.

Acknowledgments

We gratefully acknowledge John Caoile (of Ecology and Environment, Inc.) for obtaining the soil samples and Carl Bailey and Angelo Carasea (of the Region VII Environmental Protection Agency Laboratory) for providing technical assistance.

Registry No. TCE, 79-01-6; DCE, 540-59-0.

Literature Cited

(1) "Ambient Water Quality Criteria for Trichloroethylene"; U.S. Environmental Protection Agency: 1980; EPA 440/5-80-077 (NTIS #PP81-117871).
(2) Pearson, C. R.; McConnell, G. *Proc. R. Soc. London, Ser. B* 1975, *189*, 305–332.
(3) McConnell, G.; Ferguson, D. M.; Pearson, C. R. *Endeavour* 1975, *34*, 13–18.
(4) Van Dyke, R. A. *Environ. Health Perspect.* 1977, *21*, 121–124.
(5) Wilson, J. T.; Enfield, C. G.; Dunlap, W. J.; Cosby, R. L.; Foster, D. A.; Baskin, L. B. *J. Environ. Qual.* 1981, *10*, 501–506.
(6) Tabak, H. H.; Quave, S. A.; Mashni, C. I.; Barth, E. F. *J. Water Pollut. Control Fed.* 1981, *53*, 1503–1518.
(7) Haider, K. *Comm. Eur. Communities, [Rep.] EUR* 1980,

(8) Bouwer, E. J.; Rittman, B. E.; McCarty, P. L. *Environ. Sci. Technol.* 1981, *15*, 596–599.
(9) Bouwer, E. J.; McCarty, P. L. *Appl. Environ. Microbiol.* 1983, *45*, 1286–1294.
(10) Parsons, F.; Wood, P. R.; DeMarco, J. *J.—Am. Water Works Assoc.* 1984, *76*, 56–59.
(11) Caoile, J. "Field Investigations of Uncontrolled Hazardous Waste Sites", 1983, task report submitted to the Environmental Protection Agency, Contract 68-01-6056.
(12) Easley, D. M.; Kleopfer, R. D.; Carasea, A. M. *J. Assoc. Off. Anal. Chem.* 1981, *64*, 653–656.
(13) Longbottom, J. E.; Lichtenberg, J. J. "Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater"; U.S. Environmental Protection Agency: 1982; EPA 600/4-82-057, Method 624.
(14) Kaufman, D. D. In "Pesticides in Soil and Water"; Guenzi, W. D, Ed.; SSSA Publishers: Madison, WI, 1974; pp 133–202.
(15) Stanier, R. Y. *J. Bacteriol.* 1947, *54*, 339–348.
(16) Sprague, R. T., Post, Buckely, Schuh and Jernigan, Denver, CO, private communication, 1983.

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Gas-Phase Hydrogenolysis of Polychlorobiphenyls

Jeffrey A. Manion, Peter Mulder, and Robert Louw*

Gorlaeus Laboratories, The University of Leiden, 2300 RA Leiden, The Netherlands

■ Chloroarenes in an atmosphere of hydrogen are thermally dechlorinated to yield HCl and benzene as major products between 700 and 925 °C, with residence times of ca. 10 s. Polychlorobiphenyls (PCBs) are both dechlorinated and split into chlorinated benzenes, with splitting about twice as fast as dechlorination. Thermal hydrogenolysis, which occurs via radical mechanisms involving H atoms, may therefore be considered as a useful method for workup of (toxic) chlorinated wastes.

Following studies on thermolysis (*1–3*) and on several free-radical gas-phase aromatic substitutions—chlorination (*4*), cyanation (*5*), nitration (*6*), and oxidation (*7*)—we are now engaged in thermal conversions of benzene and derivatives with hydrogen. Within this category, "hydrocracking" of chlorinated arenes deserves special attention. In general, reaction 1 is of potential interest as a method

$$\mathrm{Ar(R)Cl + H_2 \xrightarrow{\Delta} Ar(R)H + HCl} \qquad (1)$$

for dechlorination of (highly) chlorinated industrial waste materials etc. Thermolysis of chlorinated benzenes in an excess of H_2 (quartz flow reactor, atmospheric pressure, residence time 5–15 s) proceeds smoothly at 750 °C and shows very high degrees of conversion (HCl formation) at ca. 900 °C (*8*). Sooting is unimportant even at 900 °C provided that the H_2:arene molar intake ratio is above 10. Aliphatic and olefinic chlorides, in general, react much faster than chlorobenzenes (*8*).

Polychlorobiphenyls (PCBs) have found widespread application, especially as transformer oil, its use and disposal entailing considerable environmental problems. We therefore thought it worth while to examine the behavior of PCB in hydrocracking (eq 1). Our observations, including those on appropriate model compounds reported below, confirm our expectation that PCB can be completely converted into HCl and non-chlorinated organic products, mainly benzene. Hydrocracking thus constitutes an environmentally clean alternative to incineration.

Representative examples with Aroclor 1248 (Cl = 48% wt) are outlined in Table I. That conversion of PCB is essentially complete and is illustrated by Figure 1. Dechlorination of chlorobenzene (PhCl) is ≥97%; monochlorobiphenyls are seen in minor amounts only, biphenyl comprising ca. 0.7% on the PhCl feed. This biphenyl stems from PhCl—or better, from benzene made

Table I. Thermolysis of PCB in Chlorobenzene with Hydrogen[a]

	run no.			
	1	2	3	4
T, °C	715	760	805	875
τ, s	8.9	8.3	8.3	7.6
conversion[b] of PCBs, %	(ca. 10)	28	70	>99.9[g]
$PhCl_2$,[c,e] %	4.8	8.5	1.5	0.2
$PhCl_3$,[c] %	1.2	1.5	0.10	0
Ph_2,[c] %	0.010	0.034	0.040	0.60
$ClPh_2$,[d,f] %	0.053	0.18	0.13	<0.03
PhH:PhCl molar ratio	0.059	0.19	0.92	35

[a] Spiralized quartz tubular flow reactor (3.5 m, 46 cm³); inflow (mmol/h): H_2, 221 ± 4; PhCl, 10.2; Arochlor 1248 (0.69); duration of runs 40–65 min.; product collected in a trap cooled with liquid N_2. [b] By GLC with PhBr as internal standard; total of surface area from dichlorobiphenyl on (retention time > 27 min, Figure 1), assuming response to be independent of chlorine content. These numbers parallel those for degrees of dechlorination of PhCl, $PhCl_2$ or $PhCl_3$ under the same conditions. [c] Mole percent on PCB in × 0.5. [d] Mole percent on benzenes out. [e] Isomer distribution (ortho:meta:para, %): run 1, 40:25:35; run 2, 37:27:36; run 3, 32:33:35. [f] Isomer distribution (ortho:meta:para, %): run 1, 31:34:35; run 2, 32:35:33; run 3, 34:38:28. [g] Confirmed by GC with electron capture detection.

The di- and trichlorobenzenes clearly stem from splitting of PCB and account for ca. 6% of the Arochlor feed. Chlorobenzene is produced via the same route but is obscured by its use as diluent. Its amount can be estimated from what is known about the composition of the PCB mixture. Specifically, the identified portion of Arochlor 1248, ca. half, is composed of the following ratios of phenyl units: Ph:PhCl:$PhCl_2$:$PhCl_3$ = 0.02:1:1.3:0.16. If changes due to the small degree of dechlorination are neglected, PhCl from PCB would thus be 1:(1.3 + 0.16) × 6 ≃ 4%, so as to give a total degree of splitting of about 10%. PhCl alone yields ca. 6% of HCl under these conditions so this mode of hydrogenolysis is about twice as fast as dechlorination.

As we have reported elsewhere (*8*, *9*), methane is also formed, ranging from 0.2% (run 1) to 1% (run 4) on PhCl feed; small amounts of C_2H_4 and C_2H_6 and traces of C_2H_2 are also produced.

Simultaneous splitting and dechlorination of PCB will cause the yields of $PhCl_3$ and $PhCl_2$ to pass through a maximum with increasing temperature. The same holds

THE DOW CHEMICAL COMPANY

THE DOW CENTER
MIDLAND, MICHIGAN 48640

October 5, 1984

AIRBORNE

Document Control Officer
Management Support Division
Office of Toxic Substances (WH-557)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Sir/Madam:

Attached for your information please find a copy of a summary of a report on a Lifespan Oral Carcinogenicity Study of Vinyl Chloride in Rats which we recently received and which I discussed with David Williams on Tuesday, October 2, 1984. This study was conducted in Europe by Civo Institutes TNO and was sponsored by Verband Kunstofferzeugende Industrie E.V. (VKI).

It is our understanding from VKI that the EPA will soon be receiving a copy of the final report. We do not have a copy.

Upon review of this summary, we have been unable to determine whether this study presents any substantial risk information under the EPA's Statement of Interpretation and Enforcement Policy. 43 Fed. Reg. 11110 (March 16, 1978). It appears from the minimal data presented in this summary that the study is corroborative of effects already documented in the scientific literature.

Sincerely,

John A. Gray

John A. Gray
Attorney
2030 Willard H. Dow Center
517/636-0933

To: Bob Oubre
From Fred Hoerger

Page 1 of 4

Attachment

bcc: F. D. Hoerger, 2020 WHDC
H. Schumacher, Horgen

1. The oral carcinogenicity of vinyl chloride monomer (VCM) was examined in a lifespan study (149 weeks) with five groups of Wistar rats, each consisting of 100 males and 100 females, except for the top-dose group which comprised 50 males and 50 females. VCM was administered by incorporating polyvinyl chloride (PVC) powder with a high VCM content into the diet. The diet was provided daily for a period of 4 consecutive hours, whereas food was withdrawn during the other 20 hours. The use of this way of oral VCM administration resulted in the following exposure levels: 0 (control), 0.014, 0.11 and 1.1 mg VCM/kg body weight/day. An extra control group of 100 rats/sex was housed in a separate room.
Additional satellite groups of 18 male and 10 female rats, each receiving the same treatment as the main groups were used for determinations of glutathione levels in the liver after 9 and 18 months.
Observations were made of general appearance mortality, growth, food intake, thrombocyte count, prothrombin time, glutathione levels in the liver, gross pathology and microscopic pathology of the liver and of all grossly visible tumours or presumable tumours in the abdominal cavity, the glands of Zymbal and the mammary glands.

2. General health, behaviour, body weight and food intake were not adversely affected by the test substance.

3. In the second half of the experimental period, mortality in the extra control group was higher than in all other groups. This was most probably due to a high incidence of chronic respiratory disease in the extra control group. In the final stage of the study, the mortality in the top-dose group was slightly higher than in the lower dose groups and the controls.

4. Thrombocyte count, prothrombin time and liver glutathione levels did not show treatment-related differences among the groups.

5. A clearly higher incidence of grossly visible, tumourous, liver nodules was found in both males and females of the top-dose group than in any of the other groups. Moreover, in females of the top-dose group the incidence of hepatic cysts was considerably higher than in controls.

6. Microscopic examination of the liver revealed increased incidences of liver-cell polymorphism, hepatic cysts, foci of cellular alteration, neoplastic nodules and hepatocellular carcinomas in the top-dose group as compared to the control group. Moreover, a hepatic angiosarcoma was found in one male and two females of the top-dose group, whereas no such tumours were encountered in any of the other groups.
The number of animals bearing foci of cellular alteration in the liver was also statistically significantly increased in females of the mid-dose group as compared to controls. In addition, in females but not in males, the incidence of basophilic foci of cellular alteration in the liver was statistically significantly higher in both the low- and the mid-dose group than in the control group.

7. There was no evidence of VCM-feeding affecting the incidence of abdominal mesotheliomas or the type and incidence of mammary gland tumours. No Zymbal gland tumour was found.

8. It was concluded that under the conditions of the present experiment:

- VCM at a level of 1.3 mg/kg body weight/day induces neoplastic and non-neoplastic changes in the liver of rats,

- VCM at a level of 0.13 mg/kg body weight/day may lead to more female rats bearing foci of cellular alteration in the liver,

- VCM at levels of 0.014 or 0.13 mg/kg body weight/day may result in an increased incidence of basophilic foci of cellular alteration in the liver of female rats,

- 0.13 mg VCM/kg body weight/day is a "no-observed-adverse-effect-level" with respect to the induction of tumours in rats.

9. Risk estimation based on the results of the present rat study and taking into account the prudence of the linear model applied and a lesser sensitivity of humans to the carcinogenic action of VCM in comparison with rats, indicates that the cancer risk of a likely maximum oral daily intake of 0.1 µg VCM per person per day can be practically neglected.

See also 32386

RISK MANAGEMENT OF EXISTING CHEMICALS

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CHAPTER 10

VINYL CHLORIDE AND TSCA

John T. Barr
Air Products and Chemicals, Inc.[1/]

INTRODUCTION

The well-known regulatory history of vinyl chloride and its role as a bellwether of current regulatory philosophy makes it a useful paradigm for examining the relationship of existing laws and the Toxic Substances Control Act (TSCA) for control of chronic hazards.

To this end, we will first review some of the highlights of its regulatory history, and then engage in some speculation as to the response these events might elicit today under TSCA.

INDUSTRIAL AND COMMERCIAL USE OF VINYL CHLORIDE

Vinyl chloride became of industrial importance about fifty years ago, approximately a hundred years after its discovery, when Semons discovered that its polymer could be converted into useful articles by plastization with phthalate esters. Commercial development began first in Europe and then in this country in the late

1/ Air Products and Chemicals, Inc., 1983.

thirties, largely using existing rubber processing equipment, for it was rubber which it initially replaced in the market. For the same reason, the use of polyvinyl chloride (PVC) was sequestered by the government during the war years, and it was not until the early fifties that widespread consumer applications developed. PVC is now a mature product, and its growth rate falls in step with the Gross National Product. Presently, about six billion pounds are used annually in this country, and about four times that in the world.

Some of the broader toxicological attributes of vinyl chloride (VC) were recognized in the thirties. It was known to be an anesthetic, but problems with cardiac arrythmia prevented its use in that application.[2/] As pathological techniques improved, industry scientists recommended in the early sixties that exposure be limited to 50 ppm, because of temporary liver enlargement in animals at that level,[3/] but the American Conference of Governmental and Industrial Hygienists considered this overly conservative and accepted instead the 500 ppm recommendation of Harvard scientists.[4/] This was the value adopted by the Occupational Safety and Health Administration (OSHA) in its formative days.

Also in the early sixties, the European industry recognized among its workers a disease termed acroosteolysis, AOL, which is a degenerative disease of the bone tufts, particularly in the fingers, that is accompanied by Reynaud's phenomenon.[5/] An extensive epi-

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2/ W. F. von Oettigin, "The Halogenated Hydrocarbons, Their Toxicity and Potential Dangers," Public Health Service Publication No. 414 (Washington, D.C.: U.S. Department of Health, Education and Welfare, 1955).

3/ T. R. Torkelson, F. Oyers, and V. K. Rowe, "The Toxicity of VC as Determined by Repeated Exposures of Laboratory Animals," American Industrial Hygiene Association Journal, XXII (1961), p, 354.

4/ American Conference of Governmental and Industrial Hygienists, "Documentation of the Threshold Limit Value, 1963" (Cincinnati, OH, 1963).

5/ S. Suciu, J. Drejman, and M. Valaskai, "Study of Diseases Caused by Vinyl Chloride," Medical Intern., XV (1963), p. 967.

demiological survey here and in Europe found about a hundred possible cases which were associated closely with manual cleaning of reactor walls between polymerization batches, but neither the precise etiological agent nor the disease mechanism was identified.[6/]

An attempt was made to reproduce this disease in rats by the medical department of one of the European producers. An exact duplication of the human disease was not seen, but many of the rats developed tumors at numerous sites. The reporting of this finding by Viola[7/] in 1970 evoked little interest in the regulatory community, possibly because of the very high doses used, several thousand ppm, which were frankly toxic to the animals, and the fact that the tumors were largely metastatic from the Zymbal gland, an organ not present in humans.

Nevertheless, both the European and domestic producers formed consortia to perform bioassays at lower concentrations and also began epidemiological surveys of their employees.

Preliminary results of the European bioassay became available first in early 1973, and showed tumor development at much lower concentrations in organs which do have human counterparts. This result was transmitted to regulatory officials that summer, and industry screening of employee records was intensified.[8/] This resulted in the recognition that winter by an industry medical director of a cluster of three rare liver tumors termed angiosarcoma, ASL, in the employees of one facility.[9/] The reporting of this fact to

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6/ W. A. Cook, et al., "Industrial Hygiene Evaluation of Thermal Degradation Products from PVC Fetus in Meat-wrapping Operations," Arch. Environ. Health, XXII (1971), p. 74. Also, B. D. Diman, et al., "Occupational Acroosteolysis I, An Epidemiological Study," ibid., p. 61.

7/ P. L. Viola, "Pathology of Vinyl Chloride," Medicina del Lavoro, LXI (1970), p. 174.

8/ A. W. Barnes, "ICI Ends Its Silence on Vinyl Chloride," Chemical Engineering News, (July 8, 1974), p. 21.

9/ J. L. Creech and M. N. Johnson, "Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted for Studies in Rats," Journal of Occupational Medicine, XVI (1974), p. 150.

government officials led to the current regulatory status of vinyl chloride.

It also led to a virtual explosion of research on the chronic toxicity of VC. The body of scientific literature on the oncogenicity of vinyl chloride is as large as that for any other substance. It is recognized that VC is a classical procarcinogen. Metabolism by the mixed function oxidase in the liver converts it to the ultimate carcinogen, an epoxide. Detoxification of this intermediate by the sulfhydryl group of glutathione or other proteins removes the toxic potential.[10/] Both of those mechanisms are saturable.[11/] An overload of the metabolic step assures that the vinyl chloride will pass through the liver and some will be metabolized in other organs. An overload of the detoxification step allows escape of the toxicant into the sinusoidal passages of the liver where interaction with the chromosomal protein causes ASL to develop. An overload of both mechanisms can lead to tumor development outside of the liver, as is seen in mice and rats at very high doses. Despite the large data base, however, information on the precise mechanism of these various steps still is lacking. We do not even understand why some persons respond with AOL and some with ASL, but none with both diseases.

REGULATORY STANDARDS

OSHA proceeded promptly in early 1974 to set an emergency temporary limit of 50 ppm for worker exposure, and later that year reduced the limit to one ppm, the current figure. Industry was given a grace period during which respirators could be used to meet this requirement, but now that level must be met by engineering practices.[12/]

10/ W. K. Lelbach and H. J. Marsteller, "Advance in Internal Medicine and Pediatrics" Springer-Verlag, XLVII (New York, 1981).

11/ R. Hefner, P. Watanabe, and P. Gehring, "Percutaneous Absorption of Vinyl Chloride Gas in Rhesus Monkey," Toxicology and Applied Pharmacology, XXXIV (1975), p. 529.

12/ OSHA Standard for Vinyl Chloride, 29 CFR 1910.1017.

The Environmental Protection Agency (EPA) promulgated a combined engineering and works practice standard in 1976 which has resulted in ambient concentrations in the fractional ppb range near producing or using facilities.[13/]

In the meanwhile, the Food and Drug Administration (FDA) and Consumer Product Safety Commission (CPSC) established prohibitions on the use of VC in aerosol or other consumer applications, a practice which had been discontinued in 1973. The Bureau of Alcohol, Tobacco and Firearms of the Treasury Department (BATF) had already banned the use of PVC liquor bottles in 1973 because of concern for taste effects from migration of residual VC into the contents. In 1975 the FDA proposed revocation of the generally regarded as safe (GRAS) status of rigid PVC packaging under the Delaney clause, also because of migration concerns, but that proposal never has been promulgated, and the FDA has stated that it is considering withdrawal of the proposal and recommending to BATF the reauthorization of plastic liquor bottles in light of the current very low residual monomer levels in fabricated PVC articles.

Other regulations have followed as new statutes and rules have come into play. The Department of Transportation (DOT) and the Coast Guard regulate the transportation of VC, of course, and VC is listed as a priority pollutant and hazardous waste under various water and solid waste rules, and has a reportable quantity of one pound under Superfund.

Did the existing laws operate satisfactorily at the time of discovery of the chronic hazards of VC? It appears that they did. A leading medical authority who was deeply involved in the worker health evaluation in 1974 has termed VC a "success story." Reevaluation of the risk to employees under the one ppm standard by a conservative nonthreshold extrapolation method[14/] yields a lifetime estimate of less than 10^{-8}, a risk level which is not thought to be of concern. The comparable risk estimate for the general populace is

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13/ EPA Standard for Vinyl Chloride, 40 CFR 61.60.

14/ P. J. Gehring, P. G. Watanabe, and C. N. Park, "Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted for Studies in Rats," Toxicology and Applied Pharmacology," XLIX (1979), p. 15.

several orders of magnitude lower. EPA has stated on several occasions that it believes that vinyl chloride is regulated adequately.

RISK ASSESSMENT

Risk assessment has been a popular avocation among those interested in VC, and more than a dozen have been performed.[15/] These can be divided generally into two classes: those which rely solely on animal data; and those which attempt to incorporate the human experience.

Those in the first class yield similar results, and show the normal spread of estimates from the various mathematical models in common use. These range from 1,500 to 10^{-5} ppb for a lifetime risk of 10^{-6}, or eight orders of magnitude. It is necessary to eliminate the high-dose data points, that is, those over 2,500 ppm from the Maltoni data[16/] in order to get reasonable fits to most models, because these doses show broad systemic toxicity. The lower doses, 500 ppm and below, as a group fall into a general pattern on a log-probit plot, but individual two or three dose experiments show tremendous differences in slope when plotted separately. The popular multihit model predicts a lifetime risk of 10^{-6} at fractional ppb levels.

The human factor was accounted for in two ways. The EPA used some preliminary employee epidemiological data to confirm its animal-based extrapolation.[17/] Unfortunately, the human data were

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15/ J. T. Barr, "Risk Assessment for Vinyl Chloride in Perspective," (Paper 82-9.2 presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, LA, 1982), Lines 20-25.

16/ C. Maltoni, et al., "Vinyl Chloride Carcinogenicity Bioassays (BT Project)," (Paper presented at "Le Club de Cancerogenese Chemique," Institute Curie, Paris, November 10, 1979).

17/ A. M. Kusmack and R. E. McGoughy, "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride," (Washington, D.C.: U.S. Environmental Protection Agency, December 5, 1975).

selected from those locations known to have ASL cases, while other facility data were omitted. They also were in error on the past exposures by more than an order of magnitude. This resulted in an estimate of 20 cases per year from the estimated 1974 ambient concentrations for the population within five miles of production and processing facilities.

The EPA seldom bothers to check its estimates against available data, so it sometimes comes up with results such as that made for arsenic a few years ago that would have predicted 18 million cases of skin cancer a year in this country if it had been applied to Agency data on the average arsenic concentrations in drinking water. Similarly, a survey of all known ASL cases in this country for the ten years before 1974 showed no cases associated with residency near such plants,[18/] rather than the 200 predicted cases. It is reasonable to assume that if any cases had developed since that time, the publicity associated with it would have brought them to light. Thus we have 110 million-person years of negative history for nearby residents. This places an upper limit on risk of less than 10^{-7} per ppm-yr.

Two studies applied pharmacokinetics in an attempt to obtain relevant human data. Gehring and coworkers estimated a lifetime risk of 10^{-8} at one ppm from the probit model, based on a biotransformation of rat data. The unconstrained linear model predicted no risk at less than 99 ppm.[19/]

Anderson, Hoel and Kaplan carried this procedure one step further, and applied it to bound metabolic products, rather than to the total amount metabolized. Their results gave a lifetime risk of 10^{-7} at less than one ppm, with the probit model, or at less than two ppm with the linearized multistep model.[20/]

18/ H. Popper, et al., "Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic," American Journal of Pathology, XCII (1978), p. 349.

19/ P. J. Gehring, P. G. Watanabe, and C. N. Park, Toxicology and Applied Pharmacology, XLIX (1979), p. 15.

20/ M. W. Anderson, D. G. Hoel, and N. L. Kaplan, "A General Scheme for the Incorporation of Pharmacokinetics in Low-dose Risk Estimation for Chemical Carcinogens. ibid., LV (1980), p. 154.

Thus we see that risk is in the eye of the estimator, but it is clear that estimates incorporating human data reflect the human experience for VC far better than do the direct application of animal data.

There was understandable uncertainty on the part of both the regulators and industry in 1974. This was the first commodity chemical to be regulated under the relatively new statutory situation as the result of new information. Nevertheless, both the regulatory agencies and industry acted promptly to reduce exposures and emissions to an acceptable level.

The current count of occupational ASL cases is about 100 worldwide, with 30 of these in this country.[21/] All these cases had their first exposure in 1964 or earlier, and there appears to be room for optimism that the steps taken in the mid-sixties because of the AOL information will have prevented any significant number of cases developing from exposures commencing after that date. Certainly it is reasonable to expect that there have been no new cases initiated after the early seventies.

Had TSCA been in place in the mid-sixties, would it have made any difference in the course of events? It appears unlikely that it would. Certainly the AOL discovery would have resulted in a series of 8(e) notices to TSCA. The probable outcome of that would have been either a recommendation from the Interagency Testing Committee (ITC) for more tests, or a Section 4 testing requirement. It is possible that, because of its commercial importance, VC could have been placed on the ITC list before the AOL data became available. Additional data could have been called for under Sections 8(a) and (d). The result of all this most likely would have been a negotiated testing rule, under which industry would have initiated a series of studies which would have culminated in a bioassay, and the carcinogenicity of VC would have been discovered in due time. Yet, this is precisely what did happen in the absence of TSCA, except that the preliminaries were omitted, and the bioassay was performed concurrently with the screening tests. Thus it is possible that the

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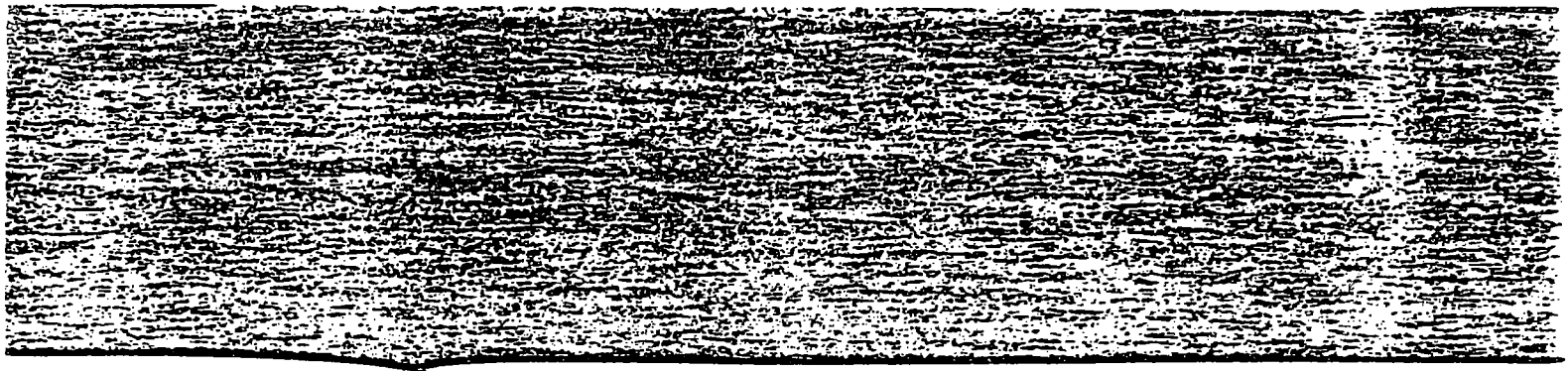
21/ J. Stafford, personal communication, Liver Angiosarcoma Cases, April 15, 1983.



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final critical data were obtained earlier than would have occurred under present conditions.

Bear in mind that most of today's powerful testing methods were not available twenty years ago. That fact would not have been changed by legislative fiat, and any decision made at that time had to be made in light of the available knowledge.

If the data of Viola suddenly became available today instead, would there be any significant difference in the outcome, or the timing of that outcome? Probably so, but only because of the vastly more powerful scientific tools which we have available to us now. Neither the speed of agency motion nor the rate at which industrial facilities can be built or modified has increased. If anything, the latter has slowed, given the multiplicity of permits and approvals now required. Overall, it is possible that if today we knew nothing more about VC than was known in 1970, we would arrive at a regulated state a few months earlier than was achieved in 1974, but scientific progress, and not legislative or regulatory advancement, should get the credit.

What if VC were to become a new product today? Would it run the same course in which it would be 40 years before there was full recognition of its chronic potential? Certainly not. Again, however, the reason is due more to scientific progress rather than statutory development.

One change might be apparent. If VC were the subject of a Premanufacture Notification (PMN) today, rather than being the model to which all other aliphatic olefins are compared for structure-activity analysis, it would be judged by the others in its family. This comparison would be less dogmatic than the reverse is now. Ethylene and vinylidene chloride are not animal carcinogens; the relevance to humans of the carcinogenicity of high doses of trichloroethylene (TCE) is equivocal and controversial; and vinyl acetate has only a preliminary "non-negative" report. Thus, this class of substances would have lost its leader for structure activity comparison, and a decision as to the need for further testing from that analysis would not be clear-cut, based on analogous compounds.

Neither would a full minimum premanufacture data (MPD) set be of any great assistance. VC responds poorly to the classical in-vitro tests, and only recently has it become possible to obtain reproducible positive results in many of these. If the position were taken

"little lists" for the executioners apparently is too great to be resisted,[26/] as Lester Lave pointed out recently.

We believe that EPA can best obey its statutory mandate by developing a more efficient system for establishing priorities, and by implementing more effectively its Section 9 procedures.

BIBLIOGRAPHY

American Conference of Governmental and Industrial Hygienists. "Documentation of the Threshold Limit Value, 1963." Cincinnati, OH, 1963.

Anderson, M. W.; Hoel, D. G.; and Kaplan, N. L. "A General Scheme for the Incorporation of Pharmacokinetics in Low-dose Risk Estimation for Chemical Carcinogens." Toxicology and Applied Pharmacology," Vol. LV (1980), 154.

Barnes, A. W. "ICI Ends its Silence on Vinyl Chloride." Chemical Engineering News, (July 8, 1974), 21.

Barr, J. T. "Risk Assessment for Vinyl Chloride in Perspective." Paper 82-9.2, 75th Annual Meeting of the Air Pollution Control Association, New Orleans, LA (1982).

Barr, J. T. "Establishing Regulatory Priorities." Toxic Substance Journal, Vol. IV (1983), 290.

Cook, W. A. "Industrial Hygiene Evaluation of Thermal Degradation Products from PVC Fetus in Meat-wrapping Operations." Arch. Environ. Health, Vol. XXII (1971), 74.

Creech, J. L., and Johnson, M. N. "Angiosarcoma of Liver in Manufacture of PVC." Journal of Occupational Medicine XVI (1974), 150.

26/ Lester Lave, "The High Cost of Regulating Low Risks," Wall Street Journal, August 19, 1983.

Diman, B. D., et al. "Occupational Acroosteolysis I, An Epidemiological Study." Arch. Environ. Health, Vol. XXII (1971), 61.

Environmental Protection Agency. "The Cost of Clean Air and Clean Water." Annual Report to Congress, Senate Document 96-38, December, 1979.

Gehring, P. J., Watanabe, P. G., and Park, C. N. "Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted for Studies in Rats." Toxicology and Applied Pharmacology, Vol. XLIX (1979), 15.

Hefner, R.; Watanabe, P.; and Gehring, P. "Percutaneous Absorption of Vinyl Chloride Gas in Rhesus Monkey." Toxicology and Applied Pharmacology, Vol. XXXIV (1975), 529.

Kusmack, A. M., and McGoughy, R. E. "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride." U.S. Environmental Protection Agency, Washington, D.C.; December 5, 1975.

Lave, L. "The High Cost of Regulating Low Risks." Wall Street Journal, August 19, 1983.

Lelbach, W. K., and Marsteller, H. J. "Advance in Internal Medicine and Pediatrics." New York: Springer-Verlag, Vol. XLVII (1981).

Maltoni, C., et al., "Vinyl Chloride Carcinogenicity Bioassays (BT Project)." Paper presented at "Le Club de Cancerogenese Chemique," Institute Curie, Paris, November 10, 1979.

National Research Council. "Regulating Pesticides." Environmental Studies Board, Committee on National Resources, Washington, D.C., 1980.

Popper, H., et al. "Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic." American Journal of Pathology, Vol. XCII (1978), 349.

Stafford, J. Personal communication, Liver Angiosarcoma Cases, April 15, 1983.

Suciu, S.; Drejman, J.; and Valaskai, M. "Study of Diseases Caused by Vinyl Chloride." Medical Intern, Vol. XV (1963), 967.

Torkelson, T. R.; Oyers, F.; and Rowe, V. K. "The Toxicity of VC as Determined by Repeated Exposures of Laboratory Animals." American Industrial Hygiene Association Journal, Vol. XXII (1961), 354.

Viola, P. L. "Pathology of Vinyl Chloride." Medicina del Lavoro, Vol. LXI (1970), 174.

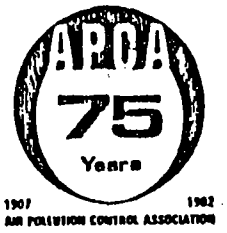
Von Oettigin, W. F. "The Halogenated Hydrocarbons, their Toxicity and Potential Dangers." Public Health Service Publication No. 414, U.S. Department of Health, Education and Welfare, Washington, D.C., 1955.

82-9.2

Risk Assessment for Vinyl Chloride in Perspective

John T. Barr

Air Products and Chemicals, Inc.
Allentown, Pennsylvania



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troduction

e combination of circumstances which found the carcinogenic hazard vinyl chloride (VC) being discovered at about the same time as the ience of risk analysis was undergoing rapid development, and the eat commercial interest and long history of use of the substance has sulted in a body of literature and pharmacological data greater than e can expect to have for most substances. It is therefore instruc- ve to review the many risk assessments which have been prepared for against the available biological information to determine if we can aluate the extrapolation methods used, and to discuss the current gulations for VC in light of this comparison.

zards of Vinyl Chloride

is necessary to decide first which of the hazards presented by VC ould be the basis for the risk estimation. The substance presents e acute hazards of frostbite from exposure to the liquid, of anes- esia at concentrations over 8,000 ppm and suffocation at higher ncentrations (von Oettinger, 1955). It also forms explosive mixtures air above 3.75 volume percent, and so the efforts to control the ysical safety of operations generally preclude exposure to acutely xic concentrations.

ese control efforts were reinforced in the mid-1960's where it was scovered (Suciu, 1963) that workers who had been exposed to very gh levels of VC developed "vinyl chloride disease," the primary nifestation of which was acroosteolysis (AOL), a degenerative disease the bone tufts in the hands, and more rarely of the feet and lumbar lon. Although crippling to some degree, this disease is not fatal, i is at least partially reversible if exposure is eliminated (Graniger, lker and Ward, 1980).

nost ten years later it was found that some of the workers having nilar exposure also were developing angiosarcoma of the liver (ASL), apidly fatal disease. Oddly enough, there is only one possible e of a worker developing both AOL and ASL (Stafford, 1981) among 80-plus cases of AOL and 90-plus cases of ASL now known worldwide, hough both are diseases of the vascular system. Several large demiology studies were conducted on workers exposed to VC (Baxter Fox, 1976; Chiazze, 1980; Duck, Carter and Coombu, 1975; Equitable ironmental Health, 1978; Fox and Collier, 1977; Frentzel-Beyme, nitz, and Theiss, 1978; Theriault and Allord, 1981), and ASL was only fatal disease found consistently to be in excess in these

persons. Animal studies have shown an excess of tumors at other sites, but the lowest exposures at which these occur are considerably higher than that for ASL. For example, Maltoni (1979) reported the following data:

Site	Concentration For Significant Elevation
Forestomach papillomas:	30,000 ppm
Neuroblastomas:	10,000 ppm
Zymbal gland carcinomas:	10,000 ppm
Nephroblastomas:	250 ppm
Liver angiosarcoma male:	200 ppm, 50 mg/kg
female:	50 ppm, 16.7 mg/kg
Mammary adenocarcinoma:	5 ppm

The low concentration for onset of mammary tumors was of concern when a preliminary study of fabrication employees reported an excess of breast tumors (Chiazze, et al., 1979) but a follow-up case-controlled study (Chiazze, 1980) found no association between the cases and VC exposure. The largest study of VC-PVC workers in the United States reported slight excesses of brain and lung tumors (Equitable Environmental Health, 1978), but this was not seen in the other studies referenced above. The excess of brain tumors was small, and not dose- or exposure-related. The overall excess of lung tumors resulted from an excess in one plant only, and reexamination of those cases also showed no association with VC exposure (Waxweiler, 1978).

Vinyl chloride has been found to be active in several in vitro mutagenetic tests with bacteria and yeasts (Hopkins, 1979) and it appears to cause chromosome abnormalities in exposed workers, but these changes are reversible when exposure is reduced (Hansteene, 1978) and several studies of neighborhoods around PVC plants have failed to show a supportable association with birth defects (Edmonds, 1975, 1976). It is not a teratogen in rodents (Johns, 1977).

Therefore it appears reasonable to assume that if there is any significant chronic risk other than ASL, it is considerably smaller than that for ASL, and that an adequate risk assessment can be based on only the liver tumors.

NOTE TO EDITORS

Review of Risk Assessments

1. Schneiderman, 1975

One of the first attempts to utilize animal data to estimate risks at very low exposures was that of Schneiderman, Mantel and Brown (1975). They used preliminary Maltoni results to compare the estimates obtained from three possible mathematical models. The 99% assurance level of a "safe" dose at a lifetime risk of 10^{-6} was estimated from several extrapolation models as follows:

Log Probit (slope = 1)	73 ppb
Logit (slope = 3.45)	119 ppb
Logit (slope 2.3, one-hit)	2.1 ppb

The authors discussed the recognized difficulties of extending these rat data to humans and of providing animal experiments that could answer satisfactorily the question of human risk at very low doses.

2. Kuzmack and McGaughy, 1975

The EPA was the first group to attempt a human risk assessment for vinyl chloride (Kuzmack and McGaughy, 1975). This pioneering effort attempted to use both animal and human data, and to show comparative results from both the linear and log-probit models. It concluded that there was an individual risk of 71×10^{-6} per ppm of lifetime exposure to VC by the linear extrapolation method, and that the log-probit results were one-tenth to one-hundredth of that.

This effort is subject to several serious criticisms. The exposure data used for human experience was that from a group with less than average exposure, while the ASL rate was chosen from only those plants which did report cases, and ignored the remainder of the population. Thus, their incidence rate of 7.5% compares to an actual figure of about 0.1%.

They used as their primary method a linear extrapolation of rat data, which often has been seen to overestimate the actual rates by at least two orders of magnitude, and they assumed the total cancer rate to be twice that found for ASL.

This same estimate was used by the EPA (1979) to estimate the concentration of VC in drinking water which would produce various levels of risk. These estimates are, of course, subject to the same criticisms.

Nisbet (1978) challenged the estimate of Kuzmack and McGaughy (1975) when it was used by Wilson in testimony before the OSHA hearing on its generic cancer policy. Nisbet stated that his calculations showed the risk to be 10-30 times greater, by the same calculation method. Wilson (1978) suggested several flaws

in the Nisbet procedure, including the fact that he chose for his extrapolation one point at 25 ppm from Maltoni experiment BT-15, and that this point is not in good agreement with the whole body of data. Further, he chose to use total cancer incidence in the rats, including those at zymbal glands, which have no counterpart in humans. Both Wilson and Kuzmack and McGaughy had used a factor of two times ASL to account for possible cancer at other sites. Wilson did acknowledge a mathematical error which made his results half the proper number.

Albert (1978) applied this same general procedure to other potentially carcinogenic air pollutants in the United States and calculated the expected annual cancer deaths as follows:

Arsenic	15.6
Benzene	77.8
Cadmium	26.2
Coke ovens	149.5
VC (after regulation)	1.0

3. Gehring, 1979

Gehring, et al., (1979) applied an experimentally derived biotransformation correction (Gehring, et al., 1978) to rat data and estimated the incidence in humans at two different exposures by means of four different extrapolation models. Their estimates at 500 and 200 ppm TWA bracket the observed experience for humans when derived from the probit and the unconstrained linear models. The linear-through-zero and one-hit models consistently overestimated the incidence. Although not considered by the authors, the linear and probit models match rather closely the total U.S. experience of occupational ASL at an assumed 1,000 ppm exposure. The linear model predicts no incidence below 99 ppm. The probit model predicts a human risk of 1.5×10^{-8} at 1 ppm. Thus, a mechanism for adjusting for the difference in metabolism between animals and humans appears to be useful.

A limitation of the Gehring procedure is that it uses partial Maltoni data, and tests the results against the CMA epidemiology study. That study was not the "end of the experiment"; it stopped at the end of 1973, and several deaths have occurred since then. Neither did it cover the entire population, but only the employees of those plants which met certain criteria for data retention and length of operation. The Stafford (1981) data does cover the entire population and extends the history for seven years. The size of the population is not known, but a reasonable estimate, based on normal worker turnover rates and the number of plants not included in the CMA study, is certainly not less than 25,000. This would give a gross incidence of about 0.1%. Of these, the number actually exposed to substantial exposures would be about 25-30 per plant at any one time. Multiplication by 25 plants, and a factor of three for the turnover during this period, would give about 2,000 highly exposed persons, for an effective inci-

dence of just over 1%. Personal experience would indicate that, for the period prior to 1964, when all of the first exposures of the fatal 26 cases had occurred, the average exposures of this highly exposed group certainly was in excess of 1,000 ppm for the working day. Maltoni (1979) found a 1% incidence at about 1-10 ppm in rats. Calculation of the dose equivalent to a 1% incidence in rats gives 0 ppm by the linear method and 7.5 ppm from the log-probit equation for the combined Maltoni inhalation experiments. This crude and subjective estimate would then say that man is about 100 times as resistant as the rat to VC inhalation, a figure generally in agreement with other estimates (NCAB, 1979).

Food Safety Council 1978, 1980

The Food Safety Council has recommended (FSC, 1978) the use of the gamma multi-hit model because of its flexibility in handling dose response data of varying curvilinearity at low doses. It has calculated (FSC, 1980) the maximum likely and lower 97.5% limit doses for substances at various risk levels and with different models. For VC, at 10^{-6} risk, these results are as follows (based on early Maltoni data):

One-hit	2.0×10^{-2} ppm
Armitage-Doll	2.0×10^{-9} ppm
Weibull	2.1×10^{-10} ppm
Multi-hit	3.9×10^{-10} ppm

For this substance, the goodness of fit of the Weibull model (0.56) was superior to that of the multi-hit (0.32). Neither of the other two models gave acceptable fits. This was in part because of the concave shape of the curve, which included all of the high doses in the dose response data.

5. Dow, 1979

A Dow Heath Team performed a relative risk estimation for several compounds (Langer, et al., 1979) which considered probable exposure, the consequence of exposure, the physical state of the substance during processing, and the current exposure standards. This resulted in a value of 480 for VC in a "closed system but with employees in the vicinity." The same procedure assigned hazard rating values to some other substances as follows: benzene, 10; phosgene, 410; hydrogen sulfide, 5; arsine, 9,700; and bis-chloromethyl ether, 69,700. In a batch operation with occasional manual handling, the hazard rating for VC increased to 9,700 by this method.

6. Mehir, 1980

Mehir, et al., (1980) conducted a series of tests for the Consumer Product Safety Commission, a part of which consisted of exposing rats and mice to a series of short, high exposures, rather than

the usual extended low dosage. They included one-hour exposures to rats and mice at 50, 500, 5,000, and 50,000 ppm, 10 and 40 hour exposures at 500 ppm, and 49 and 100 one-hour exposures at 50 ppm. After lifetime observation they found no effects on rats, or their offspring, nor on mice exposed to less than 500 ppm. Those exposed to over 500 ppm developed pulmonary adenomas, but they also had suffered from pneumonitis.

They considered the published data on animal exposures and concluded that there was a lifetime dose below which no oncogenic response is seen. This was estimated to be 5,000 ppm-hrs for mice and greater than 50,000 ppm for rats, regardless of whether the dose was administered over a short or long period. This concept of equality of effectiveness for all modes of exposure does not have general acceptance and would not appear to be correct, based on our present understanding of carcinogenesis. Dose-rate effects are, of course, well known. However, the degree to which this can be extended to all types of effects is not known.

These authors also used the Crump-Guess model (Crump, Guess and Deal, 1977) to evaluate their data on mouse pulmonary cancer, and estimated that exposure to 5,000 ppm VC doubles the probability of cancer, while 50,000 ppm increased the risk nine-fold. In view of the fact that pneumonitis was present in all animals exposed above 500 ppm, it is questionable if this was a direct oncogenic response, or the result of an nongenetic event because of severe lung damage. Maltoni (1979) also reports an increase in lung tumors in mice, but not in rats or hamsters. Thus, the significance of this finding to risk in humans is questionable.

7. Anderson, 1980

Anderson, et al., (1980) extended the work of Gehring, et al., (1978 and 1979) to incorporate the amount of metabolic products from VC which actually was bound to the DNA of exposed rats, (Gehring and Blau, 1977) rather than the total amount metabolized. They assigned various values to the parameters in a Michaelis-Menten equation depicting the kinetics of the metabolic process, and compared the results from extrapolation to low doses by log-probit and multi-hit models. They found that the two extrapolation models responded quite differently to these variations at very low doses, and that it was not possible to select one model as the more appropriate from the high-dose data. Use of the values of Gehring for the primary parameters gave estimates of the dose equivalent to lifetime risks of 10^{-7} of less than 1 ppm for the probit model and less than 2 ppm for the multistage model, a correspondence which the authors pointed out was better than the precision of interspecies comparisons.

8. EPA, 1980

The final version of the water quality criteria document for VC (EPA, 1980) used a different approach for risk estimation. The slope of the incidence of all tumors at the lowest doses of Maltoni experiment BT-1 was adjusted for the fraction of exposure, the equivalent feeding level to give the same blood concentration of VC as by inhalation (see Withey and Collins, 1976), and the ratio of the surface area of humans vs. rats, to produce an estimate that a lifetime risk of 10^{-5} would be caused by drinking 2 l/day of water containing 20 g/l. There is some confusion in the mathematics given in the report, and the assumptions on which the adjustments are made are far from having general acceptance, although generally following NAS recommendations. It appears that this procedure overstates the risk by several orders of magnitude.

9. NAS, 1980

The National Academy of Science (1977) calculated the upper 95% confidence limit for risk from drinking water containing vinyl chloride from the probabilistic multistage model and early Maltoni rat data. They report (NAS, 1980) a lifetime risk of 10^{-5} as being equivalent to $3.08 10^{-3}$ mg/kg/day. For a 70 kg person consuming 2 l/day, this would calculate to an acceptable level of 1 g/l. The difference between the EPA and NAS numbers comes from the different curve-fitting methods for the animal data.

10. Gaylor and Kodell (1980) applied linear "interpolation" to the same early Maltoni data used by the Food Safety Council (1978) to arrive at a predicted maximum risk of 10^{-6}. The upper 97.5% confidence limit of the animal data was taken as one point on the interpolative line, and zero incidence at zero exposure as the other. This produced a lower 97.5% confidence limit dosage of 7.1×10^{-4} ppm for a lifetime risk of 10^{-6} in rats. Their application of the Armitage-Doll multistage model gave 5.2×10^{-4} ppm as the dosage at 10^{-6} lifetime risk compared to 2×10^{-2} by the Food Safety Council. The difference is due to alternative assumptions on the value of the exponential dose term.

11. Crump and Guess (1980) reviewed some of the earlier risk estimates for vinyl chloride in drinking water, and recalculated the risks, using the one-hit and multistage models. They arrived at an upper 95% confidence limit of lifetime risk for drinking water containing 1 g/l of VC of 4×10^{-6}, based on early Maltoni inhalation data. Using the assumption that a 0.2% incidence of ASL in workers had resulted from a lifetime exposure of 70 g/kg, they obtained a maximum likelihood risk of 10^{-6} from 0.34 g/l by both the multistage and linear models, with 95% lower confidence limits of the same risk at 0.24 g/l. These two models reduce to a linear form when used at very low doses and with the assumption of no threshold value.

These authors cite EPA data on the occurrence of VC in public water supplies which by their methods yield a lifetime risk of 3.7×10^{-6}, or 12 deaths per year from this cause in the United States. None of these has been observed, despite the accumulation of 15 years' data on ASL deaths (Popper, 1978).

12. Scott (1981) ascribed the decreased incidence of tumors in rats at the higher doses to a cell killing process, and adopted the Weibull model to account for this. Application of the model to some early Maltoni data produced a curve which fit the data from 50-10,000 ppm. He did not attempt to extrapolate to doses beyond the experimental range.

13. Carlborg, 1981, also applied the Weibull model to 31 bioassay reports on a variety of animal carcinogens. He concluded that the one-hit model was not appropriate and that carcinogens could be divided into categories according to the shape of the curve, e.g., concave or convex. He found that the early Maltoni data on VC fell into the former category. Application of his parameter estimates to those data, assuming no spontaneous incidence of ASL, gives 2.5×10^{-8} ppm for a lifetime risk of 10^{-6} for rats. Later calculations including all of the published Maltoni data did not change the results significantly (personal communication).

He found the Weibull shape parameter to be approximately 0.5, which is assumed to be the number of stages for tumor initiation. This is consistent with the finding by Gehring (1977) of a saturable metabolic path which produces the proximate carcinogen. It also suggests that the number of "stages" is the number of finite-rate steps before the rate-limiting step. There may be other stages following, but they are not rate controlling. Actually, there appears to be at least two saturable mechanisms involved in the pharmacokinetics of VC, the metabolism to the ultimate carcinogen and the detoxification by sulfhydryl groups.

14. One further evaluation of human risk can be made from the experience of persons residing near VC-PVC plants. The EPA estimated (Kuzmack and McGaughy, 1975) that five million persons lived within five miles of these plants, and were exposed to an annual average concentration of 17 ppb. The present distribution of plants was generally well-established by 1959, thus we have 22 years of history, or about 110 million person-years. About five or six of these plants, with 1-2 million neighbors, go back another 20 years, but these data are not firm enough for inclusion.

The fact that no case of ASL has been confirmed as arising from these ambient exposures places the upper bound of risk at less than 2.7×10^{-9} per ppm-yr. It is believed that the exposure data were overestimated by EPA, and thus this result may be too low, but it is in the same general range as that arrived at by Gehring (1979) and Anderson (1980) after making corrections for pharmacokinetics.

Extending this crude calculation, these five million persons are now supposed by EPA to be exposed to 0.2 ppb (probably a high figure), which would predict no more than 0.0003 deaths per year, or one per 3,700 years in that whole population due to VC exposure. But it also must be recognized that with approximately 20 cases per year of ASL in the general population, there can be expected from a purely statistical basis that there should be one case every two years or so among this group of 5 million plant neighbors.

The results of these estimates discussed above are compared in Table I, after conversion to a uniform 10^{-6} lifetime risk. Estimates 5, (Dow 1979) and 12 (Scott, 1981) were not in a form to permit this comparison. See OSHA, (1980), for references to a few other estimates that were not considered here.

It can be seen that the results fall into two major categories, those which project that the risk of 10^{-6} occurs at exposures of greater than 1 ppm, and those which find that risk in the ppb range. The estimates which yield the higher allowable exposures are based on human data (Nos. 3, 7 and 14) or use a log-probit extrapolation model (No. 2, second estimate), or predict a threshold (No. 6). The remainder generally are based on the linear, non-threshold model, and make no biological correction. The result is a difference of 3 or 4 orders of magnitude. The estimates which yield the higher allowable exposures are in better agreement with human experience than are those of the other group.

Additional Data

All of the extrapolations reported here have used for the original Maltoni data from his experiment BT-1. He has now reported (Maltoni, 1979) three other comparable inhalation experiments on the same strain of rats, and one on another strain, in addition to two ingestion studies. The results of these experiments are shown in Figure 1, on a log-probit scale. It can be seen that they all follow a similar pattern, but that there are large variations in slope between the various data groups. Table III contains the log-probit equations calculated from some of the individual experiments, and various groups of experiments. Excellent fits are obtained for a single experiment, as would be expected from the small number of data points, but adequate fits are obtained for the group as a whole. Inclusion of the historic control data on ASL (0.09% spontaneous incidence) did not affect the fit substantially, except for the very low dose data. Inclusion of the 0,0 (origin) as a data point did give significantly poorer fits. The combined experiments indicate that a lifetime risk of 10^{-6} for rats is obtained from a dose in the 1-2 ppb range.

Similar variation is seen with the other mathematical expressions, such as linear or exponential equations.

Regulatory Status

The current regulatory status of vinyl chloride is summarized in Table II. The first regulatory action on VC was taken in 1973 when the Bureau of Tax, Alcohol and Firearms prohibited the use of rigid PVC as liquor containers. This was based on it being present as an adulterant, and not on any consideration of risk. The Consumer Product Safety Commission (CPSC), the Food and Drug Administration, (FDA), and the EPA all acted to ban the use of VC as an aerosol propellant thus establishing a zero risk position. The FDA proposed (FDA, 1975) to withdraw the prior sanction status of rigid PVC as a food package component because of the concern for residual VC that might migrate. The FDA has taken no further action on this proposal, and now is considering a "constituent" policy which would permit a lifetime exposure at some acceptable risk level. This risk has been proposed recently to be 10^{-6} lifetime for the gluttonous consumer. As was discussed above, the EPA required a best available technology approach which reduces the average exposure to those within 5 miles of a plant to about 0.2 ppb, by EPA estimates. OSHA established a rule in 1974 which set 1 ppm for 8 hours as the maximum permissible exposure, and also set 0.5 ppm as an action level below which most features of the regulation did not apply. These were chosen as feasible levels, and not necessarily "safe" doses (OSHA, 1974; EPA, 1976).

The EPA has established an exposure to the general population only 0.1% of that allowed in the workplace. The CPSC has required zero exposure, and the FDA has considered that approach. Depending on which method of estimation the FDA may choose, its allowable exposure could be either greater or less than those currently set by EPA and OSHA. It has been estimated that the maximum amount of VC ingested by the average European, who uses much more plastic packaging than we, is less than 2_6 g/day, (CEFIC, 1976) which would be in the order of a 10^{-5} or 10^{-6} lifetime risk by even the most conservative models.

There have been various estimates made of the cost-effectiveness of the Federal regulation for vinyl chloride. Graham and Vaupel (1981) estimated that the OSHA rule cost $7.5 million per life saved, and $490 thousand per life-year saved over the option of leaving the exposure limit at 50 ppm. Luken and Miller (1981) state that the imputed value of a life from the OSHA standard is $4 million. Morrell (1982) uses an annual cost of $20 million and an annual benefit of 0.1 life saved to derive a cost/benefit of $200 million per life for the OSHA rule. The EPA has reported (EPA, 1979) that the cost of compliance with its VC standard was $296 million through July 7, 1981, and will be an additional $470 million during the next five years, all in 1977 dollars. If the EPA estimate of up to 20 deaths per year were correct, this would be a cost of $4.7 million per life. However, as discussed here, there is no evidence that any lives have been saved by this rule.

There are many difficulties in obtaining accurate estimates of this type, and serious problems in determining the proper value to be assigned to a life. nevertheless, the doubtful nature of the claims

for any significant benefit from these rules suggests that at best, these regulations are excessively costly to society. Therefore, we must attempt to improve both our data base and our methods for interpreting and applying the data.

Discussion

What can be learned from this exercise other than the already recognized fact that various extrapolation models can yield very different results? In this case, at least, there are several points which are worth considering.

1. Vinyl chloride is no exception to the rule that human data always must be incorporated whenever possible. The epidemic of occupationally induced ASL which was feared in 1974 has not materialized, probably due to the steps that were taken in the early 1960's to reduce exposure because of the discovery of AOL. No instances of ASL from exposure to VC in the general population have been substantiated. The overprediction of occupational cases was due to the underestimation of worker exposure and overreliance on raw animal data without proper pharmacokinetic adjustment. We are not now able to extrapolate reliably between similar species and certainly not from rodents to humans, without much additional data.

2. The regulations for vinyl chloride were not based primarily on scientific data, but on socioeconomic and political decisions. This is no surprise (Crandall and Lave, 1981), but is a fact which should be acknowledged openly, along with the understanding that this position will continue to penalize good science.

3. Mathematical extrapolation models are not adequate in themselves for predictions of risks much beyond the experimental range, no matter how good the fit is to the data in the observed range. The variability of relatively small experimental groups adds to the error range. Thus, bioassays intended for quantitative risk assessment applications should be at as low doses as possible, and as large as possible, and should be interpreted very cautiously.

4. The current state of the art is such that quantitative risk assessments may be useful for determining relative risks from similarly acting carcinogens, but are not suitable for across-the-board application to all mechanisms of carcinogenesis.

   This is not to say that we should abandon efforts at developing more effective risk assessment methods. We must, however, recognize the problems inherent in blind application of mathematical models without proper assessment of the available biochemical data, or an understanding of how applicable the experimental data are to humans.

We have available to us at least as much data regarding vinyl chloride as we have for any other substance, and we still have difficulty in deriving a suitable expression for risk from a purely mathematical or statistical basis. Only when human relevance is considered can we arrive at a prediction that approximates actual experience.

The regulators are faced with a tremendously difficult task when they are presented with a few pieces of animal data which suggest the need for concern and potential regulation. We must develop a suitable program to obtain and use as much relevant data as possible to assure that rational regulations are possible. The vinyl chloride experience can help us understand the kind of data which are needed.

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2/19/82
lbh

References

Albert, R. E., letter to R. S. Naveen, EPA, "Comparison of vinyl chloride carcinogenic risks with risk from other pollutants", Washington, DC, 16 June 1978.

Anderson, M. W., et al., Tox. Appl. Pharm. 55, 154 (1980).

Baxter, P. J., and A. J. Fox, Lancet, 1976 245.

Carlborg, F. W., Fd. Cosmet. Tox. 19 255 (1981).

CEFIC Committee for the Toxicity of Vinyl Chloride, "Vinyl Chloride Toxicity and the use of PVC for Packaging Foodstuffs," Brussels, Feb. 1976.

Chiazze, L., J. Occup. Med. 22 (10) 677 (1980).

Chiazze, L., Jr., W. E. Nichols, and O. Wong, J. Occup. Med., 19 623 (1977).

Crandall, R. W., and L. Lave, "The Scientific Basis of Health and Safety Regulations," Brookings Institution, Washington, 1981.

Crump, K. S., and H. A. Guess, "Drinking Water and Cancer", PB81-128167, December, 1980.

Crump, K. S., H. A. Guess, and K. L. Deal, Biometrics, 33 4370451 (1977).

Duck, B. W,, J. T. Carter, and E. J. Coombes, Lancet 1975 ii, 1197.

Edmonds, L., "Birth Defects and Vinyl Chloride", Proc. Conference on Women and the Workplace, Washington, DC, 1976, also Teratology, 17 137 (1978).

Edmonds, L. D., H. Falk and J. E. Nissim, The Lancet 1975 1098.

Environmental Protection Agency, Standard for Vinyl Chloride, 41 Fed. Reg. 46,560 (1976).

Environmental Protection Agency "Vinyl Chloride, Ambient Water Quality Criteria", PB-292446, Washington, DC, 1979.

Environmental Protection Agency "Ambient Water Quality Criteria for Vinyl Chloride," EPA 440/5-80-078, October, 1980.

Envirnomental Protection Agency "The Cost of Clean Air and Clean Water", Annual Report to the Congress, December, 1979b. Senate Document No. 96-38. U.S. Government Printing Office, Washington, DC.

Equitable Environmental Health, Inc., "Epidemiological Study of Vinyl Chloride Workers, Final Report". Prepared for Manufacturing Chemists Assoc., Washington, DC, January, 1978.

Food and Drug Administration, Notice of proposed rulemaking, 40 Fed. Reg., 40,529 (1975).

Food Safety Council Final Report "Proposed System for Food Safety Assessment", Washington, DC, June, 1980.

Food Safety Council, Scientific Committee "Proposed System for Food Safety Assessment." Food and Cosmet. Tox. 16 Suppl. 2 December 1978.

Fox, A. J., and P. F. Collier, Br. J. Ind. Med. 34 1 (1977).

Frentzel-Beyme, R., T. Schmitz, and A. M. Thiess, Arb. Socialmed. Pravent., 13 218 (1978).

Gaylor, D. W., and R. L. Kodell, R. L., J. Environ. Pathol. Tox. 4 305 (1980).

Gehring, P. J., and G. E. Blau, J. Environ. Pathol. Toxicol, 1 163 (1977).

Gehring, P. J., P. G. Watanabe, and C. N. Park, Tox. and Appl. Pharm. 49 15 (1979).

Gehring, P. J., et al., Tox. Appl. Pharmacol. 44 581 (1978).

Graham, J. D., and J. W. Vaupel, Risk Analysis 1 89 (1981).

Graniger, R. G., A. E. Walker, and A. M. Ward "Vinyl Chloride Monomer-induced Disease: Clinical, Radiological and Immunological Aspects," Chapter 11 in "Induced Disease; Drug, Irradiation, Occupation", L. Preger, ed., Grune and Stratton, London, 1980.

Hansteene, J.-L., et al., Mut. Res. 78 211 (1978).

Hehir, R. M., et al., "Toxicology, Carcinogenicity and Reproductive Effects of Single and Multiple Exposures to Vinyl Chloride in Rats and Mice", Pre-publication draft, Feb. 6, 1980, U.S. Consumer Product Safety Commission, Washington, DC.

Hopkins, J., Fd. Cosmet. Toxicol., 17 542 (1979).

John, J. A., et al., Tox. and Appl. Pharmacol. 39 497 (1977).

Kuzmack, A. M., and R. E. McGaughy, "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride", U.S. EPA, Washington, DC, December 5, 1975.

Langer, R. R., S. K. Norwood, G. E. Socha, and H. R. Hoyle, Am. Ind. Hyg. Assn. J., (12) 1039 (1979).

, R.H., and S. G. Hiller, J. Air Pol. Control Assoc, 31 1254
).

ıi, C., G. Lefemine, A. Ciliberti, G. Cotti, and D. Carretti,
Chloride Carcinogenicity Bioassays, (B T Project) as an
imental Model for Risk Identification and Assessment in
ınmental and Occupational Carcinogenesis" Presented at "Le Club
ıcerogenese Chimique", Institute Curie, Paris, Nov. 10, 1979.

ıal Academy of Science, "Drinking Water and Health", National
ıy Press, 1977.

ıal Academy of Science, "Drinking Water and Health", Vol. 3, p.
ıtional Academy Press, 1980.

ıal Cancer Advisory Board, "The Relation of Bioassay Dose to the
ıment of the Risk of Carcinogens for Humans under Conditions of
ıposure", Subcommittee on Environmental Carcinogenesis, Draft of
citing data from Meselson and Russell, 1979.

., I.C.T., Post-hearing statement to OSHA docket 090, September
978.

ıtional Safety and Health Administration, Standard for Exposure
ıyl Chloride, 39 Fed. Reg. 35,890 (1974).

', H. et al., Am. J. Pathol. 92 349 (1978).

ıderman, M. A., N. Mantel, and C. C. Brown, Ann. NY Acad. Sci.,
17 (1975).

B. R., Bull. Mathematical Biology, in press, 1981.

ırd, J., private communication (1981).

J., J. Drejman, and M. Valaskai, Med. Intern. 15 967 (1963).

ult, G., and P. Allard, J. Occup. Med., 23 (10) 671 (1981).

ttingen, W. F., Public Health Service Publication No. 414, U.S.
ment of Health, Education and Welfare, Washington, DC, 1955.

ler, R., et al., "An Epidemiological Investigation of an Excess
ancer Risk in a Synthetic Chemicals Plant", Presented at the
enth International Congress for Occupational Health, Dubrovnik,
Sept., 1978.

, R. "Response to comments of I. C. Nisbet," Post-hearing record
ocket 090, 1978.

', J. R., and B. T. Collins, J. Tox. Envir. Health, 2 311 (1976).

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FIGURE 1
GRAPHICAL REPRESENTATION OF TABLE III
LOG-PROBIT PLOT

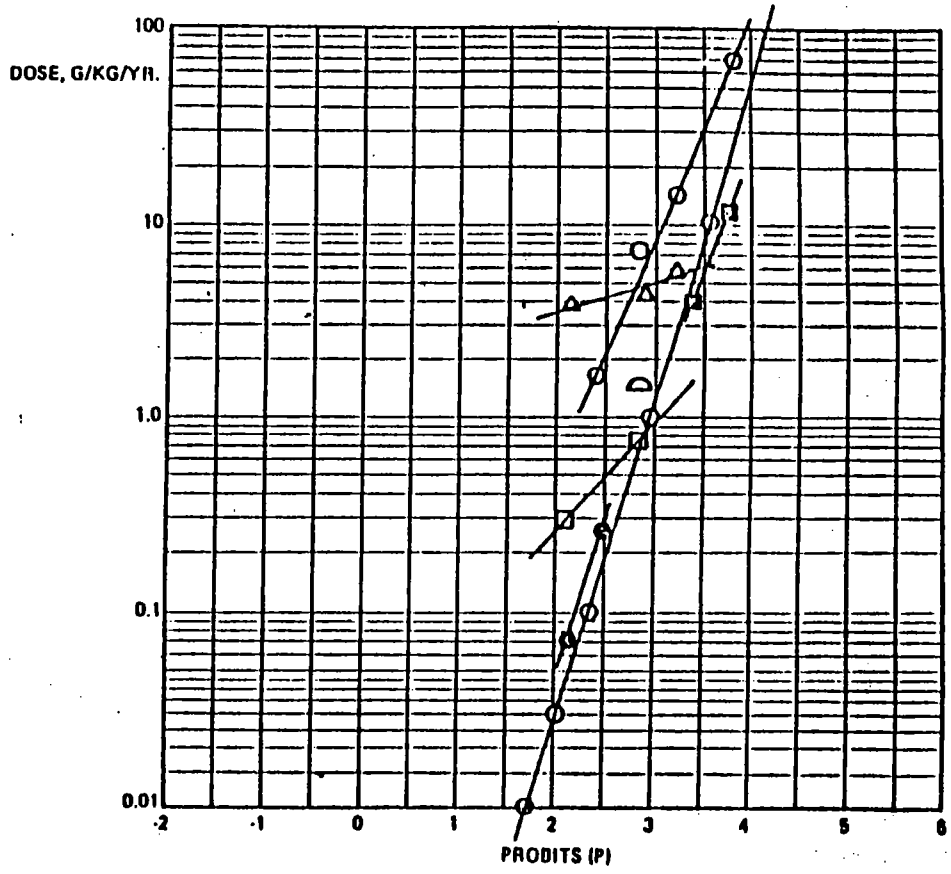


TABLE I
SUMMARY OF
QUANTITATIVE RISK ASSESSMENTS FOR VC

ESTIMATE NO.	AUTHOR	BASE SPECIES	EXPOSURE FOR 10^{-6} LIFETIME RISK	COMMENTS
1	SCHNEIDERMAN, 1975	RAT	73 ppb 119 ppb 2 ppb	LOG-PROBIT LOGIT SLOPE = 3.45 LOGIT SLOPE 2.3, 1-HIT
2	KUSMACK & McGAUGHY, 1975	RAT, HUMAN	14 ppb 140-1400 ppb	LINEAR THROUGH ZERO LOG-PROBIT
3	GEHRING, 1975	RAT, HUMAN	>1 ppm	BIOTRANSFORMAL DATA AND LINEAR OR LOG-PROBIT
4	FOOD SAFETY COUNCIL, 1980	RAT	2×10^{-6} ppb	WEIBULL
6	HEIIR, 1980	RAT, MOUSE	THRESHOLDS SEEN IN BOTH SPECIES	
7	ANDERSON, 1980	RAT, HUMAN	>1 ppm	DNA BINDING
8	EPA, 1980	RAT	4 μG/DAY	FOOD OR WATER
9	NAS, 1980	RAT	3×10^{-5} MG/KG/DAY	WATER
10	GAYLOR & KODELL, 1980	RAT	0.7 ppb 0.5 ppb	UPPER 97.5% CONFIDENCE LIMIT OF LINEAR MODEL ARMITAGE-DOLL MODEL
11	CRUMP & GUESS, 1980	HUMAN RAT	0.7 μG/DAY 0.6 μG/DAY	APPLYING WORKER DATA TO WATER, UPPER 95% CONFIDENCE LIMITS
13	CARLBORG, 1981	RAT	2.5×10^{-5} ppb	WIEBULL
14	THIS PAPER	HUMAN	>1 ppm	NEGATIVE EPIDEMIOLOGY

TABLE II
REGULATORY STATUS OF VINYL CHLORIDE

AGENCY	CONTROLLED LEVEL	PHILOSOPHY
BATF	BANNED AS LIQUOR BOTTLE	ADULTERANT
CPSC	BANNED IN CONSUMER PRODUCTS	ZERO RISK
FDA	USE IN RIGID FOOD PACKAGING QUESTIONED	CONSIDERING ACCEPTABLE RISK
EPA	APPROXIMATELY 0.2 ppb	BEST AVAILABLE TECHNOLOGY
OSHA	1 ppm 8-HR TWO MAXIMUM 0.5 ppm ACTION LEVEL	LOWEST FEASIBLE LEVEL

TABLE III
EQUATIONS FOR CURVES FITTED TO VARIOUS SINGLE AND COMBINED MALTONI EXPERIMENTS

EXPERIMENT	LINEAR y=ax + b			LOG PROBIT P=a IN DOSE + b			CONCENTRATION AT 10^{-6} RISK, (LOG-PROBIT), ppm
	a	b	r	a	b	r	
BT-1	0.26	3.36	0.97	0.35	2.76	0.99	0.03
PLUS CONTROLS	0.27	2.47	0.97				
BT-2	3.05	-8.59	1.0	1.60	0.88	1.0	23
PLUS CONTROLS	1.52	-1.13	0.88				
BT-15	6.5	-1.06	1.0	0.69	3.46	1.0	0.34
PLUS CONTROLS	5.28	-0.30	0.95				
ALL INHALATION STUDIES (4)	0.26	3.07	0.91	0.27	2.98	0.82	0.002
PLUS CONTROLS	0.27	2.80	0.91				
ALL INGESTION STUDIES (2)	1.75	0.15	0.95	0.30	3.22	0.88	0.002
PLUS CONTROLS	1.74	0.20	0.95				
ALL STUDIES (6)	0.29	3.60	0.73	0.27	3.05	0.82	0.001
PLUS CONTROLS	0.29	3.41	0.72				
ALL STUDIES; LOW DOSES ONLY				0.51	2.53	0.75	0.42
PLUS CONTROLS	1.03	0.97	0.79	0.17	2.71	0.49	0.0002

APPENDIX V

HEALTH EFFECTS REQUEST TO DHS AND LETTER OF RESPONSE

Memorandum

To : Kenneth Kizer, Director
Department of Health Services
714 P Street
Sacramento, CA 95814

Date : June 17, 1985

Subject: Evaluation of Vinyl Chloride

From : James D. Boyd
Executive Officer
Air Resources Board

I am writing to request formally that the Department evaluate the health effects of vinyl chloride as a candidate toxic air contaminant in accordance with Assembly Bill 1807 (Tanner). According to Health and Safety Code Sections 39660-62, your Department has ninety days to submit a written evaluation and recommendations on the health effects of vinyl chloride to the Air Resources Board and may request a thirty day extension.

Attached for your staff's consideration in evaluating vinyl chloride are: Attachment I - a suggested list of topics that we believe should be included in your vinyl chloride evaluation and recommendations; Attachment II - a list of references on vinyl chloride health effects which were presented in an ARB letter of public inquiry; Attachment III - additional references and comments received from the public in response to the inquiry letter; and Attachment IV - ambient vinyl chloride concentration data and emission data which should be used to estimate the range of risk to California residents as required in Health and Safety Code Section 39660(c).

My staff is available for consultation in conducting this health effects evaluation. We look forward to continuing to work closely with you and your staff in carrying out this legislative mandate. If you have any further questions regarding this matter, please contact me at 445-4383.

Attachments

cc: Jananne Sharpless
Alex Kelter, w/attachments
Raymond Neutra, w/attachments
Peter D. Venturini
Assemblywoman Sally Tanner
Claire Berryhill
Emil Mrak, Chairman and Members
of the Scientific Review Panel
Senator Ralph Dills
Senator Art Torres
John Holmes ARB

ATTACHMENT IV A

SUMMARY OF AMBIENT VINYL CHLORIDE CONCENTRATIONS

Vinyl chloride has been produced in one industrial facility and used by four facilities in California, all of them in the South Coast Air Basin (SCAB). In May 1978, the Air Resources Board (ARB) adopted an ambient air quality standard for vinyl chloride of 10 ppb, 24-hour average. Subsequent ambient monitoring in the SCAB found the 10 ppb standard to be exceeded frequently in the vicinity of these facilities from 1979-1981. However, since 1982 the recent monitoring data for VC near these vinyl chloride facilities has shown all values to be below 10 ppb, without a determination of the actual value. These reductions in ambient concentrations are likely due to the closure of the production facility in 1982 and implementation of regulations by the South Coast Air Quality Management District (SCAQMD) designed to reduce vinyl chloride emissions.

Vinyl chloride has been detected in the community near the BKK Class I landfill in West Covina. In 1983, the Department of Health Services (DHS), ARB, and the South Coast Air Quality Management District issued a report detailing ambient concentrations (report attached). As the report indicates, the average vinyl chloride concentrations varied with location. The worst case residential location, Station A, had mean 24-hour VC concentrations of 7.1-7.3 ppb, with a maximum reading of about 39 ppb. Data for this report were collected over three months (July 19-October 15, 1982), with 24-hour samples taken five days per week.

A newly discovered potential source of vinyl chloride emissions into the air is that of sewage treatment facilities. An EPA contractor recently made some estimates of vinyl chloride emissions, as well as other volatile aromatic compounds, from the "Top 20" sewage treatment plants, nationwide. (Please see Appendix D of Versar Memorandum, Attachment IVC.) In this document, the Hyperion facility, which is located in the SCAB, was calculated to release 171 metric tons/year of vinyl chloride. ARB staff modeled this emission estimate (assumptions on Attachment IVB) and predicted 8 ppb above any background as an annual average vinyl chloride concentration. The 24-hour maximum VC concentration prediction is 23 ppb above background. ARB and SCAQMD plan to confirm these estimates with source and ambient vinyl chloride testing at the Hyperion facility in the summer of 1985.

Summary of the Health Effects of Vinyl Chloride

I. HEALTH EFFECTS

The health effects of vinyl chloride have been reviewed by several sources. Two good reviews are by the International Agency for Research on Cancer (IARC, 1979) and the U.S. Department of Health, Education and Welfare (U.S. HEW, 1978).

A. Carcinogenicity

1. Humans - Epidemiological studies have shown that vinyl chloride causes angiosarcoma of the liver in humans. Strong evidence also exists that vinyl chloride may cause cancer of the central nervous system, especially glioblastoma multiforme. Evidence also exists that vinyl chloride induces cancers of the lung and lymphatic system but this evidence is weaker. (IARC, 1979; U.S. HEW, 1978)

2. Animals - Vinyl chloride has been shown to be carcinogenic in several animal species after oral and inhalation administration. Liver angiosarcomas were observed in mice, rats and hamsters exposed to vinyl chloride. Other tumors seen were mammary adenocarcinomas, lung adenomas, Zymbal gland tumors and angiosarcomas at sites other than the liver. Doses in the inhalation experiments ranged from 50 to 10,000 ppm. A significant increase in some tumors (angiosarcomas) was seen at the low dose (50 ppm) level. (IARC, 1979; U.S. HEW, 1978)

B. Mutagenesis

Vinyl chloride is mutagenic in several test systems. Vinyl chloride has been found to be mutagenic in several strains of bacteria, insects and mammalian cells. Chromosomal aberrations have been induced in workers exposed to vinyl chloride. (IARC, 1982)

C. Teratogenicity

Evidence that vinyl chloride causes teratogenic effects in humans or animals is equivocal. Vinyl chloride has been implicated in causing increased fetal deaths in the wives of vinyl chloride exposed worker's and birth defects in children of workers. Evidence is inconclusive. (IARC, 1979)

D. Pharmacokinetics

The metabolism of vinyl chloride has been reviewed by several authors (IARC, 1979). Absorbed vinyl chloride is eliminated predominantly via metabolism and exretion of metabolites into the urine. A small amount is excreted via the expired air as unchanged vinyl chloride. As the concentration of vinyl chloride to which an animal is exposed is raised, a larger percentage of the absorbed dose is eliminated as unchanged vinyl chloride in the expired air. The initial product of metabolism is believed to be chloroethylene oxide. Vinyl chloride, in the presence of a microsomal enzyme fraction, binds to RNA *in vitro* and to RNA and DNA *in vivo*. Chloroethylene oxide is believed to be involved in the covalent

binding to RNA and DNA. Since an abundance of animal pharmacokinetic data exists, it may be possible to incorporate it into the dose-response assessment. (IARC, 1979)

E. Acute and Chronic Effects (non-carcinogenic)

Acute exposure to vinyl chloride causes narcosis, cardiac irregularites and liver and kidney toxicity. These effects are seen at relatively high doses. Liver toxicity is evident as centrilobular degeneration, hepatic fibrosis and necrosis. Degeneration of bone, nerves and connective tissue is seen after chronic exposure. Acroosteolysis, a degeneration of the bones in the fingers, occurs in workers. Disturbances in liver, kidney and pulmonary function also occur after chronic exposure.

II. THRESHOLD

The U.S. EPA proposed a National Emission Standard for vinyl chloride in 1975, which was promulgated in 1976. The proposal for the emission standard states that there is no known threshold for vinyl chloride's toxic effects. (Federal Register, 1975)

III. DOSE-RESPONSE ASSESSMENT

The U.S. EPA's Carcinogen Assessment Group has performed a risk assessment of vinyl chloride's carcinogenic effects (U.S. EPA, 1975). The potency slope for vinyl chloride, derived from an animal inhalation study, is $1.75 \times 10^{-2} (mg/kg/day)^{-1}$.

REFERENCES

Federal Register, 1975, Vinyl Chloride National Emission Standard for Hazardous Air Pollutants, FR 40:59532.

IARC, 1979, International Agency for Research on Cancer, IARC monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 19, pages 377-438.

IARC, 1982, International Agency for Research on Cancer, IARC monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4, pages 260 - 262.

U.S. EPA, 1975, Carcinogen Assessment Group, "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride", Arnold M. Kuzmack and Robert E. McGaughy, December 5, 1975.

U.S. HEW, 1978, U.S. Department of Health, Education and Welfare, Vinyl Chloride: An Information Resource, DHEW Publ. No. (NIH) 78-1599

State of California — Department of Health Services

Memorandum

To : Peter Venturini
Chief, Stationary Sources Division
Air Resources Board
1102 Q Street
Sacramento, CA 95814

Date : JAN 25 1989

Subject: Health Effects of Vinyl Chloride

RECEIVED
JAN 30 1989
Stationary Source Division
Air Resources Board

From : Public Health
714 P Street
Sacramento, CA 95814
(916) 445-2927

Attached is the document prepared in response to your request for the assistance of the Department of Health Services in evaluating the health effects of vinyl chloride as a potential toxic air contaminant.

Harvey F. Collins, Ph.D.
Deputy Director

Attachment

cc: Jack C. Parnell, Director of Food & Agriculture
California Department of Food & Agriculture
1220 N Street
Sacramento, CA 95814

Jananne Sharpless, Chairwoman
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Assemblywoman Sally Tanner
The State Capitol
P. O. Box 942849
Sacramento, CA 94249-0001

Copies of document can be requested from:

California Department of Health Services
Hazard Evaluation Section
2151 Berkeley Way, Room 515
Berkeley, CA 94704

APPENDIX VI

LANDFILL GAS TESTING PROGRAM

APPENDIX VI

LANDFILL GAS TESTING PROGRAM DATA

State law (Health and Safety Code Section 41805.5) requires owners or operators of all active and some inactive landfills to perform air quality solid waste assessment testing to characterize the gas within landfills and the ambient air around the landfills, and to determine if the landfill gas is migrating underground beyond the site boundaries. Ten specified air contaminants were selected to be tested for based on health effects associated with long term exposure, particularly carcinogenicity, and the availability of sampling and analysis methods. The ten specified contaminants were as follows: vinyl chloride, benzene, ethylene dibromide, ethylene dichloride, methylene chloride, perchloroethylene, carbon tetrachloride, 1,1,1-trichloroethane (methyl chloroform), trichloroethylene, and chloroform. In addition, landfill gas samples were also analyzed for oxygen, nitrogen, methane, and carbon dioxide.

To accomplish the testing required by state law, the Air Resources Board (ARB) and the California Air Pollution Control Officers Association (CAPCOA) prepared guidelines outlining a testing program to identify sites that pose a potential risk to public health. These guidelines were approved by the ARB for non-hazardous waste sites in December 1986 and for hazardous waste sites in January 1987.

State law requires landfill operators to report the testing results to their local air pollution control district. The districts, in turn, submit summaries of the testing results to the ARB and determine if the sites pose a threat to human health or the environment. The ARB was required to summarize the data submitted by the districts in two reports to the Legislature, due by July 1, 1988 and July 1, 1989. The first report described the early implementation of the landfill testing program. The second report, presented to the Board on June 9, 1989, summarized statewide results of the solid waste disposal site testing reported to the ARB. The report presented preliminary findings based on the results, and described ongoing testing and evaluation activities.

The preliminary findings were that: 1) one or more of the specified contaminants, selected as indicators of hazardous waste, were present in approximately 240 out of the 356 landfills tested, regardless of whether the site accepted hazardous waste or non-hazardous waste; 2) hazardous and non-hazardous waste sites appeared to be similar in their ability to produce toxic gases; 3) in some cases, toxic gases escaped from landfills and dispersed into the ambient air; and 4) methane at concentrations exceeding the regulatory standard of five percent was found to be migrating off-site underground at approximately 20 percent of the sites. The Board asked that the staff return in 1990 with further analysis of the data.

Since the 1989 report was presented, further analysis has been conducted and additional data has been collected. In September 1990, the further analysis will be presented to the Air Resources Board as an informational presentation. The following tables are excerpted from the ARB staff report and summarize the findings regarding the presence of vinyl chloride in the landfill gas and in the ambient air surrounding landfills tested. The landfill testing detected vinyl chloride inside of approximately half of the landfills tested and in the ambient air at approximately ten percent of the sites tested.

The limited testing conducted was designed to be used for screening purposes as described in the testing guidelines. For that reason, vinyl chloride may be present in the ambient air at additional landfills, but was not detected in the limited one to three days of ambient testing specified in the testing guidelines for the program. Further interpretation of the data from specific sites must also consider factors such as how the testing was carried out, along with location, size and proximity to sensitive receptors. Further information may also be available in the complete testing reports submitted by site operators to the air pollution control districts.

TABLE 1

CONCENTRATION STATISTICS OF VINYL CHLORIDE IN LANDFILLS*

Number of Landfills Where Detected:	160
Total Landfills Tested:	340
50th percentile (median):	106 ppbv (detection limit)**
75th percentile:	1000 ppbv
95th percentile:	9800 ppbv
Maximum:	72,000 ppbv

* See Attachment A for landfill gas testing guidelines.

** The Testing Guidelines for Active Solid Waste Disposal Sites suggest an analytical procedure for internal landfill gas testing with the same method of determining the limit of detection (LOD) described in Appendix VII of this document. The Guidelines specify that the detection limit is not to exceed 500 ppbv. Because many results below 500 ppbv were measured and reported, a statistical detection limit of 106 ppbv was calculated by averaging the results below 500 ppbv.

Landfill Gas Testing

If the disposal site has an operating interior gas collection system, samples should be taken from the system; additional wells need not be installed. Each installed well should be to a depth of at least 6 feet below the bottom of the intermediate or final cover. The well should not penetrate any leachate liner. During installation the contractor should take appropriate steps to mitigate the public nuisance of gas escape. All wells should be capped when not being sampled.

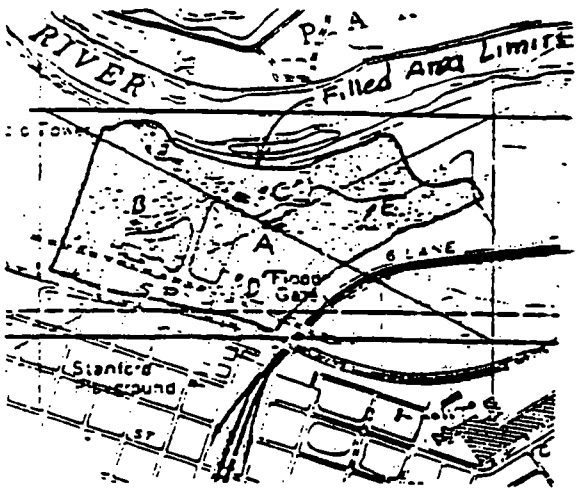


Figure 1: Well Location Example

To locate the wells, draw a box around the disposal site on a scale map with the box sides 100 feet outside the filled area edge. The sides should run north-south, east-west. Connect the opposite corners with diagonals. Locate 5 points: Point A at the diagonal intersection, point B at the center of the largest sector formed by the diagonals and the filled area, point C at the center of the next larger sector, point D at the center of the next larger sector, and point E at the center of the smallest sector. Figure 1 is an example. Five samples should be taken, one sample from each well and analyzed for the Attachment 1 compounds.

To complete the HSC 41805.5 requirements for characterizing landfill gas, the owner should perform an investigation of methane emissions from one 50,000 square-foot grid of the disposal site along with the landfill gas test. The grid selected should be approved by the APCO and the owner should use methods described in these guidelines.

1. Protocol

The technician should make certain the seal around the top of the well does not allow air infiltration. The well should not be sampled until 24 hours after the installation is complete. To sample the well, the technician attaches the pump and withdraws at least 2 well volumes from the well. The technician then attaches the bag and draws a ten liter sample at a one liter per minute rate. The bag should be in a light sealed container and should be analyzed within 72 hours.

If the owner chooses to leave the well intact for future sampling, the pipe should be capped or a valve installed to prevent gas leakage. If the owner removes the well, the hole should be filled and resealed to prevent gas escape.

2. Data

For each sample, the owner should record:

a. Date, time, and sample location.

b. Methane, CO_2, oxygen, and nitrogen concentrations.

c. Concentrations of compounds listed in Attachment 1. Analytical methods are included in Attachment 2.

d. The operating schedule, status, and gas quantity extracted for any landfill gas collection system for the previous 3 days for each day sampled.

ATTACHMENT 1

SPECIFIED AIR CONTAMINANTS

COMPOUND		Detection Limits, ppb Air	Disposal site
Chloroethene (Vinyl Chloride)	CH_2:CHCl	2	500
Benzene	C_6H_6	2	500
1,2-Dibromoethane (Ethylene Dibromide)	$BrCH_2CH_2Br$	0.5	1
1,2-Dichloroethane (Ethylene Dichloride)	$ClCH_2CH_2Cl$	0.2	20
Dichloromethane (Methylene Chloride)	CH_2Cl_2	1	60
Tetrachloroethene (Perchloroethylene)	Cl_2C:CCl_2	0.2	10
Tetrachloromethane (Carbon Tetrachloride)	CCl_4	0.2	5
1,1,1-Trichloroethane (Methyl Chloroform)	CH_3CCl_3	0.5	10
Trichloroethylene	HClC:CCl_2	0.6	10
Trichloromethane (Chloroform)	$CHCl_3$	0.8	2

ATTACHMENT 2

The choice of analytical method is left up to the individual laboratory performing the analysis. The methods provided in Attachment 2 are provided as examples of methods which can be used to sample and analyze for the specified air contaminants identified in Attachment 1. The methods are used by ARB laboratories to quantify the compounds listed *at or below the detection limits specified in Attachment 1.* Table 2-1 summarizes the method detection limits achievable by these methods and the detection limits to be reported for these guidelines:

TABLE 2-1: METHOD DETECTION LIMITS

COMPOUND	Guideline	Method Detection Limits, ppb	
		Haagen-Smit Laboratory	Aerometric Data Division
Chloroethene (Vinyl Chloride)	2	-	1
Benzene	2	0.5	0.5
1,2-Dibromoethane (Ethylene Dibromide)	0.5	0.01	0.005
1,2-Dichloroethane (Ethylene Dichloride)	0.2	0.2	0.1
Dichloromethane (Methylene Chloride)	1	1	0.6
Tetrachloroethene (Perchloroethylene)	0.2	0.004	0.01
Tetrachloromethane (Carbon Tetrachloride)	0.2	0.02	-
1,1,1-Trichloroethane (Methyl Chloroform)	0.5	0.004	0.004
Trichloroethylene	0.6	0.005	0.02
Trichloromethane (Chloroform)	0.8	0.004	0.02

AMBIENT AIR MONITORING

HSC 41805.5 requires that air adjacent to disposal sites be tested and analyzed for specified air contaminants. To comply with HSC 41805.5, disposal site owners should conduct ambient air monitoring at the perimeter of the disposal site. The test should adequately characterize the contaminants in the air. The air column listed in Attachment 1 shows the lower detection limits to be achieved in parts per billion. Each disposal site should perform the ambient air sampling on three separate, not necessarily consecutive, days.

At sites where the owner has chosen to characterize only the gas above the disposal site using the integrated surface sampling technique, all specified air contaminants must be tested and analyzed for in the air samples. A site where landfill gas testing is used *and* where chloroethene (vinyl chloride) is identified in the landfill gas, then the ambient air samples need only be tested for chloroethene (vinyl chloride).

The guidelines contain three suggested procedures for testing the ambient air. These procedures were developed to cover differences in topography and climate which may occur at different sites. Each option has two parts. One addresses sites with different day and night wind patterns and one addresses sites with the same day and night wind patterns. The option chosen will depend on the results of the meteorological survey.

A. OPTION 1

1. General Procedures

HSC 41805.5 requires that air adjacent to disposal sites be tested and analyzed for specified air contaminants. If the disposal site has a gas collection system which does not operate continuously, at least one of the sampling days should be a day before the gas collection system is turned on after a typical inoperative period. This option requires twenty-four hour samples to be taken on 3 separate, not necessarily consecutive, days.

2. Meteorological Survey

A meteorological survey should be conducted prior to ambient air sampling in order to determine the local wind flow patterns which will subsequently be used to help identify the number and location of samplers required for an effective ambient air monitoring program. The operator should submit the survey to the APCO prior to ambient sampling, as part of the monitoring plan. The survey should summarize how wind flow patterns at the site will be characterized based on: previously collected on site meteorological data, data collected nearby (e.g., local airport data), proximity to water or terrain which may influence diurnal variations (e.g., daytime upslope winds, nighttime downslope, or sea breeze conditions), or a plan for on site meteorological data collection prior to ambient monitoring. In completing an on site meteorological survey prior to monitoring, wind sensors should be located nine to twelve feet above the ground and a minimum of sixty feet from obstacles such as trees, shrubbery, and buildings.

3. Ambient Air Sampling

a. General Sampling Criteria

At the completion of the meteorological survey, and on approval of the APCO, ambient air

TABLE 2

CONCENTRATION STATISTICS OF VINYL CHLORIDE IN AMBIENT AIR SAMPLES COLLECTED AT THE PERIMETERS OF LANDFILLS*

Number of Landfills Where Detected:	24
Total Landfills Tested:	251
50th percentile (median):	2 ppbv (detection limit)
75th percentile:	2 ppbv
95th percentile:	2 ppbv
2nd highest value:	13 ppbv
Maximum:	15 ppbv

* See Attachment B for ambient air testing guidelines.

sampling equipment will be installed at the appropriate locations which will be determined by:

1. Site topography,

2. Meteorological survey, and

3. Local land use patterns.

The sampling equipment should be located at or near the perimeter of the waste disposal site, in the clear and away from surrounding obstructions. The inlet probes for the ambient samplers should be located between six and nine feet off the ground (reaching height) and a minimum of sixty feet from obstacles such as trees, shrubbery and buildings. Air flow around the inlet probe should be unrestricted in an arc of at least 270 degrees with the predominant wind direction for greatest expected. pollutant concentration potential included in the 270 degree arc. The sampler locations should be carefully selected to ensure the predicted prevailing wind patterns for the sampling date will come across the main body of the disposal site to the downwind station. Wind speed and direction measurements will continue to be collected throughout the ambient air sampling period to verify that the meteorological criteria are met.

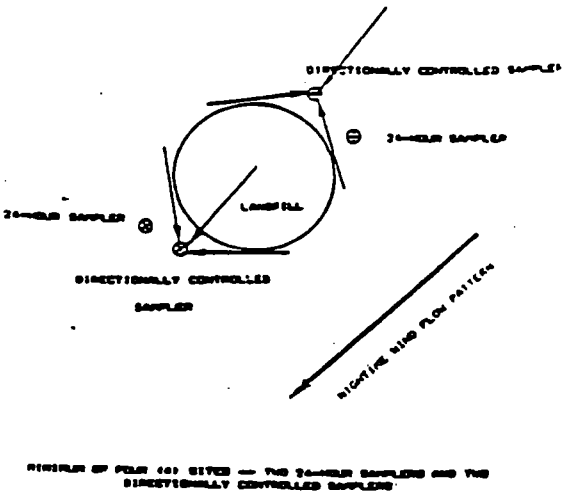


Figure 4: Option 1
Source: South Coast AQMD

Ambient air samples will be collected over a 24-hour period beginning and ending at 10:00 A.M. using the self-contained portable sampling units described in Equipment Description. In general, 24-hour and directionally controlled sampling will be required to ensure that maximum contaminant concentrations are identified for each sampling period. However, directionally controlled sampling may not be required at sites which have a constant wind direction for 24 hours. All samples will be removed from the samplers immediately after the 24-hour sampling period and analyzed for the required compounds. It is recommended that the sample be analyzed within 72 hours of collection.

b. Specific Sampling Criteria

i. At sites that experience different day and night wind flow patterns, a minimum of two 24-hour samplers and two directionally controlled samplers will be required. Twenty-four hour samplers will be placed at the upwind and downwind site perimeters based on the

prevailing wind direction. The directionally controlled sampler(s) located downwind of the disposal site should be placed at sites which will sample under the stable (drainage) wind conditions identified in the meteorological survey. The directionally controlled sampler located upwind of the disposal site should be placed near the upwind 24-hour sampler. The 24-hour samplers will operate continuously for the specified 24 hours and the directionally controlled samplers will only operate when the wind direction is within a wind sector allowing air to pass across the disposal site to the downwind sampler. This will allow the downwind directionally controlled sampler(s) to only collect air that has *passed* over the disposal site and the upwind directionally controlled sampler to only collect air that has *not passed* over the disposal site.

ii. At site that experience a constant wind direction for 24 hours, a minimum of two 24-hour samplers will be required. A 24-hour sampler will be place both upwind and downwind of the site based on the prevailing wind direction so that the upwind sampler only collects air that has *not passed* over the disposal site and the downwind sampler only collects air that has *passed* over the disposal site. Additional 24 hour samplers should be placed at locations which will sample under the stable (drainage) wind conditions identified in the meteorological survey. Since the wind direction does not change, these 24-hour samplers will act as directionally controlled samplers as well as 24-hour samplers. Comparison of the results from these samplers will provide information on ambient air quality standards and the effects the disposal site has on the ambient air quality.

4. Sampling Conditions

Ambient air sampling should be conducted on days when stable and unstable meteorological conditions are characterized by the following meteorological conditions:

a. Stable nights with average wind speeds of five miles per hour or less.

b. Daytime conditions with average wind speeds of ten miles per hour or less.

No sampling will be conducted under the following adverse meteorological conditions:

a. Precipitation

b. Twenty-four hour average wind speeds greater than ten miles per hour.

5. Equipment Description

a. Bag Sampler

1. Pump with a diaphragm made of non-lubricated Viton® rubber. The maximum pump unloaded flow rate is 4.5 liters per minute.

2. One 10-liter Tedlar® bag with a push-pull valve constructed of aluminum and stainless steel with a Viton® o-ring seal.

3. Rotameter made of borosilicate glass with a flow range of three to fifty cubic centimeters per minute. The scale is in millimeters with major graduations (labeled) every 5 mm and minor graduations every 1 mm.

4. Air flow control orifice made with 316 stainless steel capillary tubing.

5. Bypass valve.

6. Fittings, tubing and connectors made with 316 stainless steel or teflon.

7. Clock timer with an accuracy that should be better than 1%.

b. Wind directionally controlled system

1. Wind direction sensor with a vane which has a range of 0 - 540 degrees and a threshold of 1.00 mile per hour or less.

2. Controller and indicator console with an indicator range of 0 - 360 degrees and an accuracy of ± 2% of full scale.

c. Wind speed and direction monitoring with continuous recorder.

1. Anemometer three cup assembly with a range of 0-50 miles per hour and a threshold of 0.75 miles per hour or less.

2. Wind vane with a range of 0 - 540 degrees and a threshold of 1.00 miles per hour or less.

6. Wind Data Reporting

Wind data (speed and direction) will be reported as an hourly average. For example, the data collected between 1:00 P.M. and 2:00 P.M. will be averaged and reported as the 1:00 P.M. hourly average. Wind speeds will be reported in miles per hour. Wind directions will be reported using the sixteen point scale (sixteen directional points corresponding to the mariner's compass rose on which each direction is equivalent to a 22 1/2 degree sector of a 360 degree circle). For example, wind directions would be N, NNE, NE, E ESE, SE, SSE, S, SSW, SW, WSW, W, WNW, NW, and NNW.

B. OPTION 2

1. General Procedures

HSC 41805.5 requires that air adjacent

See Option 1.

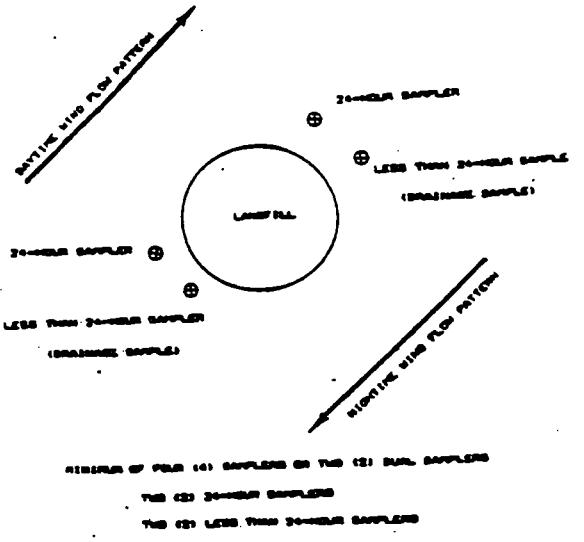


Figure 5: Option 2
Source: South Coast AQMD

to disposal sites be tested and analyzed for specified air contaminants. These guidelines require that 24-hour and less than 24-hour ambient air sampling be conducted on three different, not necessarily consecutive, days.

2. Meteorological Survey

See Option 1.

3. Ambient Air Sampling

See Option 1, Subsection 3a, General Sampling Criteria.

a. At sites that experience different but predictable day and night wind flow patterns, a minimum of two 24-hour samplers and two less than 24-hour samplers will be required. One 24-hour sampler will be placed both upwind and downwind of the site based on the prevailing wind direction. The less than 24-hour sampler(s) located downwind of the disposal site should be placed at sites to sample under the stable (drainage) wind conditions identified in the meteorological survey. The less than 24-hour sampler located upwind of the disposal site should be placed near the upwind 24-hour sampler. The start and stop times for the less than 24-hour samplers will correspond to the stable (drainage) conditions identified by analyzing the the hourly wind roses. The 24-hour samplers will operate continuously for the specified 24 hours and the less than 24-hour samplers will only operate when the wind direction is coming across the disposal site to the downwind sampler. This will allow the downwind less than 24-hour sampler(s) to only collect air that has *passed* over the disposal site and the upwind less than 24-hour sampler to only collect air that has *not passed* over the disposal site.

b. At sites that experience a constant wind direction for 24 hours, a minimum of two 24-hour samplers will be required. A 24-hour sampler will be place both upwind and downwind of the site based on the prevailing wind direction so that the upwind sampler only collects air that has *not passed* over the disposal site and the downwind sampler only collects air that has *passed* over the disposal site. Additional 24 hour samplers should be placed at locations which will sample under the stable (drainage) wind conditions identified in the meteorological survey. Since the wind direction does not change, these 24-hour samplers will act as directionally controlled samplers as well as 24-hour samplers. Comparison of the results from these samplers will provide information on ambient air quality standards and the effects the disposal site has on the ambient air quality.

4. Sampling Conditions

See Option 1.

5. Equipment Description

See Option 1.

6. Wind Data Reporting

See Option 1.

C. OPTION 3

1. General Procedures

HSC 41805.5 requires that air adjacent to disposal sites be tested and analyzed for specified air contaminants. These guidelines require that 24-hour ambient air sampling be conducted on three different, not necessarily consecutive, days.

2. Meteorological Survey

See Option 1.

3. Ambient Air Sampling

See Option 1, Subsection 3a, General Sampling Criteria.

a. At sites that experience different day and night wind flow patterns, a minimum of three 24-hour samplers will be required. One 24-hour sampler will be placed on both upwind and downwind of the site based on the prevailing wind direction. Additional 24 hour samplers will be located downwind of the disposal site at sites which will sample under the stable (drainage) wind conditions identified in the meteorological survey. In addition, one 24-hour sampler will be placed in the vacinity of the disposal site, approximately one mile away, so it will not be affected by the disposal site emissions. This 24-hour sampler should also be approximately one mile away from other possible major emission sources so that the sample it collects will represent the background concentrations for the area. This background sampler whould be located in the clear and away

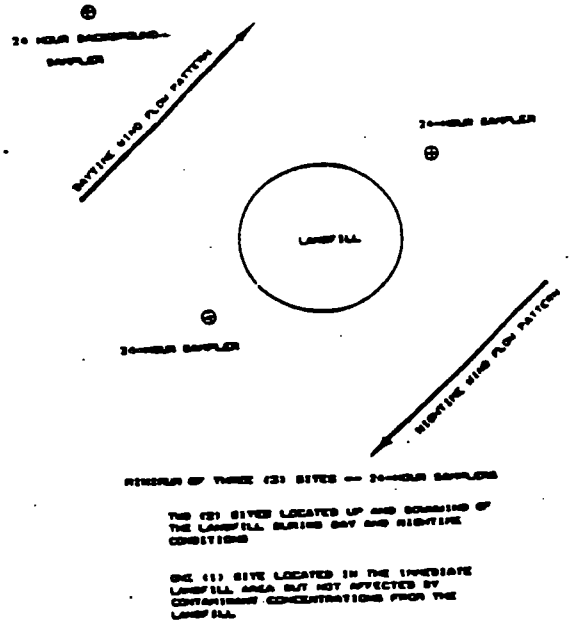


Figure 6: Option 3
Source: South Coast AQMD

from surrounding obstructions. Its inlet probe must be located between six and nine feet off the ground (breathing height) and a minimum of 60 feet from obstacles such as trees, shrubbery, and buildings. Air flow around the inlet probe must be unrestricted. All of the 24-hour samplers will operate continuously for the specified 24 hours. Comparison of the results from the samplers will provide information on the ambient air quality standards.

b. At sites that experience a constant wind direction for 24 hours, a minimum of two 24-hour samplers will be required. A 24-hour sampler will be placed both upwind and downwind

of the site based on the prevailing wind direction so that the upwind sampler only collects air that has *not passed* over the disposal site and the downwind sampler only collects air that has *passed* over the disposal site. Additional 24-hour samplers should be placed at locations which will sample under the stable (drainage) wind conditions identified in the meteorological survey. Since the wind direction does not change, these 24-hour samplers will act as less than 24-hour samplers as well as 24-hour samplers. In addition, one 24-hour sampler will be placed in the vicinity of the disposal site, approximately one mile away, so it will not be effected by the disposal site emissions. This 24-hour sampler should also be approximately one mile away from possible major emission sources so that the sample it collects will represent the background concentrations for the area. This background sampler should be located in the clear and away from surrounding obstructions. Its inlet probe should be located between six and nine feet off the ground (breathing height) and a minimum of sixty feet from obstacles such as trees, shrubbery and buildings. Air flow around the inlet probe should be unrestricted. All of the 24-hour samplers will operate continuously for the specified 24 hours.

4. Sampling Conditions

See Option 1.

5. Equipment Description

See Option 1.

6. Wind Data Reporting

See Option 1.

D. GENERIC ANALYTICAL METHODS

HSC 41805.5 directs the ARB to publish testing guidelines "specifying air contaminants to be tested for and identifying acceptable testing, analytical and reporting mehtods. The following generic analytical methods contain a brief description of the standard operating procedures (SOP) used by the ARB to sample and analyze specific compounds. Specific SOPs are contained in Attachment 2.

1. Method for Vinyl Chloride

Ambient samples are collected over a 24-hour period in a thirty liter Tedlar® bag using a low-volume sampler.

Samples are analyzed using chromatography with Flame Ionization or Photo Ionization Detection and preconcentration techniques. Resultant concentration peak is identified by retention times and quantified by reference to calibration standards.

2. Method for Carbon Tetrachloride, Chloroform, Ethylene Dibromide, Ethylene Dichloride, Methyl Chloroform, Methylene Chloride, Perchloroethylene, and Trichloroethylene

Ambient samples are collected over a 24-hour period in a thirty liter Tedlar® bag using a low volume sampler.

Samples are analyzed using-gas chromatography with Electron Capture Detection and preconcentration techniques. Resultant concentration peaks are identified by retention times and quantified by references to calibration standards.

ATTACHMENT 1

SPECIFIED AIR CONTAMINANTS

COMPOUND		Detection Limits, ppb Air	Disposal site
Chloroethene (Vinyl Chloride)	CH_2:CHCl	2	500
Benzene	C_6H_6	2	500
1,2-Dibromoethane (Ethylene Dibromide)	$BrCH_2CH_2Br$	0.5	1
1,2-Dichloroethane (Ethylene Dichloride)	$ClCH_2CH_2Cl$	0.2	20
Dichloromethane (Methylene Chloride)	CH_2Cl_2	1	60
Tetrachloroethene (Perchloroethylene)	Cl_2C:CCl_2	0.2	10
Tetrachloromethane (Carbon Tetrachloride)	CCl_4	0.2	5
1,1,1-Trichloroethane (Methyl Chloroform)	CH_3CCl_3	0.5	10
Trichloroethylene	HClC:CCl_2	0.6	10
Trichloromethane (Chloroform)	$CHCl_3$	0.8	2

ATTACHMENT 2

The choice of analytical method is left up to the individual laboratory performing the analysis. The methods provided in Attachment 2 are provided as examples of methods which can be used to sample and analyze for the specified air contaminants identified in Attachment 1. The methods are used by ARB laboratories to quantify the compounds listed *at or below the detection limits specified in Attachment 1*. Table 2-1 summarizes the method detection limits achievable by these methods and the detection limits to be reported for these guidelines:

TABLE 2-1: METHOD DETECTION LIMITS

COMPOUND	Guideline	Method Detection Limits, ppb	
		Haagen-Smit Laboratory	Aerometric Data Division
Chloroethene (Vinyl Chloride)	2	-	1
Benzene	2	0.5	0.5
1,2-Dibromoethane (Ethylene Dibromide)	0.5	0.01	0.005
1,2-Dichloroethane (Ethylene Dichloride)	0.2	0.2	0.1
Dichloromethane (Methylene Chloride)	1	1	0.6
Tetrachloroethene (Perchloroethylene)	0.2	0.004	0.01
Tetrachloromethane (Carbon Tetrachloride)	0.2	0.02	-
1,1,1-Trichloroethane (Methyl Chloroform)	0.5	0.004	0.004
Trichloroethylene	0.6	0.005	0.02
Trichloromethane (Chloroform)	0.8	0.004	0.02

APPENDIX VII

ARB MONITORING AND LABORATORY DIVISION'S METHOD FOR CALCULATING THE LIMIT OF DETECTION

Analytical Limits of Detection (LOD) must be calculated. The LOD for each method must be calculated by the following equation (reference):

LOD = A + 3S

where

A is the least squares intercept calculated from the multipoint data (section 4.1.2).

S is the standard deviation of replicate determinations of the lowest standard. At least 3 replicates are required. The lowest standard must be run at 1 to 5 times the estimated detection limit. If data is not available in the concentration range near the detection limit, S may be estimated by:

S = RSD x A

where RSD is the relative standard deviation of the lowest standard analyzed.

The equation as listed above was obtained from the Compendium of Methods for the Determination of Toxic Organics in Ambient Air. Research Triangle Park, North Carolina: U.S. Environmental Protection Agency; 1984 April: Method T)1. Publication No. EPA-600/4-84-041.

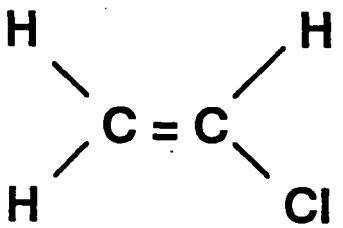
Note that the Laboratory Services Section policy is to report all analysis results above the analytical limits of detection. However, data errors may approach ± 100% at levels < 10 x LOD.

All analysis methods must be written in detail as a Standard Operating Procedure to be used in the laboratory. Any subsequent revisions or improvements are documented. The procedures are reviewed yearly by laboratory management and the Quality Assurance Section to insure that they are being followed properly.

TECHNICAL SUPPORT DOCUMENT

PART B

PROPOSED IDENTIFICATION OF



VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California

Air Resources Board

Stationary Source Division

1.5 – 20 × 10^{-5} / ppbv Unit Risk

HEALTH EFFECTS OF AIRBORNE VINYL CHLORIDE

CALIFORNIA DEPARTMENT OF HEALTH SERVICES

October 1990

Prepared by: California Department of Health Services

Stanley V. Dawson, Sc.D., Staff Toxicologist
George V. Alexeeff, Ph.D.
Michael J. Lipsett, M.D.
Douglas N. Cox, Ph.D. (California Public Health Foundation)

Based in part on work submittted by:

Carla C. Christensen and C. Tucker Helmes,
Biological and Environmental Chemistry Department,
SRI International, 333 Ravenswood Avenue,
Menlo Park, California 94025,
Under Contract 85-86676 (045A)

and by:

Deborah Grady, M.D., M.P.H.
School of Medicine,
University of California, San Francisco,
and
Allan Smith, M.D., Ph.D. University of California, Berkeley

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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.

II. Exposure Sources

A. Air Levels

1. Throughout 1987 the South Coast Air Quality Maintenance District monitored near two landfill sites in the Los Angeles area. The highest annual average obtained at any of three stations near the BKK site was 2.6 ppb, and the

highest annual average at any of three stations near the OII site was 2.0 ppb.

III. Quantitative Risk Assessment

A. Range of Extrapolation: Animal to human exposures in air for calculated lifetime daily exposure.

1. Experimental to ambient: Vinyl chloride has not been detected in ambient air, except at "hot spots".

2. Experimental to "hot spots": The lowest exposures in the animal studies are approximately 10- to 20-fold higher than the highest residential exposures.

B. Range of Risks:

The human risks associated with the equivalent of a continuous, lifetime exposure to vinyl chloride have been estimated using the linearized multistage model from both animal carcinogenicity bioassays and epidemiological studies of exposed workers. The current DHS analysis obtained UCLs on unit risks for humans estimated from animal data in the range from 3.7×10^{-5} ppb^{-1} to $20. \times 10^{-5}$ ppb^{-1}, depending on experimental exposure levels, tumor type observed, and sex, species, and age of animal evaluated. The DHS analysis also obtained a UCL on unit risk of 4.5×10^{-5} for liver, lung, and brain cancer and 2.5×10^{-5} for liver cancer only from an occupational study.

2.0 METABOLISM AND PHARMACOKINETICS

2.1 Summary

Experimental evidence has suggested that vinyl chloride must undergo transformation to a reactive metabolite(s) by the liver to be toxic. Based on this information, the best dose-response data would consider the amount of vinyl chloride actually absorbed and metabolized rather than the reported exposure or administered dose concentrations. Reports of the vinyl chloride metabolism in humans are sparse, but limited evidence indicates that, after inhalation exposure to low concentrations, up to 71% (average = 42%) of a given dose was absorbed (Krajewski et al., 1980). Based on this study it is assumed that 71% of an inhaled vinyl chloride exposure may be absorbed by humans at ambient concentrations. Unmetabolized vinyl chloride is eliminated primarily via the lungs. Unlike the results in other species, the percent absorption of vinyl chloride at the concentrations tested in humans did not depend upon concentration. Data from rodent studies suggest that the absorption of vinyl chloride depends on its rate of metabolism and the extent of metabolic saturation. The metabolic pathways of vinyl chloride exhibit substantial satuation at exposure concentrations above 100 ppm in the monkeys and above 200 ppm in rats.

Metabolism of vinyl chloride involves the cytochrome P-450 mixed-function oxidase system. The first step is thought to be epoxidation of the double bond to form the reactive epoxide chloroethylene oxide, which may undergo a number of further reactions, including binding to cellular macromolecules. Intramolecular rearrangement of the chlorine atom may also occur, resulting in the formation of chloroacetaldehyde, another reactive intermediate. In addition, alcohol dehydrogenase has a role in vinyl chloride biotransformation, because inhibitors of this enzyme can significantly reduce the amount of vinyl chloride metabolized. Section 2.3 of this report provides a detailed discussion of vinyl chloride metabolism.

2.2 Absorption, Distribution and Excretion

2.2.1 Inhalation

The pharmacokinetics of vinyl chloride following inhalation has been studied in five species of experimental animals. The uptake of vinyl chloride at higher doses appears to depend on its metabolism. The metabolic breakdown of vinyl chloride in rats and monkeys (and perhaps in other species) is a dose-dependent, saturable process (Buchter et al., 1980, Filser and Bolt, 1979). Substantial species differences have been observed in the rates of vinyl chloride clearance, with first-order metabolic clearance rates (in liters/hour/kg body weight) for the elimination of vinyl chloride decreasing in the order of mouse (25.6) > gerbil (12.5) > Wistar rat (11.0) > Rhesus monkey (3.55) > rabbit (2.74) > human (2.02) (Buchter et al., 1980).

Results from inhalation exposure studies in humans, monkeys, and rats using direct and indirect test methods indicate that vinyl chloride is rapidly absorbed and metabolized, quickly distributed throughout the body, and excreted by the kidneys. Unmetabolized vinyl chloride is expired by the lungs and, to a limited extent, expelled in the feces.

Several limited studies have been conducted in humans measuring vinyl chloride absorption following inhalation exposure. Krajewski et al. (1980) observed that five male volunteers exposed to 3, 6, 12, or 24 ppm vinyl chloride for six hours by a "face only" chamber absorbed an average of 42% of the dose regardless of concentration. Large interindividual variation in the degree of vinyl chloride retention was observed, with one individual retaining 71% of the dose at the time exposure was terminated; no other individual retained greater than 45%. This finding indicates a large range of interindividual variability. Concentration of vinyl chloride in expired air, measured for 90 minutes after cessation of exposure, decreased to negligible amounts after only 30 minutes post-exposure. The quantity of unmetabolized vinyl chloride exhaled was considered negligible and constituted roughly 4% of the inhalation concentration of vinyl chloride to which subjects were exposed (Krajewski et al., 1980). Thus, humans metabolized up to 96% of the absorbed vinyl chloride dose.

Buchter et al. (1978) reported that humans exposed to 2.5 ppm vinyl chloride retained 26-28% of the administered dose (Krajewski et al., 1980). Substantial interindividual differences were reported in this study. These differences appear due to differences in the adipose tissue mass among individuals, although this hypothesis has not been confirmed in follow-up studies (Buchter, 1979; Buchter et al., 1978; Bolt et al., 1981).

Pulmonary absorption of vinyl chloride by rats occurs rapidly. Blood levels of vinyl chloride increase with the dose. Blood concentrations quickly decline after cessation of exposure; unmetabolized vinyl chloride is exhaled (Withey, 1976; Hefner et al., 1975a; 1975b; 1975c).

Evidence from both whole animal and "nose-only" inhalation studies in rats indicates that the rate of pulmonary uptake of vinyl chloride in a closed system is partially dependent on the extent of metabolism (Bolt et al., 1977; Hefner et al., 1975a; 1975b; Withey, 1976). In the "nose-only" exposure system used by Hefner et al. (1975a), pretreatment of rats with either pyrazole or 95% ethanol significantly reduced both the uptake (as calculated from the disappearance of vinyl chloride from the exposure chamber) and metabolism of vinyl chloride. This held true for both exposure levels. Pyrazole- pretreated rats were exposed to either 65 or 1234 ppm, while ethanol-pretreated rats were exposed to 56 or 1034 ppm.

Several groups of investigators have presented additional data concerning the uptake, metabolism and disposition of vinyl chloride following inhalation exposure (Bolt et al., 1976; 1977; Hefner et al., 1975a; 1975b; Buchter et al., 1977). In an investigation into the disposition of vinyl chloride, Bolt and co-workers (1976) exposed male Wistar rats to initial concentrations of "less than 100 ppm" ^{14}C labeled vinyl chloride (apparent range 1-50 ppm) in a closed system for six hours. The half-life for vinyl chloride disappearance from the chamber was about 68 minutes. From this study, the authors estimated that approximately 40% of the inspired vinyl chloride was absorbed by the lungs (Bolt et al., 1976). Pulmonary uptake of vinyl chloride by rats was completely blocked following pretreatment with the cytochrome P-450 inhibitors 6-nitro-1,2,3-benzothiadiazole or 3-bromophenyl-4(5)-imidazole (Bolt et al., 1976). Uptake of vinyl chloride appeared to be linked to its metabolism, since 24 hours after pretreatment with the relatively short-lived P-450 inhibitor 3-bromophenyl-4(5)-imidazole the uptake

of vinyl chloride had returned to control levels. Following exposure, the liver and kidney contained the highest levels of vinyl chloride metabolites (Bolt et al., 1976). In an attempt to determine the exact minimal concentration of vinyl chloride in air necessary to achieve metabolic saturation, Bolt et al. (1977) exposed groups of rats to a wide range of vinyl chloride concentrations and showed that saturation occurred at 250 ppm. First-order kinetics occurred at exposures less than 250 ppm, while zero-order kinetics predominated at higher exposures.

Hefner and colleagues (1975a; 1975b) exposed male Sprague-Dawley rats to initial vinyl chloride concentrations ranging from 50 to 1,167 ppm in a closed nose-only inhalation system. The rate of uptake of vinyl chloride by the animals (as calculated from the rate of disappearance of vinyl chloride from the chamber atmosphere) was approximately three times greater for doses less than 105 ppm (range 50 to 105 ppm) than for doses greater than 220 ppm (range 220 to 1,167 ppm). After an initial equilibration period and regardless of the administered concentration, vinyl chloride disappearance from the chamber apparently followed first- order kinetics. The half-life for atmospheric vinyl chloride at concentrations below 100 ppm was 86 minutes compared with 261 minutes for concentrations greater than 220 ppm. Hefner et al. (1975b) concluded that the predominant pathway for metabolism of vinyl chloride by rats exposed to 100 ppm or less is saturable and that this metabolism was inhibited by pyrazole and ethanol.

Studies in rats and monkeys suggest that, after absorption, vinyl chloride is rapidly distributed to all tissues reached by the bloodstream (Duprat et al., 1977; Buchter et al., 1980). Lipids or lipoproteins, rather than proteins, transport vinyl chloride in the blood (Bolt et al., 1977). Studies of the distribution of ^{14}C-labeled vinyl chloride in rats indicated that, immediately after inhalation administration, the liver (predominant site of metabolism) and the kidneys (site of excretion of polar metabolites) contained the highest concentrations of ^{14}C activity, followed by lungs, spleen, and small intestine (Watanabe et al., 1976a; Bolt et al., 1976). However, ^{14}C counts quickly decreased after cessation of exposure. In one study, vinyl chloride metabolite concentrations decreased significantly in these tissues 48 hours after a single inhalation exposure (50 ppm for five hours) compared to measurements made immediately after exposure ended (Bolt et al., 1976).

Watanabe and co-workers (1976a) also examined the fate of ^{14}C-vinyl chloride following inhalation exposure in rats. Male Sprague-Dawley rats were exposed to 10 or 1,000 ppm vinyl chloride in whole-body metabolism cages for six hours and were observed for an additional 72 hours. After exposure to 10 ppm vinyl chloride, urinary radioactivity accounted for 68%, expired vinyl chloride for 2%, expired CO_2 for 12%, feces for 4%, and carcass and tissues for 14%, respectively, of the recovered radioactivity. After exposure to 1,000 ppm, urinary radioactivity accounted for 56%, expired vinyl chloride for 12%, expired CO_2 for 12%, feces for 4%, and carcass and tissues for 15% of the recovered radioactivity. The patterns of pulmonary elimination of unmetabolized vinyl chloride following exposure to 10 or 1,000 ppm were similar and could be described by first-order kinetics, with half-lives of 20.4 and 22.4 minutes, respectively. A corresponding biphasic elimination of urinary radioactivity following inhalation exposure to 10 or 1,000 ppm vinyl chloride was observed; the half-lives for the initial phase were 276 and 246

minutes, respectively. The liver and skin contained the highest concentrations of radioactivity 72 hours after exposure to either dose. The authors concluded that since "the rate of elimination of vinyl chloride per se from the lungs or ^{14}C activity in the urine was not different in rats exposed to 10 or 1000 ppm," the dose-dependent fate (the relative amount of vinyl chloride excreted by the two different routes) was not attributable to saturation of the excretion pathways. The results are in agreement with the hypothesis that the metabolism of vinyl chloride becomes saturated at high exposure levels (Watanabe et al., 1976a).

Gehring et al. (1978) have investigated the extent to which the metabolism of vinyl chloride in rats quanitatively follows Michaelis-Menten kinetics. Over the exposure range of 1.4 to 4600 ppm for six hours the data follow approximately the Michaelis-Menten equation with:

Vm = 8558 ± 1147 (SD) μg/6 hr, maximum velocity;
Km = 860 ± 159 (SD) μg/liter (336 ± 62 (SD) ppm), saturation constant;
R = 0.88, correlation coefficient.

The pharmacokinetics of inhaled vinyl chloride in a closed system has also been examined in Rhesus monkeys (Buchter et al., 1980). Uptake of vinyl chloride appeared to depend on its metabolism and to be a dose-dependent, saturable process. When monkeys were exposed to concentrations up to 200-300 ppm in a closed system, vinyl chloride disappearance from the chamber followed apparent first-order kinetics. At higher exposure levels (up to 800 ppm), zero-order kinetics were observed, implying metabolic saturation. The first-order clearance rate was 3.55 liters/hour/kg. The clearance rate fell by 90% after pretreatment with the aldehyde dehydrogenase inhibitor, disulfiram (Buchter et al., 1980).

Gargas et al. (1986, 1988) have used gas uptake data to determine the kinetic constants of vinyl chloride and other organic gases in the F-344 male rat. The results for vinyl chloride are V_{max} = 40 μmol/h, near previous values; K_m = 0.1 mg/l blood, lower than previous values by 10-fold; and blood-air partition coefficient = 1.68, near recent determinations. See also Chen and Blancato (1989).

Liver microsomal enzyme activities and macromolecular covalent binding in rats following either single or repeated exposures to vinyl chloride were compared by Watanabe et al. (1978a). One group of rats was exposed by inhalation to 5,000 ppm nonlabeled vinyl chloride 6 hours/day, 5 days/week for 7 weeks, and then exposed to carbon-labeled vinyl chloride on the last day. The fate of the labeled vinyl chloride from these rats was compared with a separate group exposed for a single 6-hour period to 5,000 ppm of labeled vinyl chloride. The activities of aniline hydroxylase and p-nitroanisole O-demethylase were the same in rats exposed once or repeatedly or in unexposed control rats. Covalent binding to hepatic macromolecules was greater in rats repeatedly exposed as compared to those given a single exposure. Watanabe et al. (1978a) concluded that this "increase in hepatic macromolecular binding indicates that repeated exposure augments the reaction of electrophilic metabolites with macromolecules, and this may be expected to enhance potential toxicity, including carcinogenicity". Chronic exposure (28,000 ppm, seven hours/day, five days/week for 2, 4 or 6 weeks) was found to increase glutathione reductase activity, glutathione-S-epoxide transferase activity,

glutathione-S-aralkyl transferase activities, and glutathione levels in rat liver and to depress cytochrome P-450 levels (Du et al., 1982). This suggests that a reactive metabolite of vinyl chloride can destroy cytochrome P-450 and disrupt several enzymes that may effect its chronic toxicity.

2.2.2 Intragastric, Intraperitoneal, Intravenous, Dermal, and Oral Administration

Uptake and absorption of vinyl chloride administered by intragastric (IG), intraperitoneal (IP) and intravenous (IV) administration follows the patterns observed in inhalation studies. It appears from these studies that the quantity of vinyl chloride metabolized by these routes is dependent on the quantity administered.

Green and Hathway (1975) examined the excretion pattern of single doses of 0.25 and 450 mg/kg of radiolabeled ^{14}C-vinyl chloride administered to rats by the IG, IP, and IV routes. More than 90% of the administered dose was excreted within the first 24 hours. Exhalation of unmetabolized vinyl chloride is the predominant route of excretion for each route of exposure at the high dose and for the low-dose intravenous exposure. After IG administration of the high dose, more than 90% of the dose was exhaled as unmetabolized vinyl chloride and less than 1% as CO_2, while 5% of the administered radioactivity was found in the urine. At the low dose, urinary excretion accounted for 72% of the dose, unchanged exhaled vinyl chloride for 4% of the dose, and CO_2 for 13% of the dose. About 100 times more vinyl chloride was metabolized at the higher dose level than at the lower dose (an 1,800-fold difference in dose). These observations suggest that the metabolism of vinyl chloride is saturable by administration of a single dose. In another experiment, chronic IG dosing with unlabeled vinyl chloride at 3, 30, or 300 mg/kg daily for 60 days did not affect the rate or route of elimination of a single dose of radiolabeled vinyl chloride from the body. Based on these results, the authors suggested that vinyl chloride excretion data for a single dose may also apply for chronic exposure to vinyl chloride.

Watanabe and associates (1976b) examined the excretion of ^{14}C-labeled vinyl chloride following single oral doses of vinyl chloride in rats. Their results were similar to those of Green and Hathway (1975). After administration of a single oral dose of 0.05, 1, or 100 mg/kg of the labeled vinyl chloride to male rats, urinary metabolites accounted for 68, 59, and 11%, respectively, of the administered dose while the $^{14}CO_2$ in expired air accounted for 9, 13, and 3%, respectively. Pulmonary elimination of unmetabolized vinyl chloride represented only 1 to 3% at the lower dose levels, but 67% at the higher dose level. Pulmonary clearance of the 0.05 and 1 mg/kg doses was monophasic, with half-lives of 53.3 and 57.8 minutes, respectively. Clearance of the 100 mg/kg dose was biphasic, with half-lives of 14.4 and 40.8 minutes for the fast and slow phases, respectively.

Absorption of vinyl chloride after oral administration has been measured in rats, both in diet studies (Feron et al., 1981) and gavage studies (Withey, 1976; Watanabe, 1976b). In these reports, almost 100% of the administered dose was absorbed, suggesting extensive gastrointestinal uptake of vinyl chloride. Maximum blood concentrations of vinyl chloride were observed within 10-20 minutes following dosing with aqueous or vegetable oil solutions (dose

range 12.5-28.2 mg per rat (Withey, 1976). Green and Hathway (1975) observed absorption of 98.7% from the gastrointestinal tract following an oral dose of 450 mg/kg.

Limited percutaneous absorption (0.03% of dose) following whole body exposure (excluding the head) to either 800 or 7000 ppm of vinyl chloride has been demonstrated in monkeys (Hefner et al., 1975c). The usefulness of this study is limited, however, since only one monkey was exposed at each dose level. Exposure times were limited to 2.5 hours for the 800 ppm group and 2 hours for the 7000 ppm group. The majority of the absorbed vinyl chloride was eliminated in the expired air (Hefner et al., 1975c).

2.3 Metabolism

Metabolism of vinyl chloride involves both microsomal and nonmicrosomal enzymes and results in the conversion of vinyl chloride to 2-chloroethylene oxide and subsequent oxidation to 2-chloroacetaldehyde and monochloroacetic acid. This saturable pathway appears to operate at low exposures ($\leq$ 100 ppm), leading to the production of polar metabolites, which are predominantly excreted in the urine.

The initial studies of Hefner and colleagues (Hefner et al., 1975a; 1975b), suggested a possible role of alcohol dehydrogenase in the metabolism of vinyl chloride. Following exposure of Sprague-Dawley rats to low concentrations (< 200 ppm), vinyl chloride was metabolized to 2-chloroethanol, chloroacetaldehyde, and monochloroacetic acid by an alcohol dehydrogenase (ADH)-mediated pathway. Pretreatment of rats with pyrazole or 95% ethanol significantly reduced both the uptake and metabolism of inhaled vinyl chloride (Hefner et al., 1975a). This inhibition now appears more likely due to competition by a P450 isozyme (Brady et al. 1989).

Another proposed pathway, which involves only microsomal enzymes, is that following the formation of chloroethylene oxide, it may spontaneously rearrange to form 2-chloroacetaldehyde and, subsequently, monochloroacetic acid (Kilbey, 1981). The epoxide, chloroacetaldehyde, and monochloroacetic acid can then undergo conjugation with glutathione. Further metabolism of these glutathione conjugates can produce a number of compounds, some of which have been identified in the urine of animals treated with vinyl chloride (Figure 2.1). Specifically, monochloroacetic acid, S-(carboxymethyl)cysteine, N-acetyl-S-(2-hydroxyethyl) cysteine, N-acetyl-vinylcysteine, and thiodiglycolic acid have been found in the urine of rats exposed to vinyl chloride by the inhalation and oral routes (Green and Hathway, 1975; 1977; Watanabe et al., 1976a; 1976b). Thiodiglycolic acid and chloroacetic acid have been detected in the urine of workers exposed to atmospheric vinyl chloride (Muller et al., 1978; Heger et al., 1982). The generation of CO_2 from vinyl chloride has been postulated to occur through the tricarboxylic acid cycle or the one- or two-carbon pools, with chloroacetic acid or chloroethylene glycol as the starting intermediate (Woo et al., 1985).

Studies by Bolt and co-workers (1976) indicate that the cytochrome P-450 system is involved in vinyl chloridemetabolism. Their results demonstrated that the uptake of 50 ppm vinyl chloride in a closed system was completely blocked by inhibitors of cytochrome P-450, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiodiazole. Pretreatment with the

insecticide dichlorodiphenyl trichloroethane (DDT), an inducer of cytochrome P-450, was effective in enhancing uptake and absorption. However, phenobarbital, another P-450 inducer, has shown no effect on vinyl chloride metabolism (Guengerich and Watanabe, 1979), possibly due to selective induction of different cytochrome P-450 isozymes by the two compounds.

Chronic ethanol treatment has been shown to potentiate the carcinogenic effect of vinyl chloride in male Sprague-Dawley rats (Radike et al., 1981). Animals were exposed by inhalation to 600 ppm vinyl chloride four hours/day, five days/week, for one year. Ingestion of 5% ethanol in water (volume/volume, v/v) ad libitum was begun four weeks prior to vinyl chloride exposure and continued for life or until the termination of the experiment, 2.5 years after the first vinyl chloride exposure and 1.5 years after vinyl chloride exposure was terminated. The incidence of liver angiosarcoma in rats exposed to vinyl chloride and ethanol was 50% (40/80) versus 23% (18/80) in rats exposed to vinyl chloride alone and 0% (0/80) in animals treated only with ethanol. Radike and associates have suggested that this potentiation of tumor formation may be due to the effect of alcohol on vinyl chloride metabolism and a shared step in the oxidation of ethanol and vinyl chloride. The acetaldehyde product in ethanol metabolism may compete with chloroacetaldehyde for ADH. This would result in higher levels of chloroacetaldehyde. However, this metabolite may not be the ultimate carcinogen. Chloroacetaldehyde buildup may result in a decrease in epoxide-to-aldehyde conversion, leading to epoxide buildup and increased interaction with cellular macromolecules.

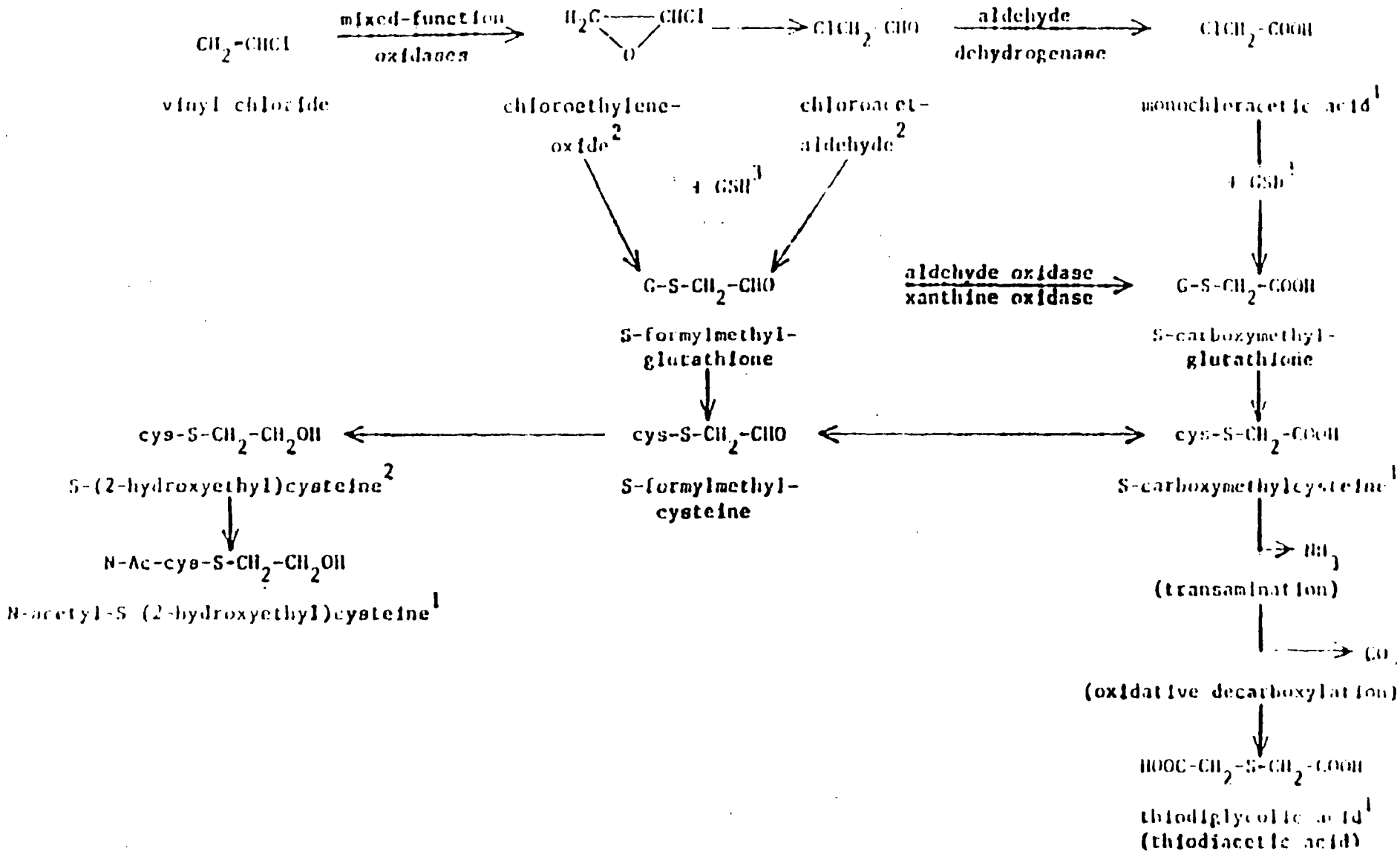
Radiolabeled vinyl chloride has been shown to bind covalently to cellular macromolecules in vivo and in vitro (Watanabe et al., 1978b; Woo et al., 1985; International Agency for Research on Cancer [IARC] 1979). Watanabe et al. (1978b) exposed rats to C-vinyl chloride (range 1-5000 ppm) for six hours, and measured covalent binding of radioactivity to hepatic macromolecules, RNA and DNA, along with levels of hepatic glutathione. Binding of vinyl chloride metabolites to liver macromolecules did not increase proportionately with dose, but was instead related to the total amount of vinyl chloride metabolized. Binding appeared to plateau above 500 ppm, while below 100 ppm binding was approximately proportional to the increase in exposure. Depression of hepatic glutathione occurred only at exposure levels of 100 ppm or higher. Covalent binding to RNA or DNA was not detected for any exposure group (Watanabe et al., 1978b). However, a subsequent study found covalently bound vinyl chloride metabolites attached to proteins and nucleic acids isolated from the livers of rats exposed to either 10 or 250 ppm vinyl chloride for two hours. (Guengerich and Watanabe, 1979). Rat liver DNA isolated from the two groups of exposed animals contained 0.04 and 0.9 pg of total bound metabolites per gram of wet liver, respectively. Pretreatment with phenobarbital had no apparent effect on metabolism or DNA-binding of metabolites, but did increase binding to protein and RNA at the 10-ppm dose level. In vitro binding of 14C-vinyl chloride to proteins and nucleic acids appeared to be dependent on the thiol content of the proteins and the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH), oxygen, and microsomal enzymes (Guengerich and Watanabe, 1979).

Both chloroethylene oxide and chloroacetaldehyde have been studied as possible reactive intermediates that could act as the "ultimate" mutagen or carcinogen formed from vinyl chloride. The epoxide is considered to be the

most biologically active metabolite (Bartsch et al., 1975; Laib and Bolt, 1977). Other researchers have proposed that chloroacetaldehyde may be a more effective alkylating agent (Woo et al., 1985). In vivo and in vitro studies by Guengerich and Watanabe (1979) suggest that the mechanism for activation and binding of vinyl chloride involves the release of the chloride atoms as chloride ions, either in the actual activation mechanism or in rearrangment of the metabolite or adduct. However, Guengerich and Strickland (1977) have demonstrated that neither chloroethylene oxide nor 2-chloroacetaldehyde appear to be responsible for destruction the heme group of cytochrome P-450 occuring after administration of vinyl chloride. Other mechanisms (or reactive metabolites) may account for the destruction. See also Sections 6.2 and 6.6 for recent discussions of the role of metabolites in the mechanisms of genotoxicity.

Figure 2-1

Metabolism of Vinyl Chloride



Source: IARC (1979)

1 Detected In vivo

2 Detected In vitro

3.0 ACUTE TOXICITY

Several investigators have reviewed the toxic effects of acute exposure to vinyl chloride. (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984b). The sections below present a brief account of the principal findings.

3.1 Summary

The acute effects of vinyl chloride are similar for humans and animals: central nervous system depression (anesthesia) and cardiac, circulatory, and respiratory irregularities. Frostbite from contact of skin with liquid vinyl chloride has been reported. Repeated inhalational exposure of humans to high concentrations of vinyl chloride has been associated with narcosis, damage to the liver, spleen, and circulatory system, and a complex of symptoms identified as occupational acro-osteolysis. With the exception of acro-osteolysis, the occurrence of these toxic symptoms has also been confirmed in experimental animals. The exact occupational exposure levels associated with these symptoms are not known, but are thought to be above 100 ppm.

3.2 Animal Studies

A report of exposures causing 50% lethality (LD_{50}) in groups of animals exposed to vinyl chloride by inhalation for two hours indicates a low acute toxicity: 27,419 ppm in mice, 47,640 ppm in rats, 236,215 ppm in guinea pigs, and 263,215 ppm in rabbits. Toxic symptoms following exposure included narcosis accompanied by respiratory and circulatory disturbances. Death was caused by respiratory failure. Microscopic examination of all animals indicated damage to the lungs, liver, and kidneys (Prodan et al., 1975a).

3.3 Human Data

Several human deaths following very high exposure (concentrations unreported) to vinyl chloride have been reported. Autopsies revealed congestion of the liver, spleen, and kidneys (Danziger, 1960, cited in Maltoni et al., 1984). Lester and co-workers (1963) estimated that the short-term (five minutes) exposure limit (STEL) of vinyl chloride to which a human could be exposed without symptoms of acute toxicity was between 8,000 and 13,000 ppm. Suciu et al. (1975) reported that workers exposed to vinyl chloride (levels not given) experienced euphoria, intoxication, and narcosis. They also reported generalized transient contact dermatitis after dermal exposure.

4.0 SUBCHRONIC AND CHRONIC TOXICITY

Several investigators have reviewed the toxic effects resulting from subchronic and chronic exposure to vinyl chloride. (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984b). The sections below present a brief account of the principal findings.

4.1 Human

Reports on the adverse effects of repeated occupational exposure to vinyl chloride are based mainly on the observations of workers who have been the most heavily exposed. Those individuals were involved in occupations such as cleaning autoclaves and centrifuges, or engaged in drying and shifting processes. They experienced a wide range of symptoms: a vasospastic disorder in the hands similar to Raynaud's syndrome; occupational acro-osteolysis, which included clubbing-like swellings and loss of bone from the terminal phalanges, scleroderma-like skin changes, and dermatitis; acrocyanosis, consisting of vascular changes and impaired thermoregulation; positive cold test reactions; capillaroscopic alterations; paresthesias; and central nervous system symptoms. These clinical symptoms (classified as "vinyl chloride disease") were accompanied by circulatory disturbances, thrombocytopenia, splenomegaly, and changes in the liver. The period of exposure before the first sign of symptoms was as short as one month to as long as three years. A year or two after removal from exposure, most of the abnormalities disappeared (Veltman et al., 1975; Wilson et al., 1967; Harris and Adams, 1967; Lilis et al., 1975).

Several studies have reported hepatotoxicity and impaired liver function in humans resulting from exposure to vinyl chloride at concentrations ranging from 1 to 470 ppm (Marstellar and Lelbach, 1975; Lilis et al., 1975; Thomas and Popper, 1975; Suciu et al., 1975).

Repeated occupational exposure to vinyl chloride has also been noted to result in impaired pulmonary function (Miller et al., 1975; Gamble et al., 1976). Interstitial pulmonary fibrosis has been reported, but these particular workers were also exposed to polyvinyl chloride dust. It has been proposed, but not satisfactorily demonstrated, that interstitial pulmonary fibrosis may be caused by vinyl chloride-altered immune status (Lilis et al., 1975; Ward et al., 1976). In a study of present and past workers affected with vinyl chloride disease, Ward et al. (1976) observed a range of symptoms associated with immune system dysfunction in 19 of the 28 affected workers.

From their study of occupationally exposed workers, Spirtas et al. (1975) concluded that a dose-response relationship existed between exposure to vinyl chloride and certain acute (primarily neurological) symptoms. The investigators examined the frequency of eight symptoms indicative of central nervous system disturbance, peripheral neuromuscular and neurovascular disturbance, and local irritation. Vinyl chloride doses were estimated from company data describing probable exposure scenarios for different job descriptions. Exposure concentrations appeared to range from 0 to 200 ppm. They observed a statistically significant dose relationship in the occurrence of five of the eight symptoms (dizziness, nausea, headache, tingling sensation in arms and legs, and fatigue). These symptoms occurred after exposures to less than 50 ppm. These data support other observations in humans that indicate vinyl chloride may produce adverse health effects even at levels below 50 ppm (Spirtas et al., 1975). However, it should be noted

the exposure estimates based on probable scenarious may not reflect individual exposures due to person-specific work practices.

4.2 Animals

Repeated inhalation exposure to vinyl chloride has been reported to result in osteoporosis and toxicity to the liver, kidney, spleen, lung, and testes in certain animals. The results of some of these studies are reported in Table 4.1.

TABLE 4.1

SUBCHRONIC AND CHRONIC TOXICITY OF VINYL CHLORIDE ADMINISTERED TO ANIMALS BY INHALATION

Species	Dose	Duration (months)	Observations	Reference
Guinea Pig	100,000 ppm 2 hr/day	3	Liver, kidney, spleen toxicity.	Prodan et al., 1975b
Rat	500, 100, 50 ppm 7 hr/day	6	Increase in liver weights; 100 ppm NOAEL.	Torkelson et al., 1961
Rat	100 ppm 2 hr/day	6	No effects observed.	Torkelson et al., 1961
Rat	20,000 ppm 8 hr/day	3	Increased mean liver and spleen weight.	Lester et al., 1963
Rat	5,000 ppm 7 hr/day	12	Growth retardation; shortened blood-clotting time; increased kidney, heart, spleen weight; increased mortality; degenerative and hyper-plastic changes in the liver.	Feron et al., 1979a,b
Rat, rabbit	0.03-0.04 mg/L 4 hr/day	6	Cardiovascular disorders, changes in the bioelectric activity of the hypothalamus, hyperadrenalemia, osteoporosis.	Basalaev et al., 1972

Table 4.1 continued

Species	Dose	Duration (months)	Observations	Reference
Rat	20,000, 500, 50 ppm 5 hr/day	10	Liver and testes lesions at exposures of 50 and 500 ppm, respectively; depression of body weight gain at dose levels.	Sokal et al., 1980
Rat	10, 100, 3000 ppm 6 hr/day 60/wk	up to 12	Increased kidney, liver, spleen, and heart weight; decreased testis weight in all within 6 months; testis damage.	Bi et al., 1985
Mice	1,000, 250, 50 ppm 6 hr/day	up to 12	Deaths at high dose caused by hepatitis; at 50 ppm, lethargy, weight loss, rough coat, hepatitis.	Lee et al., 1977
Mice	6,000, 2,500 ppm 5 hr/day	5 to 6	Proliferation and hypertrophy of terminal bronchiolar cells at both dose levels.	Suzuki 1980, 1981

5.0 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

5.1 Summary

Experimental and epidemiologic studies have investigated the developmental and reproductive toxicity of vinyl chloride. (Barlow and Sullivan, 1982; Bardin et al., 1982; Hemminki and Vineis, 1985). Vinyl chloride crosses the placenta of experimental animals. Some data indicates it may act as a transplacental carcinogen. No teratogenic effects were observed when vinyl chloride was administered by inhalation at maternally toxic doses. A single unconfirmed report disclosed a teratogenic effect in rats after vinyl chloride exposure as low as 2.5 ppm. Evidence that vinyl chloride causes male reproductive damage has been presented in one experimental study and in a few human case studies. Epidemiologic analysis of communities located close to polyvinyl chloride plants have suggested an association between those locations and an increased risk of birth defects, but none of the studies have adequately controlled for all confounding variables, and no positive correlation has been made conclusively linking vinyl chloride exposure with harmful reproductive effects.

5.2 Teratogenic Effects in Animals

5.2.1 Inhalation Studies

Rats: John et al. (1977) reported that no developmental toxicity or defects occurred when pregnant Sprague-Dawley rats were exposed to either 500 or 2500 ppm vinyl chloride for seven hours daily on days 6 through 15 of gestation. These concentrations proved toxic to the mothers, however. In a separate experiment, pregnant rats exposed to 2500 ppm vinyl chloride by inhalation and 15% ethanol in drinking water experienced greater maternal and fetal toxicity than animals exposed only to vinyl chloride, but no teratogenic response was observed. However, fetal body measurements were lower among those rats that received ethanol and vinyl chloride. These effects on fetuses were similar to those reported following administration of ethanol only (John et al., 1981).

Ungvary et al. (1978) exposed groups of three pregnant CFY rats to 1500 ppm vinyl chloride continuously on days 1 through 9, 8 through 14, or 14 through 21 of gestation. An increased number of resorbed fetuses was found in the group exposed to vinyl chloride during the first 9 days ($p \leq 0.05$), but no significant effects were observed in rats exposed at other stages of gestation.

In a recent study reported in abstract form, Radike et al. (1988) reported that vinyl chloride was a transplacental carcinogen capable of causing perinatal oncogenesis. An increase in the numbers of liver carcinomas and angiosarcomas in the offspring of pregnant rats exposed to 600 ppm for four hours/day from day 9 to day 21 of gestation was observed. Post-natal exposure of the pups to 600 ppm increased the incidence of liver tumors. Co-administration of 5% ethanol with vinyl chloride did not increase the incidence of treatment-related malignancies.

A single Russian study has reported an association between vinyl chloride exposures of as low as 2.5 ppm during pregnancy and embryo lethality, teratogenicity, and fetotoxicity in rats (Mirkova et al., 1978, cited in Barlow and Sullivan, 1982). The study and its results were reported only qualitatively and no statistical data were published. Adverse effects

reported included doubling of embryo mortality, a high incidence of cerebral malformations, and fetotoxicity.

Bi et al. (1985) examined the effects of vinyl chloride on testicular seminiferous tubules in rats. Groups of 75 male Wistar rats were exposed by inhalation to either 0, 10, 100 or 3000 ppm vinyl chloride for six hours/day, six days/week for three, six, nine or twelve months. Eight to thirty rats were sacrificed after each exposure period, with remaining animals killed 18 months after the initial exposure (i.e., six months after terminating exposure). Incidence of seminiferous tubule damage for the control, 10, 100 and 3000 ppm group were 19, 30, 37 and 56%, respectively. Changes included cytoplasmic vacuolation, nuclear condensation, fusion of spermatids and spermatocytes, and epithelial necrosis and degeneration. Seminiferous tubule damage in the two higher dose groups was significantly greater than for the control group (Bi et al., 1985).

Mice: Groups of 30 to 40 pregnant CF-1 mice were exposed by inhalation to either 50 or 500 ppm vinyl chloride for seven hours/day on days 6-15 of gestation. Exposure to 500 ppm caused maternal toxicity while no maternally toxic effects were observed at 50 ppm. No developmental defects were reported in fetuses exposed to either concentration. An increased number of resorptions and decreases in litter size and fetal body weight were seen in mice exposed to 500 ppm, but these effects were considered secondary to the toxic effects of vinyl chloride in the mother (John et al., 1977; 1981).

Rabbits: No teratogenic or embryotoxic effects were observed in the offspring of pregnant rabbits (15 to 20 per group) exposed by inhalation to either 500 or 2500 ppm vinyl chloride for seven hours per day on days 6-18 of gestation. The incidence of resorptions was significantly increased in rabbits exposed to 2500 ppm vinyl chloride, a dose that produced other adverse effects in the dam (John et al., 1977; 1981). Simultaneous administration of 15% ethanol in the drinking water and 500 ppm vinyl chloride in air resulted in increased toxicity to the mother and produced defects in the developing embryo not observed in animals exposed to vinyl chloride alone.

5.3 Reproductive Effects in Humans

Several epidemiologic studies have been conducted to assess potential reproductive and developmental effects in the families of vinyl chloride workers (reviewed in Wagoner and Infante, 1980; Clemmesen, 1982). Infante (1976) analyzed birth certificate data obtained from a group of Ohio communities, three of which contained vinyl chloride polymerization plants. Although a statistically significant increase ($p < 0.01$) in birth defects was observed in the towns with vinyl chloride facilities (compared with the birth defect rate for the entire State of Ohio), several other cities without vinyl chloride factories exhibited rates equally high and higher. Spontaneous abortion rates were also elevated in wives of vinyl chloride workers (Infante, 1976). Edmonds et al. (1975; 1978) conducted two case-controlled studies evaluating CNS malformations among offspring of vinyl chloride workers and families living near polyvinyl chloride facilities in Painesville, IN and Kanawha County, WV. More cases than controls lived within three miles of the polyvinyl chloride plants ($p < 0.02$). In reviewing these three studies, Hemminki and Vineis (1985) concluded that there was inadequate evidence linking environmental or paternal exposure to vinyl chloride with birth defects in humans.

Theriault et al. (1983) measured the incidence of birth defects in infants born to residents of Shawinigan, Canada between 1966 and 1979. A vinyl chloride polymerization plant had been operating in the town since 1943. Although the authors stated that some descriptive data suggested an association between ambient exposure to vinyl chloride and birth defects in the exposed community, no significant increases in either still births or birth defects were observed (Theriault et al., 1983).

6.0 GENOTOXICITY

6.1 Summary

Several authors have reviewed the genotoxicity of vinyl chloride. (IARC, 1979; Duverger et al., 1981; Bartsch et al., 1975; SRI International, 1983; Fabricant and Legator, 1981). Vinyl chloride causes genetic damage in many test systems, including bacteria, fungi, higher plants, and in vitro mammalian systems, as well as in vivo in Drosophila (fruit fly), rodents, and humans. Previous reviews have suggested that a metabolite of vinyl chloride is the major cause of the observed genotoxicity. However, vinyl chloride has been observed to be mutagenic in some in vitro test systems without an exogenous activation system. This particular effect may be the result of endogenous cellular metabolizing enzymes, or the molecule itself may be genotoxic. From experiments in laboratory animals vinyl chloride does not appear to cause genetic damage to germ cells, but does transform mammalian cells and enhances virally-induced mammalian cell transformation in vitro. This strong evidence of the genotoxicity of vinyl chloride suggests that its reported carcinogenicity proceeds by genotoxic mechanisms. Data that support this suggestion are summarized below.

6.2 Mutagenicity

Vinyl chloride is mutagenic in most major short-term tests. Its activity is enhanced in the presence of exogenous or endogenous metabolic activation, suggesting that a metabolite may be more mutagenic than the vinyl chloride molecule itself. This observation is supported by in vitro experiments in E coli examining mutagenesis by the vinyl chloride metabolite 2-chloroacetaldehyde (CAA). CAA generated predominantly cytosine-to-thymine (C-to-T) transitions and less often cytosine-to-adenine (C-to-A) transversions or other mutations at adenine (Jacobsen et al. 1989). Further investigations (Jacobsen and Humayun, 1990) of CAA mutagenesis have provided evidence against a strong role for DNA repair by induction at SOS genes in mutagenesis at cytosine lesions, suggesting that these predominant lesions do not block DNA replication. Several investigators have marshalled evidence that chloroethylene oxide, the first metabolite of vinyl chloride and an immediate precursor for CAA, is responsible for mutagenesis in vivo. See sections 2.3 and 6.5.

6.2.1 Bacterial Assays

Several studies of vinyl chloride have been conducted using the Ames' Salmonella typhimurium (S. typhimurium) assay (McCann et al., 1975; Bartsch and Montesano, 1975; Bartsch et al., 1975; Garro et al., 1976). These studies and others have recently been summarized (IARC, 1987). These studies indicate that vinyl chloride apparently acts as a mutagen whose effect is significantly enhanced in the presence of liver microsomal enzyme preparations from mice, rats, or humans, and NADPH. For example, Bartsch and Montesano (1975) investigated the mutagenicity of vinyl chloride in air at concentrations of 0, 0.2, 2, or 20% in both the absence and the presence of S-9 fraction obtained from livers of uninduced or phenobarbitone-induced rats. In the absence of metabolic activation, a dose-related increase of up to 15 times background was observed in S. typhimurium strains TA1535 and G46. In

the presence of S-9 from uninduced rats, the frequency of revertants was increased up to 23 times above background in strain TA1530, and up to 16 and five times above background in strains TA1535 and G46, respectively. The frequency of revertants increased to approximately 28 times above background in strain TA1530, and to 18 and six times above background in strains TA1535 and G46, respectively, when S-9 from phenobarbitone-induced rats was used. In the same study, chloroacetaldehyde, a metabolite of vinyl chloride, proved mutagenic (15 times above background) in strain TA1530 in the absence of exogenous metabolic activation. Chloroethylene oxide was less toxic than chloroacetaldehyde, but was also mutagenic (nine times above background) when tested without exogenous metabolic activation. The authors proposed that the increase in revertants in the absence of an exogenous metabolic activation system was either the result of nonenzymatic breakdown products of vinyl chloride or a result of compounds formed by bacterial enzymes. However, the answer to this question was not effectively resolved by this study (Bartsch and Montesano, 1975).

Salmonella typhimurium strain TA1538, which is specifically reverted by frameshift mutagens, was unaffected by concentrations of 20% vinyl chloride in air (Bartsch et al., 1975). Vinyl chloride in water or methanol when tested in S. typhimurium strains TA100, TA1530, TA1535 or G46, even with S-9 liver fractions from phenobarbital-induced mice, did elicit a mutagenic response. The apparent inactivity of vinyl chloride might have been caused by the rapid diffusion of vinyl chloride from the solution into the atmosphere (Bartsch et al., 1975).

Other experiments have confirmed the mutagenic activity of vinyl chloride in Salmonella. Vinyl chloride was mutagenic in S. typhimurium strain TA1530, both with and without activation, after incubation in a vinyl chloride/ethanol medium. This medium probably helped retain vinyl chloride in this system. The mutation rate increased when cells were incubated in the presence of ultraviolet light and decreased when hydroquinone, a radical-trapping agent, was added to the incubation medium. These results and others suggest that radical metabolites may also be important determinants of mutagenic activity (Duverger-Van Bogaert et al., 1982; Garro et al., 1976).

In at least one study, the increases in vinyl chloride-induced mutagenicity in S. typhimurium strain TA1530 observed with the addition of liver fractions obtained from untreated or PCB-induced animals were similar, (Garro et al., 1976). Vinyl chloride was mutagenic in strain TA1530 in the presence of rat or mouse liver S-9 fraction from Aroclor-induced animals. Mutagenicity was observed even in the absence of an NADPH-generating system. Heat-inactivation of the mixed-function oxidase system did not result in decreased mutagenicity of vinyl chloride. These results suggest that the mutagenic activity observed with vinyl chloride in the Ames' test is not necessarily due to enzymatic activation by a mixed-function oxidase system.

Vinyl chloride induced forward and reverse mutations in Escherichia coli (E. coli) strain 343/113 (Mohn, 1981) and forward mutations in E. coli strain K12 with, but required metabolic activation with mouse liver microsomes (Greim et al., 1975, cited in IARC, 1979).

Chloroethylene oxide at concentrations of 2.5 mmol was more cytotoxic and mutagenic than chloroacetaldehyde at concentrations of 100 mmol when

tested in E. coli strain K12A (Perrard, 1985). These results are consistent with those obtained in the Salmonella typhimurium assay (Bartsch et al., 1975).

6.2.2 Eukaryotic Systems

Vinyl chloride induced forward mutations in the yeast Schizosaccharomyces pombe following either a host-mediated assay in mice or in vitro after metabolic activation with mouse liver microsomes (Loprieno et al., 1976; Bartsch and Montesano, 1975). Chloroethylene oxide was mutagenic without activation in the same system (Loprieno et al., 1976). In Saccharomyces cerevisiae strain D_4, vinyl chloride (in concentrations of either 16 or 48 mM) induced gene conversion at the adenine-2 and tryptophan-5 loci only in the presence of mouse liver microsomes (Loprieno et al., 1976). Vinyl chloride, both as a gas and as an ethanol solution, was tested for potential mutagenicity in two strains of the fungus Neurospora crassa. There was no detectable mutagenic effect, either with or without metabolic activation. The authors suggested this was because vinyl chloride could not penetrate the conidia (spore) (Drozdowicz and Huang, 1977).

6.2.3 Cultured Mammalian Cell Assays

Vinyl chloride was tested in the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (CHO/HGPRT) system, an assay designed to detect mutations in the gene coding for the HGPRT locus. Vinyl chloride (at concentrations of 10% in air) was mutagenic only in the presence of complete S-9 mixtures from Aroclor-induced rat livers. When various cofactors used to activate the liver enzymes (for example, NADPH) were not included in this test system, vinyl chloride was inactive even at higher concentrations (Krahn, 1979).

Forward mutations were induced in V79 Chinese hamster lung cells in the presence of phenobarbital-pretreated rat liver supernatant (15,000 x g) (Drevon et al., 1977, cited in IARC, 1979). Huberman et al. (1975) reported that at concentrations of 6-13 mmol the vinyl chloride metabolites chloroethylene oxide and 2-chloroacetaldehyde caused a dose-dependent induction of 8-azaguanine (four to eight times above background) and ouabain-resistant (up to 23 times above background) mutants in Chinese hamster V79 cells in vitro. Both 2-chloroethanol and monochloroacetic acid (at concentrations of up to 2500 mmol) were found to be inactive (Huberman et al., 1975).

6.2.4 In Vivo Mutagenicity Assays

A significant increase in recessive lethal mutations in Drosophila melanogaster was observed after exposure to 850 ppm vinyl chloride for two days. Exposure to 30 ppm for 17 days also caused an increase in recessive lethal mutations. Although vinyl chloride was tested at concentrations ranging from 30 to 50,000 ppm, the mutation frequency rate reached a plateau at 10,000 ppm, a finding the authors attributed to saturation of metabolizing enzymes (Verburgt and Vogel, 1977). However, vinyl chloride did not cause any significant increase in dominant lethal mutations, translocations, or entire or partial sex-chromosome loss following exposure to 30,000 ppm for 2 days (Verburgt and Vogel, 1977).

Maier and Schawalder (1988) found a dose-dependent increase in gene mutations at the 6-thioguanine locus in fibroblast-like cells isolated from subcutaneous granuloma tissue of male Sprague-Dawley rats dosed with vinyl chloride. This "granuloma pouch assay" is believed to detect genotoxins activated by peroxidative pathways like the xenobiotic co-oxidation pathway mediated by prostaglandin H synthase. Nevertheless, other factors precluded the conclusion that vinyl chloride was being metabolically activated by these pathways (Maier and Schawalder, 1988).

6.3 Chromosomal Damage

6.3.1 Dominant Lethal Tests

Vinyl chloride failed to produce dominant lethal mutations in offspring of male CD-1 mice exposed by inhalation to concentrations of 3,000, 10,000, or 30,000 ppm, six hours/day for five days, and then mated with successive pairs of untreated females over an eight-week period (Anderson et al., 1977). There was no evidence that vinyl chloride had any mutagenic effect on any maturation stage of spermatogenesis. In addition, no significant increase in the number of post-implantation early fetal deaths, no evidence of preimplantation egg loss, and no reduction in fertility were observed in this study (Anderson et al., 1977).

Male rats were exposed to 0, 50, 250, or 1000 ppm vinyl chloride by inhalation for six hours/day, five days/week for 11 weeks (Short et al., 1977). During the eleventh week of exposure, the rats were housed with two untreated females for seven evenings or until matings occurred in both females. Although there was a significant reduction in the number of females who became pregnant when housed with males exposed to 1000 ppm vinyl chloride, there was no significant effect on total implants/female or dead implants/female in those females that became pregnant (Short et al., 1977).

No dominant lethal mutations were produced in Drosophila melanogaster following exposures of up to 30,000 ppm for two days (Verburgt and Vogel, 1977).

6.3.2 Chromosome Aberration/Sister Chromatid Exchange Studies

6.3.2.1 Experimental Studies

Sister chromatid exchanges (SCE) and aberrant metaphases were increased in chromosomes of bone marrow cells of Chinese hamsters exposed to either 1.25, 2.5 or 5% (v/v) vinyl chloride in air for 6, 12, or 24 hours. The greatest number of SCEs were seen after exposure to 2.5% vinyl chloride for 24 hours. The greatest number of aberrant metaphases was observed after exposure to 5% vinyl chloride for 24 hours (Basler and Rohrborn, 1980).

The mutagenic potential of vinyl chloride was evaluated in the mammalian spot test. Female C57B1/6J Han mice were mated to male Han/T mice, then exposed to 4600 ppm vinyl chloride in air for five hours on day 10 of gestation. No effect on litter size or coat color was seen in F_1 offspring (Peter and Ungvary, 1980).

No individual clastogenic effect (including chromatid gaps, breaks, and fragments) was significantly increased in bone marrow cells obtained from male Wistar rats exposed to vinyl chloride at 1500 ppm, six hours per day for five days. However, there was a significant increase in the number of cells with any abnormality following this exposure scenario. Although the percent of cells with gaps was elevated, no statistically significant increase was observed when vinyl chloride exposure was extended to three months (Anderson and Richardson, 1981).

Walles et al. (1988) observed induction of single-strand breaks in liver DNA by the unwinding technique. Female mice received exposures of 100, 250, and 500 ppm vinyl chloride for 27 hours. Single-stand breaks increased in a dose-dependent manner that appeared to saturate by the 500-ppm exposure. Measurements of adduct levels in hemoglobin and inferred levels in DNA also indicated a saturation effect. Calculations indicate a greater mutagenic efficiency of vinyl chloride than other agents that have been similarly tested. The same techniques showed that 80% of the single-strand breaks are repaired in 20 hours.

6.3.2.2 Human Observations

Several studies of chromosomal abnormalities in the peripheral lymphocytes of workers exposed to vinyl chloride were reported in the IARC monograph (1979). Aberrations most frequently reported were fragments, dicentrics and rings, and breaks and gaps. These earlier studies were of limited value, involving small groups of workers with inadequate controls. For example, Leonard and associates (1977) examined lymphocytes from seven men working in a vinyl chloride plant and 11 workers in a vinyl chloride polymerization plant. The incidence of such chromosome aberrations as chromatid breaks and gaps were comparable in all groups, but the degree of severity of the abnormalities observed was more severe in ten of the 11 polymerization plant workers than in the seven workers from the other vinyl chloride factory. The lack of controlled conditions greatly reduces the usefulness of this study. Vinyl chloride levels were less than 10 ppm at the time of the study, but were estimated to have been as high as 500 ppm in earlier years. Also, several of the polymerization plant workers had been given X-ray treatment on the hands, but no controls had been exposed to similar X-rays (Leonard et al., 1977).

Another study of 56 workers in the polyvinyl chloride industry suggested that occupational exposure to vinyl chloride could have a measurable effect on the induction of chromosomal aberrations in cultured lymphocytes obtained from these workers (Purchase et al., 1975). Exposure levels were not measured. Workers from both the test and control groups who had been exposed to X-rays or had had prolonged drug treatment or recent viral infections were excluded from the study. However, the results from this study and their significance were not discussed (Purchase et al., 1975). Kucerova and colleagues (1979) found that the frequency of SCE and other chromosomal aberrations was significantly higher in workers exposed to 20-150 ppm vinyl chloride in air than in unexposed controls matched for sex and age. Chromatid and chromosome breaks were detected in the greatest frequency; chromatid and chromosome exchanges occurred only sporadically.

Some subsequent studies have verified these findings. The majority suggest that the frequency of occurrence of aberrations decreased with decreasing occupational exposure levels. For example, polyvinyl chloride workers (N = 52) exposed to mean concentrations of 2.34 ppm vinyl chloride had significantly greater numbers of chromosome breaks and chromosomal aberrations than did unexposed controls (N = 74) (Suskov and Sazonova, 1982). However, in another study, workers exposed to low levels of vinyl chloride showed no differences from controls in the number of SCE or chromosome breaks. Significant differences had been seen in the same population previously when occupational vinyl chloride exposures had been higher (Hansteen et al., 1978).

Cytogenetic studies of peripheral lymphocytes from 67 workers occupationally exposed for 15 years to vinyl chloride (current occupational level of 5 ppm) were made to determine the location and frequency of chromosomal breaks (Fucic et al., 1990). Chromosomal breakage in newborns presumed to have minimal exposure to clastogens is found to be random (Funes-Gravioto et al., 1974). In the 67 workers exposed to vinyl chloride, some chromosomal locations were found to be more sensitive to breakage (non-random pattern of breaks). The authors conclude that vinyl chloride induces localized chromosomal breaks (Fucic et al., 1990). There is however, some uncertainty concerning this conclusion since this study did not employ an unexposed control group for comparison.

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A study of a large number of polyvinyl chloride workers suggested that vinyl chloride exposures below 15 ppm did not induce chromosomal aberrations (Picciano et al., 1977). When lymphocyte cultures from a group of 109 workers who had worked in the plant (exposure periods ranged from one to 332 months) were compared with cultures from a control group of 295 pre-employment examinees, no significant chromosomal differences were observed. The workers had been exposed to levels of 15.2 ppm vinyl chloride before 1960, 11.4 ppm from 1960 to 1972, and 8.7 ppm between 1973 and 1974. The subjects and controls were not matched for age or for exposure to X-rays, however.

Cytogenetic studies performed on lymphocytes isolated from 39 workers from a polyvinyl chloride plant and 16 control males demonstrated a significant increase in chromosome-breakage frequency for the exposed workers (3.41% versus 1.79%, respectively). This study was repeated for 37 of the 39 workers 2-2.5 years later, during which time the workers had only a minimal exposure to vinyl chloride. More appropriate in-plant matched controls were selected for the follow-up study. In the repeat study no difference was found in mean chromosome-breakage frequency between the workers and their controls (Hansteen et al., 1978).

6.3.3 Micronucleus Tests

In CBA male mice exposed to 5% vinyl chloride in air, nearly a four-fold increase in micronucleated cells was observed (Jenssen and Ramel, 1980).

6.3.4 DNA Damage/Unscheduled DNA Synthesis (UDS) Tests

Vinyl chloride has been reported to induce unscheduled DNA synthesis in adult rat hepatocytes, but no experimental details were provided in the publication (Probst et al., 1981).

Differential killing was induced in the repair-deficient E. coli strain polA in assays using the standard disc and liquid suspension methods (Rosenkranz, 1981).

6.4 Mammalian Cell Transformation

Vinyl chloride, 20 to 50% in air, has been reported to transform BHK cells exposed (Styles, 1980). A clear positive transformation response was obtained in BALB/c-3T3 mouse cells exposed to vinyl chloride; in addition, vinyl chloride (chamber concentrations 0-1024 ppm) caused a dose-dependent cytotoxicity (Tu et al., 1985). An increased sensitivity to transformation by SA-7 virus was observed in primary Syrian hamster embryo (SHE) fibroblasts exposed to vinyl chloride concentrations up to 194 mg/cm^3 (75,781 ppm) (Hatch et al., 1981).

6.5 Relationship to carcinogenesis

Bolt (1986), Bolt et al. (1986). Bolt (1988) and Van Duuren (1988) reviewed DNA adduct formation by vinyl chloride (metabolites) and other halogenated mono- and bi-functional alkylating agents and related this process to carcinogenesis. Products of vinyl chloride reactions with DNA identified in vivo include 1,N^6-ethenoguanine; 3N^4-ethenocytosine (Eberle et al., 1989); 7(2-oxoethyl)guanine (Singer and Grunberger, 1983) and N^2,3-ethenoguanine (Laib et al., 1985). Singer et al. (1987) found N^2,3-ethenoguanine to be a highly efficient mutagen when incorporated into a single strand RNA template read by AMV reverse transcriptase. In contrast, 1,N^6-ethenoadenine, 3,N^4-ethenocytosine and 7-(2-oxoethyl)guanine were not markedly mutagenic (Singer et al., 1987; Barbin et al., 1985; Barbin and Bartsch, 1986; Singer and Spengler, 1986). Bolt (1988) and others have argued that chloroethylene oxide is the ultimate genotoxic metabolite of vinyl chloride based on in vitro metabolism studies, in vivo studies with a metabolic precursor of chloroacetaldehyde (2,2,-dichlorodiethyl ether), mutagencity data and carcinogenicity data. Further comparisons made between the nucleophilic selectivity of vinyl chloride metabolites (chloroacetaldehyde and chloroethylene oxide) and the carcinogenic potency of vinyl chloride support this conclusion (Barbin and Bartsch, 1989; Barbin et al., 1990).

Several investigations into the relationship between DNA alkylation by vinyl chloride and cancer susceptibility have been made. In 11-day old and adult Wistar rats administered vinyl chloride via inhalation, approximately 5-fold more 7-(2-oxoethyl)guanine adducts per mg hepatic DNA were recovered from young than from adult animals (Ciroussel et al., 1990). In 7-day old and

13-week old BD VI rats dosed with 500 ppm vinyl chloride for 2 weeks, approximately 6-fold more $1,N^6$-ethenoadenosine and $3,N^4$-ethenodeoxycytidine adducts per mg of hepatic DNA were recovered from young than from adults animals (Croussel et al., 1990). In addition the investigators found these adducts in the liver, lung and brain of the group exposed starting at 7 days of age, is consistent with tumors produced by vinyl chloride in these organs. The increased level of adduction in young animals correlates with their increased sensitivity to the carcinogenic effects of vinyl chloride (See section 7.1.4.3).

7.0 CARCINOGENICITY

7.1 Animal Studies

7.1.1 Summary

Recent reviews of the evidence for the carcinogenicity of vinyl chloride in laboratory animals include those by Kalmaz and Kalmaz, 1984, IARC, 1979, SRI, 1983, Kuzmack and McGaughy, 1975, and Purchase et al., 1987. Adequate experimental evidence exists to indicate that vinyl chloride is carcinogenic in mice, rats, and hamsters when given orally and by inhalation. Vinyl chloride has been found to cause tumors in a dose-related manner at several sites, including liver, lung and mammary gland. The oncogenic response appears to be a function of the site, vinyl chloride concentration, tumor type, species of animal, and route of administration.

Although some evidence of vinyl chloride-induced carcinogenesis has been observed by all routes of administration and in all species tested, important discrepancies in the protocols of many studies have limited their usefulness in quantitative risk assessment. These discrepancies include the lack of appropriate control groups, insufficient exposure time, or incomplete histopathology of the animals. Studies that have been used previously in risk assessment include feeding studies (Feron et al., 1981; Til et al., 1983) and a series of inhalation studies (Maltoni et al., 1984). In the Feron studies, liver angiosarcomas and hepatocellular tumors (the primary site) were produced after chronic oral administration of vinyl chloride. In the studies by Maltoni et al. (1984) a wider variety of tumor types was observed. These studies and others are reviewed below.

7.1.2 Intraperitoneal, Subcutaneous, and Transplacental Administration

Vinyl chloride has been tested in experimental animals by intraperitoneal, subcutaneous, and transplacental administration, but for various reasons all of these studies were deemed inadequate for the evaluation of the carcinogenic risk of vinyl chloride. These reports and the reasons for their inadequacy are described in Appendix A.

7.1.3 Oral Administration

7.1.3.1 Studies by Maltoni and Associates

Rats: Maltoni and associates assayed groups of 40 male and 40 female Sprague-Dawley rats after gastric intubation of 0, 3.33, 16.65, or 50 mg/kg vinyl chloride in olive oil five days/week for 52 weeks. These animals were then observed for the remainder of their lives (Experiment BT11, Maltoni et al., 1984, IARC, 1979). Dose-related increases in the incidence of several types of tumors were observed, including liver angiomas and angiosarcomas, nephroblastomas, and mammary tumors. In a subsequent experiment, 0, 0.03, 0.3, or 1.0- mg/kg was administered by the same protocol, except that the dose groups contained 75 animals of each sex. Liver angiosarcomas were found in one female in 0.3 mg/kg group and two females and one male in the 1.0 mg/kg group. No such tumors were observed in controls (Experiment BT27, Maltoni et

al., 1984). No statistical analyses were reported for any of these experiments.

7.1.3.2 Studies by Feron and Associates

Vinyl chloride in soybean oil was administered by gastric intubation at a dose of 300 mg/kg once daily, five days/week for 83 weeks, to 60 male and 60 female Wistar rats; no vehicle controls were used. Of the 109 animals examined, 56 had angiosarcomas of the liver and 52 had angiosarcomas of the lung (Feron et al., 1981). Although vinyl chloride was clearly demonstrated to be carcinogenic in this study, the data are not suitable for use in quantitative risk assessment because of the lack of vehicle-treated controls.

In conjunction with the above experiment, groups of 60-80 male and 60-80 female five-week old Wistar rats were fed polyvinyl chloride powder (10% of diet) with or without a high vinyl chloride monomer content (0 to 4000 ppm) in the diet for their lifetimes (Feron et al., 1981). The actual doses of vinyl chloride given to rats in the feed were 0, 1.7, 5.0, and 14.1 mg/kg/day. Access to food for controls and treated animals was limited to four hours per day; an additional control group was fed ad libitum. Gross pathology was performed on all animals that died or were killed; complete histopathology of all organs was performed on only 20 males and 20 females from the controls and 20 males and 20 females from each of the two highest dosage groups. The animals chosen for complete histopathology were those that lived the longest before being killed. Histopathology of all other rats was restricted to the liver, zymbal glands, lungs, kidneys, spleen, pituitary, thyroid, adrenals, grossly visible tumors, and organs containing lesions suspected of bearing tumors. Statistical significance of tumor incidence was determined by the Chi-square test.

Vinyl chloride caused a dose-related increase in the death rate in the 5.0- and 14.1-mg/kg groups; all animals receiving the highest dose were dead by week 134, with females dying earlier than males (Feron et al., 1981). In the low-dose group the mortality of male rats was comparable with that of controls; the death rate in female rats was slightly higher than that in controls. Death of treated animals was attributed to pulmonary or hepatic insufficiency due to neoplastic or nonneoplastic lesions in these organs.

Liver angiosarcomas were reported in 27/59 ($p < 0.001$) and hepatocellular carcinomas in 8/59 ($p < 0.01$) male rats receiving 14.1 mg/kg/day. Incidences of angiosarcomas and hepatocellular carcinomas were 9/59 ($p < 0.01$) and 29/59 ($p < 0.001$), respectively, in females receiving the highest dose (Table 7.1) (Feron et al. 1981). Necrosis, centrilobular degeneration and mitochondrial damage were also seen in the hepatic parenchyma of rats administered vinyl chloride. The incidence of angiosarcoma of the lung was also significantly increased in high-dose males (19/59, $p < 0.001$) and females (5/57, $p < 0.05$) (Table 7.2). Low-dose males and females showed necrotic damage of the liver and 26/58 low-dose females ($p < 0.01$) had neoplastic nodules of the liver (Table 7.1) (Feron et al., 1981). It is possible that underreporting of tumors at all sites occurred because of the incomplete histopathology performed and the fact that only the longest-surviving high-dose animals were chosen for complete histopathology.

7.1.3.3 Studies by Til and Associates

As a follow-up to the study of Feron and co-workers (1981), groups of 100 male and 100 female Wistar rats (except for the top-dose group, which was composed of 50 animals of each sex) were fed polyvinyl chloride (up to 1% of diet) with a high content of vinyl chloride monomer for up to 149 weeks (Til et al., 1983). Levels of vinyl chloride administered in the powder were 0, 0.017, 0.17, and 1.7 mg/kg/day for 149 weeks. Actual oral exposure to vinyl chloride monomer (calculated by measuring the evaporative loss of vinyl chloride during the four-hour feeding periods, the rate of food intake, and the level of vinyl chloride in the feces) was estimated to be 0.014, 0.13, or 1.3 mg vinyl chloride/kg/day for the low, middle, and high dose groups, respectively. Access to food was limited to four hours per day. An additional control group, comprised of 100 rats of each sex, received food ad libitum and were housed in a separate room. Gross pathology was performed on all animals and was restricted to the liver, all grossly visible tumors or presumable tumors in the abdominal cavity, zymbal gland, and mammary glands. No clinical signs of toxicity attributable to vinyl chloride were observed. In the lowest- and mid-dose group, body weight and survival of treated rats were not significantly different from those of controls. In the high-dose group, mortality was slightly increased.

The results of this study demonstrated significant increases in the incidences of hepatic foci of cellular alteration, neoplastic nodules, hepatocellular carcinomas, liver-cell polymorphism, and cysts in the highest dose group. Two females and one male in this group developed liver angiosarcomas. Females, but not males, of the low- and mid-dose groups developed a higher incidence of hepatic basophilic foci of cellular alteration. No pathologic effects in other organ systems were attributed to vinyl chloride exposure (Table 7.3) (Til et al., 1983).

Til and co-workers reported that a threshold of 0.17 mg vinyl chloride/kg/day for the induction of tumors in rats was observed. In fact, a threshold cannot be demonstrated. Vinyl chloride induced hepatocellular alterations at allconcentrations tested. Histopathology of all organs was not performed on all animals; therefore, tumors not grossly observable or palpable could have been missed.

Because of the shortcomings of the study, its utility for the evaluation of carcinogenic risk is limited.

7.1.4 Inhalation Exposure

Several researchers have investigated the potential carcinogenicity of vinyl chloride administered by inhalation (Viola, 1977; Caputo et al., 1974; Keplinger et al., 1975; Lee et al., 1977; Hong et al., 1981; Suzuki, 1981; Groth et al., 1981; Drew et al., 1983; Maltoni et al., 1984). All experiments confirm the carcinogenicity of vinyl chloride, although only a few of the studies are adequate for a quantitative evaluation of carcinogenic risk.

7.1.4.1 Studies in Rats

The earliest information on the experimental carcinogenicity of vinyl chloride administered by inhalation was reported by Viola (1971). Wistar rats

were exposed to 30,000 ppm by inhalation (four hours/day, five days/week) for twelve months. At the end of the treatment period, the surviving animals were killed at 20-day intervals and "the most important tissues and organs examined histologically by standard methods". The primary tumors observed were located in the zymbal gland (found only in rodents), with metastases to the skin, bone, and lung.

Caputo and associates (1974) exposed Wistar rats to 50-20,000 ppm vinyl chloride four hours/day, five days/week for 12 months. Liver angiosarcomas and skin carcinomas were observed in animals exposed to 500 ppm or greater and lung adenomas in those exposed to 2,000 ppm or more.

Bi et al. (1985) evaluated the tumorigenic potential of vinyl chloride in male Wistar rats following inhalation exposure to 0, 10, 100 or 3000 ppm (six hours/day, six days/week) for up to 12 months. The incidence of liver angiosarcomas was 0/19, 0/20, 7/19 and 17/19 for the four exposure groups, and 0/19, 0/20, 2/19 and 9/20 for lung angiosarcomas, respectively. The authors failed to discuss the specific types of tumors or their significance, focusing instead on the testicular effects of vinyl chloride (discussed in Section 5 of this document) (Bi et al., 1985).

7.1.4.2 Studies in Mice

In a preliminary paper reviewed by IARC (1979), Keplinger and co-workers (1975) reported results from ongoing tests on mice, rats, and hamsters. Vinyl chloride was carcinogenic in all three species; the female mouse was the most sensitive of the animals tested. CD1 Swiss mice were exposed to 0, 50, 200, or 2,500 ppm vinyl chloride seven hours/day, five days/week for nine months, then observed for another nine months. Primary tumors found in animals that died included liver angiosarcomas, lung adenomas, and mammary adenocarcinomas. At the time of the IARC report, histological evaluation had been carried out only on grossly visible tumors, but no final report has been published. Consequently, we cannot accurately quantify tumor incidence in the study.

Lee and co-workers (Lee et al., 1977; IARC, 1979) reported that female mice were more responsive to vinyl chloride exposure than rats. Two month-old male and female CD-1 mice were exposed by inhalation to 0, 50, 250, or 1,000 ppm vinyl chloride for six hours/day, five days/week for 52 weeks (end of experiment). Vinyl chloride induced primary tumors in mice at multiple sites after exposure to 50 ppm or more. Liver cell angiosarcomas, bronchiolo-alveolar adenomas, mammary ductular adenocarcinomas, and squamous and anaplastic cell carcinomas (with metastases to the lung) were observed in treated animals. Vinyl chloride induced tumors at all dose levels, with the incidence and severity of the tumors increasing with dose. The total tumor incidence may have been underestimated because of the short duration of the study.

Hong and colleagues (Hong et al., 1981), as a follow-up of the studies of Lee and associates (Lee et al., 1977), examined the development and incidence of vinyl chloride-related carcinogenic effects during a post-exposure follow-up period. Groups of eight to 28 two month-old male and female CD-1 mice were exposed to 0, 50, 250, or 1,000 ppm for one, three or six months and subsequently observed for 12 months before being sacrificed. Although the number of animals used in the experiment was inadequate for risk

assessment purposes, four of sixteen female mice exposed to 50 ppm vinyl chloride for one month (and autopsied one year later) exhibited mammary gland adenocarcinomas or carcinomas. In mice, the combined (male and female) incidences of hemangiosarcomas for the 250 and 1,000 ppm groups were significantly higher than in controls ($p = 0.05$). Tumor incidence was related to dose and duration of exposure. Bronchiolo-alveolar tumors were also significantly increased in the high-dose group ($p = 0.05$), but no clear trend for the other dose levels was observed (Hong et al., 1981).

In rats, tumor incidence rates following exposure for one or three months did not differ significantly from control values. After a six or ten month exposure, the combined (male and female) cumulative incidences of hemangiosarcomas, hepatocellular carcinomas, and neoplastic liver nodules in rats exposed to 250 or 1,000 ppm differed significantly from those in combined male and female control animals (statistics not reported) (Hong et al., 1981).

Suzuki (1981a) exposed male CD-1 mice (between 30 and 40 per group) to 1, 10, 100, 300, or 600 ppm vinyl chloride six hours/day, five days/week for four weeks. The animals were then observed for up to 41 weeks after cessation of exposures. One mouse in the 10 ppm group had a subcutaneous hemangiosarcoma in the left ear 29 weeks after exposure; one mouse in the 600 ppm group developed a hepatic hemangiosarcoma 65 weeks after exposure. In a separate study, Suzuki (1981b) exposed 27 mice to either 2500 or 6000 ppm vinyl chloride for five or six months. Additional mice were exposed to 0, 1, 10 or 100 ppm for four weeks, and sacrificed forty weeks after exposure. All animals were evaluated for pulmonary tumors. Twenty-six of the 27 high dose animals possessed "alveologenic" tumors. Animals in the lower dose groups exhibited a dose-related trend for pulmonary tumor formation (Suzuki, 1981b). Although this study cannot be used to quantify risk due to study design (for example, inadequate number of test animals), it did demonstrate a carcinogenic response to vinyl chloride after exposure to relatively low concentrations for short durations.

Adkins et al. (1986) exposed strain A/J mice to 50, 200, and 500 ppm vinyl chloride to test the oncogenic response of this strain via inhalation. The result was that incidence of pulmonary adenomas was statistically increased at all exposures of vinyl chloride.

7.1.4.3 Studies on the Potential Effects of Age at Time of Exposure

Groth et al. (1981) exposed groups of 110-128 male and female Sprague-Dawley rats to 948 ppm vinyl chloride in air seven hours/day, five days/week for 29 weeks, beginning at ages varying from six weeks to 52 weeks. Animals were sacrificed after termination of exposure. On the basis of this testing regime, those researchers concluded that vinyl chloride-induced liver angiosarcomas occurred with the greatest frequency in rats whose exposure period began at 52 weeks of age, with females more susceptible than males. The data and study methodology are inadequate for making this conclusion, however. If liver angiosarcomas are expressed at a later age in the rat's life cycle, animals exposed at an early age and sacrificed early in their life cycles would not have had time to express the same tumor incidence as they would if they had lived their full lifetimes. The animals exposed later in their life cycles would then seem to have the highest tumor incidence.

Drew et al., (1983) looked at the effect of age and exposure duration on vinyl chloride oncogenicity in females of several different species of rodents. Groups of female CD-1 Swiss mice, B6C3F1 mice, Fischer 344 rats, and Golden Syrian hamsters (N = 54 for mice, N = 56 for rats and hamsters) were exposed to vinyl chloride for six hours/day, five days/week for six, 12, 18, or 24 months, beginning at eight weeks of age, and observed for their lifespans. Other groups were held until six or 12 months of age, exposed for six or 12 months, and then observed for the remainder of their lifespans. The exposures were conducted at a single dose level for each species; mice, rats and hamsters were administered 50, 100, and 200 ppm, respectively. All animals exposed to vinyl chloride at age eight weeks (the start of the experiment) exhibited decreased survival relative to controls (Drew et al., 1983). B6C3F1 mice experienced the most significant life-shortening regardless of the age at which exposure was begun. No significant decrease in survival was observed in rats, hamsters, or Swiss mice initially exposed after six months of age. Other clinical signs of vinyl chloride toxicity were not evident and liver necrosis was not observed.

In rats, exposure to vinyl chloride was associated with hemangiosarcomas, mammary gland adenocarcinomas and adenomas, and hepatocellular carcinomas (Table 7.4) (Drew et al., 1983). The incidence of hemangiosarcomas was a function of the duration of exposure; the longer the exposure period the greater the incidence of hemangiosarcomas. A six-month exposure produced a low incidence of hemangiosarcomas and hepatocellular carcinomas only if begun early in life. One-year exposures produced a significant incidence of tumors, especially if begun early in life. The incidence of mammary gland adenocarcinomas and fibroadenomas was not always related to exposure duration, but the incidence was higher in rats whose exposure began at eight weeks of age. Hepatocellular carcinomas were induced in a dose-related manner in rats when exposures began at eight weeks.

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with vinyl chloride exposure (Table 7.4) (Drew et al. 1983). The highest incidence of hemangiosarcomas and stomach adenomas occurred in animals exposed early in life for only six months. The highest incidence of mammary gland carcinomas was seen in animals exposed at an early age for up to twelve months. Exposure beginning at or after eight months of age resulted in a markedly lower tumor incidence, possibly because the lifespans of chronically exposed hamsters were significantly reduced to the point that late-appearing tumors would not be expressed.

Mice, especially the B6C3F1 strain, appeared to be the species most sensitive to the carcinogenic effects of vinyl chloride (Table 7.4) (Drew et al., 1983). Hemangiosarcomas and mammary gland carcinomas in both strains and lung carcinomas in Swiss mice were associated with vinyl chloride exposure. In B6C3F1 mice, exposure to vinyl chloride for six months resulted in 60-70% incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in B6C3F1 mice was greatest when the animals were exposed early in life. Lower incidences of this tumor were seen when initial exposure occurred at a later age. In Swiss mice, exposure to vinyl chloride at an early age resulted in the highest incidence of hemangiosarcomas, mammary gland carcinomas, and lung carcinomas, regardless of

duration of exposure. Lower incidences of all tumors were observed in animals exposed later in life.

The patterns of tumorigenicity produced by vinyl chloride in the study by Drew et al. (1983) are consistent with patterns reported in other inhalation studies. However, the results reported by these investigators apparently contradict those of Groth et al. (1981). This apparent contradiction can be explained by the fact that Groth et al. reported only the incidence of hemangiosarcomas, a tumor shown in the Drew study to be a relatively late-appearing tumor that developed regardless of either the age at initial exposure or the duration of exposure. In the Groth et al. study, animals exposed at a young age were also sacrificed at a young age, thereby decreasing the probability of hemangiosarcoma development relative to the older exposed animals who were allowed to live.

7.1.4.4 Studies by Maltoni and Associates

Maltoni and co-workers performed a series of chronic inhalation studies on rats, mice, and hamsters in the Bentivoglio Laboratories (BT) or the Bologna Institute of Oncology (Maltoni et al., 1984). The investigators studied the effects of exposure to 14 concentrations of vinyl chloride (1-30,000 ppm) in male and female rats and six concentrations of vinyl chloride in male and female mice and male hamsters. A summary of some of these experiments are included both in this section and in Appendix A. In each experiment, animals were exposed to vinyl chloride for four hours daily, five days per week for various durations, and observed for the rest of their lives. A number of the experimental procedures were not described or were inadequately described in the report by Maltoni et al. (1984). A full necropsy was performed on each animal and the following tissues reportedly were routinely excised for histopathology: brain, zymbal glands, interscapular brown fat, salivary glands, tongue, thymus, lungs, liver, kidneys, adrenal glands, spleen, pancreas, esophagus, stomach, intestine, bladder, uterus, gonads, and any organ in which pathologic lesions were observed. Details of the experimental protocol for the BT experiments are provided in Table 7.5 (Maltoni et al., 1984).

Data on noncarcinogenic toxic effects of vinyl chloride were sparsely reported in the Maltoni BT experiments. Vinyl chloride appeared to be toxic at the higher concentrations, but reportedly the high mortality at these dose levels was due to a high incidence of vinyl chloride-induced tumors. The available information on survival, including Kaplan-Meier survival curves, indicates that vinyl chloride decreased survival in a dose-dependent manner.

In the Maltoni experiments, exposure to vinyl chloride was associated with an increased incidence of malignant tumors at a variety of tissue sites in all of the species tested. A summary of these tumor sites is provided in Table 7.6 (Maltoni et al., 1984). A direct relationship between exposure levels and tumor incidence was apparently demonstrated, although no statistical tests for trends were performed. Results of experiments on Sprague-Dawley rats exposed to vinyl chloride for 52 weeks were statistically analyzed using the Fischer exact probability test. Correspondence analysis was also performed on the relationship of the incidence of liver angiosarcomas, zymbal gland carcinomas, nephroblastomas, and forestomach papillomas and acanthomas to vinyl chloride exposure (Tassignon, 1980, cited

in Maltoni et al., 1984). The results of this analysis were not discussed by Maltoni et al. (1984). A summary of the lowest concentrations at which a statistically significant excess of tumors was observed is given in Table 7.7. When adjusted to average lifetime exposure, the lowest concentration associated with tumor production is 0.06 ppm (1 ppm * 4/24 * 5/7 * 12/24 = 0.3 ppm).

Experiment BT1. Most previous risk assessments have been based on the data from experiment BT1 (Maltoni et al., 1984). In this study, 30 Sprague-Dawley rats of each sex were exposed to concentrations of vinyl chloride ranging from 50 to 10,000 ppm for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age. A positive control group received 2,500 ppm of vinyl acetate. After treatment the animals were observed for their lifespans up to 135 weeks. Survival of both males and females decreased in a dose-related manner, especially at concentrations above 500 ppm. Vinyl chloride appeared more toxic to females than to males in this experiment. Vinyl chloride was associated with an increased incidence of liver angiosarcomas in a dose-related fashion. These results are presented in Table 7.8 (Maltoni et al., 1984). In addition to liver angiosarcomas, vinyl chloride (at concentrations above 2500 ppm) caused an increased incidence of zymbal gland carcinomas, nephroblastomas, hepatomas, and neuroblastomas. The incidence of liver angiosarcomas was probably underestimated at the higher exposure levels due to mortality resulting from tumors at other sites.

Experiment BT15. Groups of 60 male and 60 female Sprague-Dawley rats were exposed to 0, 1, 5, 10, or 25 ppm of vinyl chloride for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age (Maltoni et al., 1984). Following exposure the animals were observed for the remainder of their lives (up to 147 weeks). Available data, including Kaplan-Meier survival curves, indicated that vinyl chloride did not affect survival at the concentrations tested. No statistical analyses of mortality and body weight data were reported. Mortality was greater in the male control group than in the treated groups: the time at which 50% of the male control group had died was week 72, compared with week 100 in the 25-ppm vinyl chloride group. No explanation was given for this decreased survival. The incidence of mammary gland carcinomas in treated females was higher than in controls at all concentrations of vinyl chloride exposure. The differences from control values were statistically significant at concentrations of 1 ppm and above. The mammary gland adenocarcinoma incidence for this and the other relevant BT experiments are presented in Table 7.9 (Maltoni et al., 1984).

Experiment BT4. Thirty male and 30 female Swiss mice were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm of vinyl chloride four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age (Maltoni et al., 1984). The study was terminated 81 weeks after the exposure period began. Vinyl chloride was highly toxic to both males and females, but males appeared more sensitive than females to the toxic effects of vinyl chloride. Survival decreased in a dose-related manner, although statistical analysis apparently was not performed on the data presented.

A very high incidence of lung adenomas was observed in vinyl chloride-treated male and female mice. A statistically significant increase in the incidence of liver angiosarcomas was seen in male and female mice exposed to vinyl chloride, but a dose response was not seen in the male animals. In

addition, a high incidence of mammary gland adenocarcinomas occurred in treated female mice. These results are presented in Table 7.10 (data from Maltoni et al., 1984).

7.2 Human Studies on the Carcinogenic Effects of Vinyl Chloride

7.2.1 Introduction

In 1974, Creech and Johnson described three cases of angiosarcoma of the liver (LAS) among workers at the B.F. Goodrich Tire and Rubber Co. in Louisville, Kentucky. Because LAS is a very rare cancer (20-25 cases per year in the United States), the clustering of three cases in one vinyl chloride polymerization facility indicated an abnormally high incidence of this cancer. Based on this report, as well as data indicating that vinyl chloride is carcinogenic in laboratory animals, multiple studies of workers exposed to this agent were conducted. By 1985, at least 17 epidemiologic studies relating vinyl chloride exposure to the incidence of various cancers had been completed.

7.2.2 General Design of Epidemiologic Studies

Most of the epidemiologic studies have been retrospective cohort designs. Groups of workers in the vinyl chloride industry were selected by reviewing employment records. Few baseline data other than age, job classification, and length of employment were obtained.

The concentrations of vinyl chloride to which workers were exposed were generally not available, since ambient levels of vinyl chloride were not routinely measured before 1975. Almost all of the investigators estimated vinyl chloride exposure retrospectively, based on some combination of job classification and length of exposure. Only two studies (Ott et al., 1975; Buffler et al., 1979 reported measurements of vinyl chloride exposure.

All the studies traced workers to determine the number of deaths that had occurred in the defined cohort. Death certificates provided the cause of death. In the studies from Sweden and Norway, national cancer registries also provided data to assess incidence of cancer (Byren et al., 1976; Heldaas et al., 1984). The expected numbers of deaths were estimated using population-based mortality statistics. Finally, a standardized mortality ratio (SMR) was calculated from the proportion of observed to expected deaths from each cause and the statistical significance of these ratios was tested.

7.2.3 Difficulties in Interpreting the Epidemiologic Evidence

There are two major problems involved in the interpretation of these studies:

1. Inadequate information on worker outcome. In several of the studies reviewed, outcome data on approximately 10% of the original workers were not obtained (Duck et al., 1979). Since the tumor incidence in humans exposed to vinyl chloride is relatively low, the loss of 10% of the data base could have a significant effect on the observed tumor rate, and possibly allow for an underestimation of risk.

2. Inadequate exposure data. Specific exposure data did not exist in any of the studies reviewed with the exception of Ott et al. (1975) and Buffler et al. (1979). In some cases, no attempt was made to evaluate exposure. In most studies, exposure was estimated from odor levels, acute toxicity levels, job classification, or length of exposure - methods all considered unreliable for accurate exposure estimation. However, gross differences in exposure levels based on the type of job and length of exposure may have occurred, particularly before 1975, when very high levels of vinyl chloride were common in the industry (up to 500 ppm with rare excursions up to 4,000 ppm) (Ott et al. 1975). After 1975, ambient workplace levels were drastically reduced to an average of about 1 ppm, so that differences in dose estimated by job classification became small.

7.2.4 Mortality Studies

A summary of the important characteristics of individual epidemiologic studies is given in Tables 7-11 and 7-12. Each study should be evaluated keeping in mind the difficulties noted above.

Soon after the initial case reports by Creech and Johnson (1974), describing the identification of liver angiosarcomas in vinyl chloride workers, Monson et al. (1974) published a proportionate mortality analysis of the deaths of 161 vinyl chloride workers at two plants in the United States. A statistically significant 50% excess mortality for all cancers and an 11-fold increase in mortality from cancer of the digestive system, including five angiosarcomas of the liver (LAS), were observed. In addition, increases in the proportionate mortality ratios (PMR) for brain cancer, lung cancer, and lymphoma were noted. Proportionate mortality ratios do not represent a specific measure of risk, but the consistent PMR excesses for neoplasms found in this study suggests that vinyl chloride may operate as a multisystem carcinogen.

Tabershaw and Gaffey (1974) published a large cohort study of 8,384 vinyl chloride workers at 33 plants in the United States, which demonstrated a statistically significant increase in angiosarcoma of the liver and nonsignificant positive trend correlating vinyl chloride exposure with lymphoma and cancers of the buccal cavity and pharynx, CNS (primarily brain), and lung. The SMRs for all these tumor types were greater in the high exposure groups after the cohort was stratified by high and low exposure indices (estimates based on job classification and length of exposure), but the differences in SMRs for the high- and low-exposure groups were not statistically significant. Follow-up in this study was only 85% complete. The workers for whom follow-up was incomplete were mostly older workers, and Tabershaw and Gaffey (1974) suggested that these workers, who experienced a long latent period after exposure, might show a somewhat different mortality pattern from workers who were followed up. Another significant problem is that the authors reported only digestive system cancer and did not distinguish cancer of the liver from other cancers in this classification. Information on this cohort has been updated and reanalyzed by Cooper (1981). The final report included 10,173 vinyl chloride workers from 37 plants in the United States (Cooper, 1981). Follow-up had increased to 95.1% of the cohort and extended more than 20 years for 33.4% of the cohort. Statistically significant excess mortality was shown for LAS and for CNS cancers (primarily

brain). Again, SMRs for lung cancer and lymphoma were elevated but not statistically significant.

Duck and co-workers published an analysis of 2,122 vinyl chloride workers in Great Britain (1975). In this study, no excess of total or cause-specific mortality occurred. There were no cases of LAS, although one was recorded in the cohort after the study period ended. Only 16% of the cohort in this study was followed more than 15 years from the time of initial exposure, which undermines the reliability of the negative results of this study.

Nicholson and colleagues (1975) reported on 257 workers in the United States who were exposed to vinyl chloride for at least five years and whose initial exposure occurred more than ten years before the end of the study. These inclusion criteria are important because this is the first study that attempted to limit the cohort to workers who had significant vinyl chloride exposure and follow-up time. Three cases of LAS were observed and the SMRs for all deaths and deaths due to cancer were elevated. Because LAS is otherwise exceedingly rare, the increased incidence of this tumor was statistically significant, but the study lacked power to detect significant increases in other classifications of malignancy.

Based on similar criteria, Waxweiler et al. (1976) studied a larger cohort for the National Institute for Occupational Safety and Health (NIOSH). This study followed an adequate number of workers (1,294) for more than 10 years, with all having had more than five years of exposure. Separate analyses were also performed for those workers with more than 15 years of follow-up time. Significant excesses in the SMR of exposed workers were found for all deaths due to cancer, liver cancer (11 cases of LAS), and CNS cancers. Standard mortality ratios for lung cancer and lymphoma were elevated, but were not significant at the $p < 0.05$ level. Workers with more than 15 years of follow-up time showed higher mortality rates compared to those with ten years of follow-up time. The SMR for lung cancer reached statistical significance in the group with a 15-year follow-up. This cohort provides the strongest evidence for the association between length of time since exposure to vinyl chloride and the subsequent development of cancers of the liver, CNS, and lung (Waxweiler et al., 1976).

Ott and associates completed a study of 594 Dow Chemical workers in Michigan (1975). Many of these workers were also included in the study by Tabershaw and Gaffey (1974). The best available vinyl chloride exposure data are included in this study. Automated sampling of air levels began in one plant as early as 1959. Unfortunately, a large number of workers had less than one year of vinyl chloride exposure at the time of this report. Stratifying the cohort into low, medium, and high exposure groups resulted in less than 200 subjects per group, with only 20, 18, and 22 deaths per group, respectively. No cases of LAS and no significant increase in mortality from any cause for the entire cohort were noted. However, total deaths and deaths due to cancer were significantly higher in the high vinyl chloride exposure group compared to all other dose groups. These data are insufficient to develop any human dose-response relationship.

Buffler and co-workers (1979) performed the only other study using quantified human exposure data. Area sampling began after 1971 for 464 Dow

Chemical vinyl chloride workers in Texas, but data on exposure levels were not available for those workers (the majority) exposed before monitoring began. No cases of LAS were observed among these subjects. There was a statistically significant excess only for lung cancer in exposed workers. The number of deaths (N = 28) in this cohort was very small, making it impossible to perform statistical assessment of many of the causes of death. Buffler and associates have published the only information on the smoking habits of vinyl chloride workers. Even after adjustment for smoking habits, the excess of lung cancers in this group remained significant.

Byren et al. (1976) reported on 777 vinyl chloride workers in Sweden, where the investigators had access to an excellent cancer registry. The study reported a significantly increased mortality due to LAS and to CNS cancers. There was also a trend toward increased mortality due to lung cancer.

Fox and Collier (1977) studied all 7,717 workers in Britain who may have been occupationally exposed to vinyl chloride between 1940 and 1974. Four cases of liver cancer were found; two of these were angiosarcomas. No other tumor type showed a significant increase (statistical methods not reported). Because workers were added to this cohort as they entered the industry, the study included a large proportion of workers with brief exposure and short follow-up time. Approximately 75% of the subjects had been employed in the vinyl chloride industry for less than ten years and only 8% of the workers had been employed for more than 20 years. Inadequate length of exposure and follow-up make this study's negative results of questionable validity.

Jones et al. (1988) followed up the study of Fox and Collier (1977) of British vinyl chloride workers. The new study used stricter criteria for the cohort, reducing the size of the cohort to 5498 male workers, and used more detailed occupational information as well as data from the additional ten years. Deaths due to non-secondary liver tumors rose from 4 to 11 (SMR = 567). The new study could find no evidence for any other increase of cancer deaths due to vinyl chloride.

Bertazzi et al. (1979) examined the mortality rates among 5,441 Italian vinyl chloride workers. This study showed a significant increase in mortality among exposed workers only for liver cancer (three cases of LAS). Follow-up was less than optimal (14% of the total remained untraced), and person-years at risk were calculated as if the workers unavailable to follow-up were all alive and well, which contributed to the very low SMR for all causes of death.

A further study of the vinyl chloride industry in Italy (Belli, et al., 1987) has detected statistically significant excess for all malignant cancer (SMR = 159) and for lung cancer (SMR = 217). That plant had 437 workers in the cohort. A related study Pirastu et al. (1990) has reported seven cases of liver angiosarcoma and seven primary liver cancers that are not angiosarcoma. The combined study of all Italian facilities is of 5000 workers.

Masuda and co-workers studied 304 Japanese vinyl chloride workers (1979). This cohort was too small to determine statistical significance for any cause of death.

Weber, Reinl, and Greiser (1981) reported on mortality information from three cohorts of German chemical industry workers: 7,021 vinyl chloride and

polyvinyl chloride production workers (usually considered a high exposure area), 4,007 polyvinyl chloride processing workers (a lower exposure area), and 4,910 chemical workers not exposed to vinyl chloride (1981). The SMRs were determined for causes of death in each of the three groups but no statistical comparisons were made. A significant increase in mortality from liver cancer was observed in all three of the groups evaluated, most notably for the vinyl chloride processing workers (SMR = 1523). A significant increase in malignancies of the lymphatic and hematopoietic tissues was noted among the production workers, while a significant increase in brain tumors was observed among the processing personnel.

Analysis of the mortality experience of 4,524 Japanese vinyl chloride workers by Nakamura (1983) revealed a significant increase in the mortality ratio for death from all cancers and from liver cancer alone (three cases of LAS). Cancer of the lung was not elevated; cancers of the CNS and lymphoma were not reported in this study.

Theriault and Allard (1981) studied Canadian vinyl chloride workers in the only cohort to employ an occupational control group for evaluation of relative risk in workers exposed to vinyl chloride. The control cohort consisted of 870 chemical workers not exposed to vinyl chloride, while the study group comprised 585 vinyl chloride-exposed workers, with 454 of these workers exposed for more than five years. Exposure levels were not quantified. Very few deaths (59 cases) occurred in the exposed group, compared with 233 in the control group. The only significantly increased relative risk was for liver cancer (eight cases of LAS). The SMR for digestive cancer (which includes liver cancer) among workers exposed for greater than five years was 259, significantly greater ($p < 0.01$) than for the general population. The authors suggested that the small size of the study reduced the power of the study with respect to finding an excess of CNS cancer or lymphoma that may have been present. Theriault (1983) published an extended follow-up on this same cohort in 1983 with no significant changes in the initial findings.

Heldaas et al. (1984) reported a study of cancer incidence and mortality in a cohort of 454 male workers exposed to vinyl chloride and polyvinyl chloride between 1950 and 1969 in Norway. This cohort was divided into three exposure groups, as estimated from job classification, and the study population followed for 27 years. The investigation demonstrated an increased incidence of malignant melanoma, and cancer of the lung, colon, and thyroid in the exposed cohort. This study, using an excellent cancer registry, reported cancer incidence, as well as mortality, unlike most other studies.

This observation of an increased incidence of malignant melanoma is the first to be reported in humans. Four malignant melanomas of the skin were identified in the study population where only 0.8 were expected. Three of four cases of malignant melanomas occurred in the high exposure group; where 0.5 cases were expected. The fourth case was in the medium exposure group with 0.18 cases expected. After the observation period, one more case was diagnosed in the medium exposure group. The authors noted one additional case of incipient malignant melanoma in the medium exposure level group that was diagnosed in 1977 but not included in the study (Heldaas et al. 1984).

A follow-up study of 434 of the original workers has strengthened the association between vinyl chloride exposure and three categories of cancer, malignant melanoma, lung cancer and colon cancer (Heldaas et al., 1987).

Laplanche et al. (1987) compared the cancer cases occurring among 1100 exposed and 1100 nonexposed workers in vinyl chloride polymerization plants in France. One case of liver angiosarcoma of the liver occurred among those exposed. Six cases of lung cancer occurred among those exposed versus two among those not exposed. Neither of those results reached statistical significance in the comparison.

Dahar et al. (1988) recently published an update to the vinyl chloride mortality study of Ott et al. (1975). In contrast to the earlier study, the new study found there was no statistically significant excess for any neoplasm or disease of interest among the exposed cohort of 593 Dow chemical workers in Michigan. In a much larger study Rinsky et al. (1988) evaluated the mortality rate and cause of death for a cohort of 29,139 male chemical workers in West Virginia. Statistically significant increases in liver cancer (SMR = 174) and lympho- and reticulo-sarcoma (SMR = 140) were seen among the workers. For biliary and liver cancer the SMR was 301 for those who worked at least 25 years and whose deaths occurred 30 years or more after first employment.

Smelevich et al. (1988) reported a large increase in deaths from malignancies of the lymphatic and hemopoietic tissues among 43,216 (27059 men and 16,157 women) workers in the oldest vinyl chloride and polyvinyl chloride plants in the USSR. The SMR for females was 2000 for all levels of exposure and 4000 for the highest exposures. The SMR of 385 for stomach cancer in women was also significantly increased. The SMR of 500 for leukemia in men and women combined was significantly increased. None of the increases in cancer categories in males alone reached statistical significance. The study did not detect any cases of liver angiosarcoma in the cohort during the follow up period.

Wu et al. (1989) reported a cohort study and a case-control study of workers at one of the four vinyl chloride plants previously studied by Waxweiler (1976). The cohort of 3635 workers was exposed to high concentration of vinyl chloride monomer prior to 1974, when concentrations dropped dramatically. The overall SMR's for brain cancer, lung cancer, laryngeal cancer and all respiratory cancers ranged from 115 to 223, above normal but not statistically significant. The SMR for liver cancer in that cohort was statistically significant at 333, and the SMR rose to 371 when workers with less then 15 years of follow up were excluded. Among that subcohort the risk of mortality due to cancer of the liver was consistently elevated for all durations of employment beyond five years. Neither lung cancer nor brain cancer exhibited a clear increase with duration of exposure. The highest SMR in that subcohort was 1429 for liver cancer in workers with 10-15 years exposure. A brief calculation using data in their Table 5 shows that the SMR for liver cancer in all workers in that subcohort with more than five years' exposure was 1000.

Hagmar et al. (1990) reported a significant increase in total cancer morbidity among 2031 male workers at a polyvinyl chloride processor plant in Sweden (SMR = 128). Respiratory cancers were also significantly increased

(SMR =213). The six brain tumors observed, versus 2.6 expected, gave an SMR = 229, which was not statistically significant.

Their case-control study found that there was a statistically significant association between cumulative dose of vinyl chloride monomer and liver cancer, but that study did not find a significant association for any other cancer. Upon dividing the liver cancers into angiosarcomas and others, the positive dose response was found to exist only for angiosarcomas. At the highest level of exposure the odds ratio for liver cancer was 8 while for liver angiosarcoma alone the odds ratio was 110.

7.2.5 Cancer Risks Associated with Exposure to Vinyl Chloride

This summary of cancer risks assocated with exposure to vinyl chloride focuses on each of the important sites at which such association's have been reported.

7.2.5.1 Liver Cancer

Between 1961 and 1977, 23 cases of LAS were reported among approximately 20,000 vinyl chloride workers in the United States (Lelbach and Marsteller, 1981; Spirtas and Kaminski, 1978). The expected incidence of LAS is 0.014 cases per 100,000 per year in the general population in the United States (Heath et al., 1975). Based on analysis of these data, the relative risk for developing LAS following vinyl chloride exposure among this country's vinyl chloride workers is 483.

The epidemiologic studies also demonstrate a strong and consistent association between vinyl chloride exposure and primary cancer of the liver. All eight of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMR). The average relative risk for liver cancer among vinyl chloride workers is five to six times greater than the incidence of that seen in the general population. The evidence strongly suggests that exposure to vinyl chloride can cause liver cancer. All reports published to date indicate that the standardized mortality ratios of exposed workers are elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time (Table 7-13).

7.2.5.2 Other Cancers

The association between vinyl chloride exposure and increased risk for other cancers is not as clear as that for liver cancer. Some evidence associates exposure to vinyl chloride with increased mortality ratios for brain cancer, lung cancer, and lymphoma. Since these cancers appear more commonly in the general population than LAS and primary liver cancer, it becomes more difficult to show increased risk.

7.2.5.2.1 Brain Cancer

Workers exposed to vinyl chloride appear to be at greater risk for brain cancer than do non-exposed populations. Of the six studies that assessed the risk of brain cancer, five showed a positive trend for increased risk of this

cancer type following exposure to vinyl chloride, with four demonstrating statistical significance ($p < 0.05$) (Table 7-14). Cancer risk increased an average of four times above that expected in the general population in those studies that exhibited a significantly increased risk. Of the two studies not showing a significant increase in risk for brain cancer, statistical power in the Bertazzi and associates study was only about 35% (Bertazzi et al., 1979), while that of Fox and Collier (1977) was approximately 80% (Beaumont and Breslow, 1981). In the Fox and Collier study, the number of deaths overall was low and, most importantly, a large percentage of workers in the cohort was very recently employed in the vinyl chloride industry and thus had a short follow-up time. These factors may partially explain why this study failed to detect an association between vinyl chloride exposure and brain cancer.

7.2.5.2.2 Lung Cancer

The evidence linking vinyl chloride exposure with lung cancer remains inconclusive. Analyses of SMRs for cancer of the lung were performed in 12 studies (Table 7-15). Of these, seven studies showed an increased risk for lung cancer, but only one was statistically significant at the 5% level (Buffler et al., 1979). This increased risk persisted after adjusting for personal smoking habits (for this particular cohort). However, this cohort was small and the study was unable to demonstrate an increased risk for any other cancer. The Waxweiler et al. cohort (which had a follow-up period greater than 15 years) also used a small group (1976).

7.2.5.2.3 Lymphoma

An association between vinyl chloride exposure and lymphoma has not been established. Five studies evaluated the risk of lymphoma development among workers occupationally exposed to vinyl chloride (Table 7-16). Four of the studies showed a positive trend for lymphoma among vinyl chloride workers, but statistical significance was noted only by Weber et al. (1981). However, the statistical power in all of these studies was less than 80% to demonstrate a relative risk of two, and less than 40% to show a relative risk of 1.5.

7.2.5.3 Recent Review of Human Studies

Doll (1988) assessed the evidence from the epidemiologic literature that vinyl chloride workers experienced more cancer and other types of disease than did the general population. He found that (a) "men occupationally exposed to vinyl chloride have experienced a specific hazard of angiosarcoma of the liver" and (b) "any other occupational hazards that may have existed must have been small." He also concluded that "No positive evidence of a hazard of any nonmaligant disease or any type of cancer other than angiosarcoma of the liver has been found except possibly for a small hazard of lung cancer when exposure was heavy."

7.2.6 Exposure Information

Most of the published epidemiologic studies did not present quantified exposure data. Levels of exposure were estimated by job classification and length of employment. Only the studies by Ott and co-workers (1975) and Buffler and associates (1979) contain measured industrial hygiene data. After the workers were classified according to exposure levels, the cohorts were too

small to yield any statistically significant correlations. Although the United States Environmental Protection Agency (1986), reached the conclusion that a dose-response relationship cannot be constructed based on these kinds of data, the risk analysis below did use historic estimates of exposure in an occupational study having an ample cohort with well documented worker statistics.

7.2.7 Conclusions

Epidemiologic studies of workers exposed to high levels of vinyl chloride indicate that this chemical is a human carcinogen. The evidence strongly suggests that vinyl chloride causes an increased risk for angiosarcoma of the liver. The evidence also suggests that vinyl chloride may be associated with a moderately increased risk for brain cancer, and with development of lung cancer. Although actual exposure data in humans are lacking for most studies, the past exposure levels can be estimated in order to obtain useful predictions of human risk at low concentrations of vinyl chloride.

TABLE 7.1

INCIDENCE OF LIVER TUMORS AND NEOPLASTIC NODULES IN WISTAR RATS EXPOSED ORALLY TO VINYL CHLORIDE (Feron et al., 1981)

	Incidence[1]			
	Vinyl Chloride (mg/kg/day)			
Tumor Type/Sex	0	1.7	5.0	14.1
Liver Angiosarcoma				
Male	0/55	0/58	6/56*	27/59***[2]
Female	0/57	0/58	2/59	9/57**
Hepatocellular Carcinoma				
Male	0/55	1/58	2/56	8/59**
Female	0/57	4/58	19/59***	29/57***
Neoplastic Nodules				
Male	0/55	1/58	7/56**	23/59***
Female	2/57	26/58**	39/59***	44/57***

[1] Number in denominator = number of animals necropsied.

[2] Values marked with asterisks differ significantly from controls according to the Chi-square test:

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

TABLE 7.2

INCIDENCE OF LUNG ANGIOSARCOMAS, ABDOMINAL MESOTHELIOMAS AND MAMMARY TUMORS IN WISTAR RATS EXPOSED ORALLY TO VINYL CHLORIDE (Feron et al., 1981)

	Incidence[1]			
	Vinyl Chloride (mg/kg/day)			
Tumor Type/Sex	0.	1.7	5.0	14.1
Lung Angiosarcoma				
Male	0/55	0/58	4/56*[2]	19/59***
Female	0/57	0/58	1/59	5/57*
Abdominal Mesotheliomas				
Male	3/55	1/58	7/56	8/59
Female	1/57	6/58*	3/59	3/57
Mammary Adenoma or Adenocarcinoma or Anaplastic carcinoma				
Female	3/57	2/58	5/59	9/57

[1]Number in denominator = number of animals necropsied.

[2]Values marked with asterisks differ significantly from controls according to the Chi-square test:

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

TABLE 7.3

LIVER TUMOR INCIDENCE IN MALE AND FEMALE WISTAR RATS EXPOSED TO VINYL CHLORIDE BY ORAL ADMINISTRATION FOR 149 WEEKS (Til et al., 1983)

	Incidence[1]			
	Vinyl Chloride (mg/kg/day)			
Tumor Type/Sex	0	0.014	0.13	1.3
Liver Angiosarcoma				
Male	0/99	0/99	0/99	1/49
Female	0/98	0/99	0/96	2/49
Hepatocellular Carcinoma				
Male	0/99	0/99	0/99	3/49
Female	1/98	0/99	1/96	3/49
Neoplastic Nodules				
Male	0/99	0/99	0/99	1/49
Female	0/99	1/99	0/99	9/49

[1]Number in denominator = number of animals necropsied.

Vinyl chloride intake data was adjusted to compensate for loss of vinyl chloride during the four-hour feeding periods. The initial levels of vinyl chloride administered in the diet were 0, 0.017, 0.17, and 1.7 mg/kg/day.

TABLE 7.4

TUMOR INCIDENCE FOLLOWING VINYL CHLORIDE EXPOSURE IN

FEMALE RATS, HAMSTERS AND MICE FROM THE STUDY OF DREW ET AL. (1983)

Tumor Type	Length of Exposure (Months)	LDE (ppm)[1]	Tumor Frequency (%)
Female Fisher 344 Rat:	**Experimental Exposure 100 ppm**		
Liver Hemangiosarcomas	control	0	0.9 (1/112)
	6	4.46	5.3 (4/76)
	12	8.93	20.0 (11/55)
	18	13.40	23.6 (13/55)
	24	17.86	34.7 (19/55)
Mammary Gland Adenocarcinoma	control	0	4.5 (5/112)
	6	4.46	7.9 (6/76)
	12	8.93	19.6 (11/56)
	18	13.40	16.4 (9/55)
	24	17.86	9.1 (5/55)
Hepatocellular Carcinoma	control	0	0.9 (1/112)
	6	4.46	4.0 (3/75)
	12	8.93	7.1 (4/56)
	18	13.40	14.8 (8/54)
	29	17.86	16.4 (9/55)
Female B6C3F1 Mice:	**Experimental Exposure 50 ppm**		
Hemangiosarcoma (all sites)	control	0	5.8 (4/69)
	6	2.23	68.7 (46/67)
	12	4.46	76.7 (69/90)
	18	--	--
Mammary Gland Carcinoma	control	0	4.3 (3/69)
	6	2.23	43.2 (29/67)
	12	4.46	41.1 (37/90)
	18	--	--

TABLE 7.4 continued

Tumor Type	Length of Exposure (Months)	LDE (ppm)[1]	Tumor Frequency (%)
Female CD-1 Swiss Mice:	**Experimental Exposure 50 ppm**		
Hemangiosarcoma (all sites)	control	0	1.4 (1/71)
	6	2.23	43.3 (29/67)
	12	4.46	63.8 (30/47)
	18	6.69	44.4 (20/45)
Mammary Gland Carcinoma	control	0	2.8 (2/71)
	6	2.23	49.3 (33/67)
	12	4.46	46.8 (22/47)
	18	6.69	48.9 (22/45)
Lung Carcinoma	control	0	12.7 (9/71)
	6	2.23	27.7 (18/65)
	12	4.46	31.9 (15/47)
	18	6.69	24.4 (11/45)
Female Golden Syrian Hamster:	**Experimental Exposure 200 ppm**		
Hemangiosarcoma (all sites)	control	0	0.0 (0/143)
	6	8.93	14.8 (13/88)
	12	17.86	7.7 (4/52)
	18	26.79	1.9 (2/103)
Mammary Gland Carcinoma	0	0	0.0 (0/143)
	6	8.93	32.2 (28/87)
	12	17.86	59.6 (31/52)
	18	26.79	46.1 (47/102)
Skin Carcinoma	0	0	0 (0/133)
	6	8.93	2.5 (2/80)
	12	17.86	18.8 (9/47)
	18	26.79	3.3 (3/90)

[1]LDE - Lifetime Daily Exposure (in ppm)

TABLE 7.5

EXPERIMENTAL PROTOCOL FOR INHALATION STUDIES
MALTONI AND CO-WORKERS (1984)

Experiment Number	Dose (ppm)	Exposure Duration (weeks)[1]	Species/ Strain	Age at Start of Exposure (weeks)	Number of Animals per Dose Level[2]
BT1	0, 50, 250, 500, 2,500, 6,000, 10,000	52	Rat/SD	13	30 M, 30 F (30 M, 30 F)
BT2	1, 100, 150, 200	52	Rat/SD	13	60 M, 60 F (85 M, 100 F)
BT6	30,000	52	Rat/SD	17	30 M, 30 F (no controls)
BT9	0, 50	52	Rat/SD	13	150 M, 150 F (50 M, 50 F)
BT15	0, 1, 5, 10, 25	52	Rat/SD	13	60 M, 60 F (60 M, 60 F)
BT3	0, 50, 250, 500, 2,500, 6,000, 10,000	17	Rat/SD	12	30 M, 30 F (30 M, 30 F)
BT14	6,000, 10,000	5 5	Rat/SD	21 (parents) 1 day (offspring)	6 F (no controls) 21-22 M, F (no controls)
BT4001	0, 2,500	76 69	Rat/SD	13 1 day	54 F (60 F) 68 M, 64 F (158 M, 149 F)
BT4006	0, 2,500	15	Rat/SD	1 day	60 M, 60 F (60 M, 60 F)
BT5	6,000, 10,000	1	Rat/SD	19 (fetus)	30 F 13-29 M, F (no controls)
BT7	0, 50, 250, 500, 2,500, 6,000, 10,000	52	Rat/Wistar	11	30 M (40 M)
BT17	0, 1	52	Rat/Wistar	13	120 M (130 M)

Table 7.5 continued

Experiment Number	Dose (ppm)	Exposure Duration (weeks)[1]	Species/ Strain	Age at Start of Exposure (weeks)	Number of Animals per Dose Level[2]
BT4	0, 50, 250, 500, 2,500, 6,000, 10,000	30	Mouse/Swiss	11	30 M, 30 F (80 M, 70 F)
BT8	0, 50, 250 500, 2,000, 6,000, 10,000	30	Hamster/ Syrian golden	11	30 M (62 M)

[1]Exposures were for four-hours daily, five days per week.

[2]Number in parentheses = number of control animals for experiment.

TABLE 7.6

TUMORS CORRELATED TO INHALATION EXPOSURE TO VINYL CHLORIDE IN RATS, MICE, AND HAMSTERS IN THE BT EXPERIMENTS[1]

Tumors	Rat	Mouse	Hamster
Liver angiosarcomas	+	+	+
Hepatomas	+	(+)	
Encephalic neuroblastomas	+		
Lung adenomas		+	
Lymphomas/leukemias			(+)
Angiosarcomas at other sites	+	+	(+)
Zymbal gland epithelial tumors	+		
Nephroblastomas	+		
Cutaneous epithelial tumors	(+)	(+)	(+)
Mammary adenocarcinomas	+	+	
Forestomach papillomas, acanthomas	+	(+)	+

[1]Data from Maltoni et al., 1984

\+ = Tumor incidence was statistically significant ($p < 0.05$) by the Fisher exact test.

(+) = Association was not statistically significant, but was considered biologically significant.

TABLE 7.7

LOWEST CONCENTRATION AT WHICH A SIGNIFICANT ($p < 0.05$) EXCESS OF TUMORS WAS REPORTED BY MALTONI AND ASSOCIATES[1] IN INHALATION STUDIES AT SPECIFIC SITES IN SPRAGUE-DAWLEY RATS[2]

Tumor	Vinyl Chloride Concentration (ppm)
Forestomach papilloma	30,000 (male, female)
Zymbal gland carcinoma	10,000 (male, female)
Neuroblastoma	10,000 (female)
Nephroblastoma	250 (female)
	100 (male)
Liver angiosarcoma	200 (male)
	25 (female)[2]
Mammary adenocarcinoma	1 (female)

[1]Data are from Maltoni et al., 1984.

[2]Significant at this dose level when specific corrected tumor incidence is used, $p = 0.047$. Analysis by Fisher exact probability test.

TABLE 7.8

INCIDENCE OF LIVER ANGIOSARCOMAS (LAS) IN MALE AND FEMALE SPRAGUE-DAWLEY RATS EXPOSED FOR 52 WEEKS TO VINYL CHLORIDE (Maltoni et al., 1984)

Study	Experimental Dose Level (ppm)	LAS Incidence[1]		Corrected LAS Incidence[2]	
		Male	Female	Male	Female
BT1	0	0/30	0/30	0/22	0/29
	50	0/30	1/30	0/26	1/29
	250	1/30	2/30	1/28	2/26
	500	0/30	6/30	0/22	6/28
	2,500	6/30	7/30	6/26	7/24
	6,000	3/30	10/30	3/17	10/25
	10,000	3/30	4/30	3/21	4/25
BT2	0	0/85	0/100	0/61	0/68
	100	0/60	1/60	0/37	1/43
	150	1/60	5/60	1/36	5/46
	200	7/60	5/60	7/42	5/44
BT6	30,000	5/30	13/30	5/22	13/24
BT9	0	0/50	0/50	0/29	0/38
	50	1/150	12/150	2/70	12/110
BT15	0	0/60	0/60	0/25	0/44
	1	0/60	0/60	0/48	0/55
	5	0/60	0/60	0/43	0/47
	10	0/60	1/60	0/42	1/46
	25	1/60	4/60	1/41	4/40
LAS Incidence in Historical Controls:					
		1/1179	2/1202	1/364	2/541

[1]Number in denominator = number of animals necropsied.

[2]Number in denominator = number of animals alive when first liver angiosarcoma was observed.

TABLE 7.9

INCIDENCE OF MAMMARY GLAND CARCINOMAS IN FEMALE SPRAGUE-DAWLEY RATS AND SWISS MICE EXPOSED BY INHALATION TO VINYL CHLORIDE (Maltoni et al., 1984)

Study No.	Experimental Dose Level (ppm)	Tumor Incidence[1]	Corrected Tumor Incidence[2]
BT1	0	0/30	0/29
(Rat)	50	2/30	2/30
	250	2/30	2/27
	500	1/30	1/28
	2,500	2/30	2/25
	6,000	0/30	0/28
	10,000	3/30	3/29
BT2	0	2/60	2/100
(Rat)	100	4/60	4/60
	150	6/60	6/60
	200	5/60	5/60
BT6	30,000	2/30	2/30
(Rat)			
BT9	0	9/50	9/43
(Rat)	50	59/150	59/142
BT15	0	6/60	6/60
(Rat)	1	14/60	14/60
	5	22/60	22/60
	10	21/60	21/60
	25	16/60	16/60
Tumor Incidence in Historical Controls		100/1202	100/1202
BT4	0	1/80	1/67[3]
(Mice)	50	12/30	12/30[3]
	250	13/30	13/29[3]
	500	10/30	10/28[3]
	2,500	9/30	9/30[3]
	6,000	9/30	9/28[3]
	10,000	14/30	14/28[3]
Tumor Incidence in Historical Controls		21/554	21/554[3]

[1]Number in denominator = number of animals examined.

[2]Number in denominator = number of animals alive when first malignant mammary tumor was observed (type unspecified).

[3]Number in denominator = number of animals alive when first mammary tumor was observed (type unspecified).

TABLE 7.10

INCIDENCE OF PULMONARY ADENOMAS, MAMMARY CARCINOMAS, AND LIVER ANGIOSARCOMAS IN MALE AND FEMALE SWISS MICE EXPOSED TO VINYL CHLORIDE BY INHALATION (EXPERIMENT BT4)[1]

	Cancer Incidence Vinyl Chloride (ppm)							
Organ/Sex[2]	0	50	250	500	2,500	6,000	10,000	Historical Controls
Pulmonary (lung) adenomas								
Males	8/75	5/27	24/29	24/29	18/25	23/27	20/24	34/491
Females	7/67	3/30	17/29	26/29	22/30	24/29	26/28	27/533
Liver angiosarcomas[3]								
Males	0/62	1/18	9/23	6/17	6/13	2/12	1/9	0/545
Females	0/62	0/26	9/21	8/26	10/24	11/21	9/20	0/554
Mammary adenocarcinomas[4]								
Males	0/74	0/27	0/29	1/28	0/23	0/24	0/22	1/521
Females	1/67	12/30	13/29	10/28	9/30	9/28	14/28	22/545

[1] Data from Maltoni et al., 1984.

[2] Number in denominator = number of animals alive when first pulmonary (lung) adenoma was observed (11 weeks).

[3] Number in denominator = number of animals reportedly alive when first liver angiosarcoma was observed (32 weeks).

[4] Number in denominator = number of animals reportedly alive when first lung mammary tumor (type unspecified) was observed (16 weeks).

TABLE 7-11

A SUMMARY OF EPIDEMIOLOGIC DATA FOR
OCCUPATIONALLY EXPOSED VINYL CHLORIDE WORKERS

	STUDY	COHORT	F/U(%)	DEATHS(%)	EXPOSURE(YRS)	F/U TIMES(YRS)	DOSE	SMR					
								DEATH	ALL SITES	LIVER(LAS)	BRAIN	LUNG	LYMPHOMA
1.	Tabershaw & Gaffey[1] USA (1974)	8,384	1258(15%)	352(4.7%)	>1 10.2%>20yrs	>1	EST	75	110	94[3](6)	155[4]	112	106
2.	Duck et al. U.K. (1975)	2,122	7(0.3%)	152(7.2%)	>0	27%>19yrs	EST	96	96	99[3](0)	--	103	--
3.	Nicholson et al. USA (1975)	257	2(0.8%)	24(9.3%)	>5	>10	EST	126	231	- (3)	--	--	--
4.	Ott et al.[2] USA(1975)	594	0(0%)	79(13.3%)	>0	> 0	measured	89	81	- (0)	--	77	--
5.	Byren et al. Sweden (1976)	771	21(2.7%)	58(75%)	>0	55%>10yrs	EST			413[a](2)	612[a]	168	--
6.	Waxweiler et al. USA (1976)	1,294	13(1%)	136(10.5%)	>5	>10 >15	EST	108	149[a] 189[b]	1155[b](11) 1606[b]	329[a5] 498[a]	156 194[a]	159 176
7.	Fox and Collier U K (1977)	7,717	393(5.1%)	409(5.3%)	>0 8%>20yrs	> 0	EST	75.4	90.7	1408[a](2)	54.6	89.8	90.9
8.	EEH USA (1975)	10,173	496(4.8%)	707(6.9%)	>1 19.3%>20yrs	32%>20yrs	EST	89	104	75[3](5)	203[a]	107	112
9.	Buffler et al. Texas (1979)	464	0(0%)	28(0%)	>0	> 0	measured	87	138	- (0)	--	208[a]	--
10.	Bertazzi et al. Italy (1979)	4,777	659(13.8%)	62(1.3%)	>0.5	>0.5	EST	44	97	800[a](3)	125	81	133
11.	Masuda et al. Japan (1979)	304	1(0.3%)	26(8.5%)	>1	>1	EST	--	138	500[a](0)	--	125	--

TABLE 7-11 (con't)

	STUDY	COHORT	F/U(%)	DEATHS(%)	EXPOSURE(YRS)	F/U TIMES(YRS)	DOSE	SMR DEATH	SMR ALL SITES	SMR LIVER(LAS)	SMR BRAIN	SMR LUNG	SMR LYMPHOMA
12.	Weber, Reinl, Greiser Germany (1981)												
	production	7,021	700(4.4%)	414(5.9%)	>0	>0	EST	95	112	1523[b]	162	--	214[a]
	processing	4,007		360(9%)	>0	>0	EST	95	85	434[a]	535[a]	--	34
	unexposed	4,910		417(8.5%)	>0	>0	EST	78	83	401[a]	184	--	77
13.	Cooper[1] USA (1981)	10,173	496(4.8%)	707(6.9%)	>1	33.4%	EST	89	104	75[3](8)	203[a]	107	112
14.	Nakamura Japan (1983)	4,524	29(0.6%)	209(4.6%)	>1	mean 16.3yrs	EST	87	138[a]	236[a](3)	--	86	--
15.	Heldass et al. Norway (1984)	454	0(0%)	50(11%)	>1	>1	EST	84	114	(1)	--	180	--
								---------- Relative Risk ----------					
16.	Theriault & Allard Canada (1981)												
	exposed	451	0(0%)	59(2.6%)	>5	81%115yrs	EST	1.07	1.48	6.25[a](10)	--	.36	--
	unexposed	871		233(26.8%)	-	--							

1. The studies of Cooper and EEH are reanalyses of the Tabershaw and Gaffey Cohort
2. SMR subjects also in the Tabershaw and Gaffey Cohort
3. SMR is for "digestive system cancer", not liver cancer
4. SMR is for "other and unspecified cancer", 40% of which were brain cancer
5. SMR is for cancer of CNS, not Brain

F/U = Follow up time (years)
EST = Estimated dose
[a] $p < 0.05$
[b] $p < 0.01$

TABLE 7 12

A SUMMARY OF TUMOR INCIDENCES AND STANDARDIZED MORTALITY RATIOS (SMR) FOR OCCUPATIONALLY EXPOSED VINYL CHLORIDE WORKERS

	DEATH	ALL CANCER	LIVER CANCER	BRAIN CANCER	LUNG CANCER	LYMPHOMA
STUDY	O E SMR	O E SMR	O E SMR	O E SMR	O E SMR	O E SMR
1. Monson et al.	161·161·100	41·27.9·150	8··0.7·1100	5··1.2··420	13·7.9··160	5··3.4··150
2. Tabershaw & Gaffey	352·467·75[a]	79·77··110	19·21.7·94	17·11.78·155	25·23.9·112	6··6.1·106
3. Duck et al.	136·142.2·96	35·36.4·96	11·11.1·99	·····	16·15.5·103	·····
4. Nicholson et al.	24··19··126	9··3.9·····	31·····	11·····	·····	21·····
5. Ott et al.	79··89.1·89	13··16··81	·····	·····	4··5.2··77	·····
6. Byren et al.	·····	·····	4··.97··413	2··.38··612[a]	3··1.8·108	·····
7. Maxweiler et al.	136 126.3·108	35·23.5·149[a]	7·0.6·1155[b]	3 0.9·329[a]	12·7.7·156	4·2.5·159
15 year		31·16.9·184[b]	7·0.4·1606[b]	3·0.6·498[a]	11·5.7·194[a]	3·1.7·176
8. Fox & Collier	393·521.2·75.4	115·126.8·90.7	1··.71·140.8	2·3.66·54.6	46·51.2·90	9·9.0·99.9
9. EEH	707·795··89[b]	139·141.4·104	29·40.8·75	12·5.9·203[a]	45·44.3·107	11·10.4·112
10. Buffler et al.		8··5.2··154	0··.2·····	1··0.1····	5··1.7··289[a]	0··0.5·····
11. Bertazzi et al.		30·30.9·97	8··1··800[b]	1·0.8·125	7··7.7··91	4···3···133
12. Masuda et al.		8··5.8··138	1··.6··167	0···.15····	1··.8··125	0··.5·····
13. Weber et al.						
Production	414·····95	94·····112	12·····1523[b]	2·····162	·····	15·····214[b]
Processing	360·····95	62·····85	31·····434	51·····535[a]	·····	2·····34
Control	417·····78	83·····83	41·····401[a]	2·····184	·····	6·····77
14. Cooper	707·795·89[a]	139·141·104	29·40.8·75	12·5.9·203[b]	45·44.3·107	11·10.4·112
15. Heldaas	·····	23·20.2·110	·····	·····	5··2.8··180	·····
16. Theriault and Allard	·····	20·16.4·122.2	14·5.4·259.3[b]	0··0.6·····	2··5.8··34.6	·····
17. Nakamura	128·147.6·87	37·26.85·138[a]	6··2.54·236[a]	·····	2·2.3·0.86	·····

[a] $p < 0.05$

[b] $p < 0.01$ o = observed e = expected SMR = standardized mortality ratio

TABLE 7-13

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND PRIMARY CANCERS OF THE LIVER

STUDY	SMR	RESULT[4]	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	413	Significant[a]	---	Yes
Waxweiler et al.	1155	Significant[b]	---	Yes
Fox & Collier	141	Significant[a]	Yes	---
Bertazzi et al.	800	Significant[a]	---	---
Masuda	500	Significant[a]	---	---
Weber et al.	1523	Significant[b]	Yes	Yes
Theriault & Allard	(6.25)[3]	Significant[a]	---	No
Nakamura	236	Significant[a]	Yes	Yes
Wu	300	Significant[b]	Yes	Yes

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Relative risk, not SMR
4 - a: $p < 0.05$, b: $p < 0.01$

TABLE 7-14

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND BRAIN CANCER

STUDY	SMR	RESULT[4]	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	612	Significant[a]	---	---
Waxweiler et al.	329	Significant[a]	---	Yes
Fox & Collier	55	-	Yes	---
Bertazzi et al.	125	+	---	---
Weber et al.	535	Significant[a]	No	No
Cooper[3]	203	Significant[a]	---	---
Wu	145	+	No	Yes

1 - Does risk increase with higher estimated dose?
2 - F/U Time = Follow up time (years)
Does risk increase with longer latency?
3 - Cooper's data are used in the most recent reevaluation of the Tabershaw, Gaffey and EEH cohort.
4 - a: $p < 0.05$
+ = non-significant positive trend for increased risk ($p > 0.05$)

TABLE 7-15

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND LUNG CANCER

STUDY	SMR	RESULT[5]	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Duck et al.	103	+	---	No
Ott et al.	77	-	---	---
Byren et al.	168	+	---	---
Waxweiler et al.	156	+	---	Yes
Fox & Collier	90	-	No	---
Buffler et al.	268	Significant[a]	---	---
Bertazzi et al.	91	-	---	---
Masuda et al.	125	+	---	---
Cooper[3]	107	+	Yes	No
Heldass et al.	180	+	---	---
Theriault & Allard	(.36)[4]	-	---	---
Nakamura	86	-	---	---
Wu	115	+	No	No

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Cooper's data is used in the most recent revaluation of the Tabershaw, Gaffey and EEH cohorts.
4 - Relative risk, not SMR
5 - a: $p < 0.05$
+ = non-significant positive trend for increased risk ($p > 0.05$)

TABLE 7-16

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND LYMPHOMA

STUDY	SMR	RESULT	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Waxweiler et al.	159	+	---	Yes
Fox & Collier	100	-	---	---
Bertazzi et al.	133	+	---	---
Weber et al.	214	Significant[a]	+	---
Cooper[3]	112	+	---	---

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Cooper's data are used in the most recent revaluation of the Tabershaw, Gaffey and EEH cohorts.
4 - a: $p < 0.05$
+ = non-significant positive trend for increased risk ($p > 0.05$)

8.0 QUANTITATIVE CARCINOGENIC RISK ASSESSMENT

8.1 Introduction

Inhalation studies discussed in Chapter 7 have demonstrated that vinyl chloride is a carcinogen in three species of laboratory rodents: rats, mice and hamsters. Those studies generally found an elevated occurrence of the otherwise rare tumor, liver angiosarcoma, over a wide range of concentrations of atmospheric vinyl chloride. Those studies also found cases of elevated incidence of carcinoma of the liver and both angiosarcoma and carcinoma of the lung. In addition those studies found elevated incidence of tumors of the mammary gland. Feeding studies have supported the inhalation results. Epidemiologic evidence has associated occupational exposure to vinyl chloride with the development of liver angiosarcomas in chronically exposed workers, and possibly with other tumors. IARC (1979), the EPA (1984b) and the State of California (CDHS, 1985) have identified vinyl chloride as a human carcinogen. Vinyl chloride has been identified as a "chemical known to the State to cause cancer" under California's Proposition 65, California Health and Safety Code Section 25249.8.

The analyses below derive risk estimates from an occupational study and from rodent bioassays. The selected occupational study provided the best available for quantitative epidemiological analysis. The multistage model of carcinogenesis adequately characterized the results of the rodent bioassays. All of the analyses applied a simple metabolic (pharmacokinetic) model to convert atmospheric concentrations of vinyl chloride to estimates of exposure in terms of the metabolites assumed to produce tumorogenesis in the affected tissue.

8.2. The Metabolic Model

Two related aspects of vinyl chloride metabolism (reviewed in Chapter 2 of this document) are relevant to understanding the dose-response character of its carcinogenicity. First, the oncogenicity of vinyl chloride appears to be due to one or more reactive metabolites, rather than the parent molecule. Second, the metabolism of vinyl chloride is a saturable, dose-dependent process because rate of formation of the carcinogenic metabolites is limited by the metabolism of the parent compound.

Gehring et al. (1978) developed a metabolic model relating the rate of formation of adducts of macromolecules to the concentration of vinyl chloride in atmospheric exposure of rats. In the experiments used to obtain data for the model, the exposures lasted for 6 hours. The rats were of the Sprague-Dawley strain, Spartan substrain, and weighed 200-250g. The study assayed the liver tissue for adducts of macromolecules. The authors used the data to estimate the parameters of an equation of Michaelis-Menten form, relating the velocity of the reaction to the exposure concentrations:

$$F = aV_mX/(K_m + X), \qquad (8\text{-}1)$$

where F = rate of adduct formation (hr^{-1}),
V_m = maximum velocity of the reaction (lg/hr),
K_m = Michaelis saturation concentration (ppm),

X = atmospheric exposure (ppm),
a = constant (lg^{-1}).

This equation multiplied by an appropriate constant (K_m/aV_m) yields another expression for metabolite formation (Y):

$$Y = K_m/aV_m = 1/(K_m^{-1} + X^{-1}). \quad (8\text{-}2)$$

For sufficiently low concentration this measure of dose rate becomes equal to actual exposure, thus avoiding the need for conversions in low dose risk estimates for any sufficiently homogeneous group under analysis.

The present analysis will proceed to relate cancer incidence to the estimated metabolized exposure. Although there is uncertainity about the accuracy of using the adjusted exposure of Equation 8-2 as a measure of carcinogenically active metabolites, this measure appears to be superior to atmospheric exposure (Anderson et al. 1980). The accuracy of this measure is subject to improvement by adjusting parameters when applying the result to different organs and to different sizes and strains of rats and to other species. Gehring et al. (1978) determined the Michaelis saturation constant for Sprague-Dawley rats to be K_m = 336 ppm. In Appendix B the present analysis uses for humans K_m = 150 ppm, a value which was estimated from data on monkeys.

8.3 Analysis of Human Data from Waxweiler et al.

The review of the epidemiological studies (Section 7.2 of this document) strongly suggests a causal association between vinyl chloride and several different types of cancer, including liver, lung, and brain. However, none of the occupational cohort studies presented exposure data for a large enough cohort to derive a dose-response curve; so the present analysis uses historical industrial hygiene data to reconstruct a range of likely exposures, from which risk estimates can be extrapolated.

This risk analysis proceeds by selecting the Waxweiler et al. (1976) study of 1294 workers who experienced high sustained exposures to vinyl chloride and who were followed long enough (10 years) to develop substantial numbers of cancers that appeared to be related to the exposure. The retrospective estimates of Barnes et al. (1976) for the relevant industrial processes furnished concentrations of the exposures of vinyl chloride, having an overall average value of 647 ppm. The analysis converts these annual average exposure estimates to a lifetime daily equivalent tissue exposure of 3.6 ppm on the assumption of a saturable metabolic process (Michaelis-Menten) leading to active carcinogens (See equation 8-2). This is based on extrapolated measurements of binding rates to macromolecules (Gehring et al. 1977). The seven liver cancer deaths reported for that cohort project to a lifetime risk of .039 (.089 upper confidence limit) per worker for liver cancers. That risk divided by the overall lifetime daily equivalent of effective exposure yields unit risk estimates for that malignancy. See Appendix B for the calculations, which also include the case of all observed cancers.

The calculations provided the following upper confidence limits (UCL) on unit risks: 2.5×10^{-5} ppb^{-1} for liver cancers, and 4.5×10^{-5} ppb^{-1} for three

sites of cancer combined, liver, lung and brain. Each of these three sites of cancer had a significantly elevated SMR when calculated for a 15-year follow up time. The unit risks calculated in this manner are about six times greater than would be calculated by using actual exposures instead of the effective exposures that take account of the metabolic saturation in the tissue. A committee of The National Health Council of the Netherlands (1987), using mortality data from three studies including Waxweiller, calculated maximum likelihood estimates of unit risk. That council's committee obtained in present terms 1.2×10^{-6} ppb^{-1} for liver tumors and 2.5×10^{-6} ppb^{-1} for all tumors. Both these results were based on estimated atmospheric exposure. When those results are modified to take account the pharmacokinetics and to provide 95% upper confidence limits, the results are close to the present results.

8.4 Models of Carcinogenesis Fitted to Rodent Data

Mathematical models of carcinogenesis provide a means of extrapolating the results of rodent bioassays to the much lower concentrations that human society is likely to find acceptible. The present analysis employs the multistage model because it is a biologically plausible model and as used here takes into account metabolism.

Three sets of cancer bioassays provide adequate data for quantitative models of carcinogenesis. See Table 8-1 for the basic data. The Maltoni et al. experiments together provide an unusually large set of data on cancer incidence in both males and females rats over a large range of exposures at many concentrations--altogether fifteen groups beyond the four control groups. The Drew et al. experiments provide incidence data on female rodents for an unusual exposure protocol in that the duration varied -- two or three groups beyond controls -- while the concentration remained fixed for each species. The Bi et al. experiments provide incidence data on male rats for three exposures beyond controls.

Individual analyses proceeded in attempts to obtain risk estimates for each homogeneous experimental grouping within species, strain, sex and tumor type. One analysis did eventually group together experiments BT-1 and BT-2 and another grouped together experiments BT-9 and BT-15, all by Maltoni et al. These groupings, which followed from similarities of body weight, colony survival characteristics, and tumor response, tended to strengthen results, for example by reducing confidence intervals. The spectrum of risks obtained from all the acceptable analyses provides some insight into uncertainties expected in extrapolating the rodent results to humans.

8.4.1 Computational Methods

The analyses that follow used the linearized multistage computer program, GLOBAL86, to calculate potential risks associated with vinyl chloride exposure. The form of multistage model in that program may be expressed as:

$$P(d) = 1 - \exp(-q_0 - q_1 d - q_2 d^2 - \ldots - q_k d^k) \quad (8\text{-}3)$$
$$\text{with } q_i \geq 0 \text{ for all } i.$$

where P(d) is the lifetime probability of cancer for a given dose rate d of carcinogen, exp is the exponential function (e raised to the power indicated

in parentheses), q_0 is a constant that accounts for the background incidence of cancer occurring in the absence of carcinogen, and q_1, q_2, ... q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen to obtain the best fit of the model to the data. (Howe et al. 1986).

The analyses used several adjustments to the experimental exposure data in order to calculate the lifetime daily exposure (LDE) levels. For these inhalation experiments, the metabolized exposure determined by Equation 8-2 was multiplied by:

H/24: where H is the hours of exposure per day. This converts the exposure period to a time-weighted average for 24 hours daily continuous exposure. D/7: where D is the number of days of exposure per week. This converts the dosing schedule to a time-weighted average for a seven day/week continuous exposure.

Le/L: where Le is the length of the experiment and L is the lifespan of the animal (the longer of Le or 24 months). This converts the experimental protocol to a continuous lifetime exposure. Table 8-1 displays the resulting ranges and other basic data on experiments used in the analysis.

8.4.2 Model Results

Significant trends for liver angiosarcoma dominated the results of the multistage modeling. All three analyses of female rats and two of the three analyses of male rats met the statistical criterion ($p > .05$) for goodness of fit of the dose-dependent response of liver angiosarcoma (LAS) to vinyl chloride. In addition the following experimental groups met that criterion: lung carcinoma in the Swiss mice of Drew et al., lung angiosarcoma in the Wistar rats of Bi et al., and mammary tumors in both the Sprague Dawley rats of Maltoni et al. and the F-344 rats of Drew et al.

Table 8.2 gives unit risk estimates calculated by using the linearized multistage model for LAS and other tumor types from both male and female rats and for female mice for inhalation experiments done by Maltoni et al. (1984), Bi et al. (1985), and Drew et al. (1983). The entries in Table 8.2 include all those instances in which an adequate fit ($p>.05$ and $q_1^*/q_1<3$) of the data is achieved by the model using all data points for each species, sex, and tumor type at exposures not greater than 500 ppm, when practical. Because there is an abundance of experiments available for the risk assessment of vinyl chloride, this stringent measure of adequate fit ($p > 0.05$ and $q_1^*/q_1. < 3$) was chosen to focus the risk assessment on the best available studies. This exposure limitation tends to reduce the effects of the parent compound (including mortality) at the higher exposure levels. The analyses did include one higher exposure, the 3000 ppm exposure of Bi et al., which was retained in order to obtain an adequate number of exposure groups (four) to establish a clear trend.

In Table 8.2 the column indicating which coefficients were nonzero provides some evidence that two stages were appropriate for the model fitted by the maximum-likelihood procedure in these bioassays. Only for the analysis of BT-9,15 rats with liver angiosarcoma did the occurrence of an excessive ratio (16) of $q_1^*(r)/q_1(r)$ prompt the selection of a single-stage model to

human unit risk resulting from use of this formula. This surface area correction results in an estimated 2.6 fold increased risk for humans, compared to rats exposed to the same ppb concentration.

For the parameters of this equation the current analyses used values from the studies when available; otherwise standard values were used. Humans were assumed to weigh 70 kg and to inhale 20 m^3/day. The inhalation rates (I_R) for mice and rats were estimated using the following formulas (EPA, 1985c):

$$\text{For mice: } I_R = 0.0345\ [\text{wt (kg)}/0.025\ \text{(kg)}]^{2/3}\ m^3/\text{day} \quad (8\text{-}5)$$
$$\text{For rats: } I_R = 0.105\ [\text{wt (kg)}/0.113\ \text{(kg)}]^{2/3}\ m^3/\text{day}$$

The inhalation rate for hamsters was assumed to be 0.086 m^3/day (Biology Data Book, 1974). Rodent bodyweight values for the studies of Maltoni et al. (1984) and Bi et al. (1985) were derived from data provided in the respective publications. Rodent bodyweights were not given for the Drew et al. (1983) study. They were estimated to be 300 g for rats, 30 g for mice, and 92 g for hamsters. See Table 8-1 for values of body weight and inhalation rate used in the analyses.

8.6 Risk Predictions for the Regulation

The rank ordering of Table 8-3 and the points of Figure 8-1 provide the range of UCL on unit risk for humans, q_1^*, for the present assessment: from 2.5×10^{-5} to 20×10^{-5} ppb^{-1}.

In the opinion of DHS staff, the best estimate for regulation in this assessment coincides with the top of the range, when rounded, 20×10^{-5} ppb^{-1}. This is approximately the value obtained from the more recent Maltoni et al. experiments, with lower exposure concentrations than the previous experiments. That result is at the top of the range of six experiments that provided clear dose response relationships for liver cancer. The bottom of that range at 4.4×10^{-5} ppb^{-1} is not far below. The selected top of the range, 20×10^{-5} ppb^{-1} is also equal to the Drew et al. result for lung carcinoma in mice. That result is one of the lowest for mice. The other, higher results for mice are not explicitly reported in the present risk analysis because of scattering of points in each case not providing a clear exposure-response trend. The results for hamsters, not reported quantitatively for the same reason, were close to those for the rats.

As indicated in Chapter 7, based on laboratory animals, females appear to be more sensitive than males to vinyl chloride exposure. Furthermore, earlier initiation of exposure appears to increase vinyl chloride susceptibility (as discussed below, p. 8-13). Two different approaches permit indirect estimation of the unmeasured overall risk of carcinogenesis in human females, providing an instructive consistency check. The first is to take the result for all cancers in the (male) occupational study, 4.5×10^{-5} ppb^{-1}, and multiply it by ratio of female-to-male cancers in animals. The best ratio available is 3.1 for liver angiosarcoma from experiments in rats (BT-9,15). The resulting multiplication gives 14×10^{-5} ppb^{-1}. This result allows in humans for the probably greater susceptibility of the female to contracting cancer from vinyl chloride exposure, as observed in rodents. The second approach starts with the result of the analysis that uses all Maltoni et al.

obtain a more consistent ratio. In this case very little improvement was achieved by including the second stage. Despite the substantial effect on q_1, the effect of selecting the single-stage over the two-stage model was to increase q_1^* by only 4%.

The results of Table 8.2 do not include the analyses for angiosarcoma and mammary tumors in mice or the angiosarcoma, skin carcinoma, and mammary tumors in hamsters. The estimates for q_1^* for the angiosarcomas and mammary tumors in mice were in the range of 20×10^{-5} to 50×10^{-5} ppb^{-1}, greatly elevated above those for rats, while the estimates for those tumors in hamsters (6×10^{-5} and 10×10^{-5}) were about the same as the highest results in rats. None of these analyses met the stringent criteria for goodness of fit of the MLE as defined above; so they were not included in the tabulation of risk estimates.

The effect of combining the BT (Maltoni et al. 1984) experiments was to lower the value of the resulting q_1^* by a modest amount. Thus BT-1 and BT-2 individually yielded values of 2.5×10^{-5} and 2.2×10^{-5} respectively, compared to 1.9×10^{-5} when combined. Also BT-9 and BT-15 individually yielded values of 6.9×10^{-5} and 10×10^{-5}, compared to 6.7×10^{-5} when combined.

The use of metabolized exposure rather than ambient exposure had the effect of increasing the values of q_1^* by about 30-50% in the BT-1 and BT-2 experiments. The effect on BT-9 and BT-15 was virtually negligible because of the much lower exposures experienced in those experiments. In contrast, Krewski et al. (1987) found the difference obtained by using exposure only and by using a metabolic model of essentially the same type as the above was negligible at (atmospheric) exposures up to 500 ppm. Their method of analysis, robust regression, was quite different, and their selection of data points was somewhat different.

Uncertainties in estimates of unit risk arise from uncertainties mentioned earlier about the accuracy of the model used to determine metabolized exposure. Departures from the present fit of the Michaelis-Menten model could cause calculations of risk to lose accuracy. Cumulative effects or different metabolism, for example, may cause the true risk to differ from that predicted. Nevertheless, uncertain as it is, the metabolic model appears much more likely to provide a more accurate measure of risk than does ambient exposure.

8.5 Extrapolating Rodent Risks to Humans.

Estimates of human risks from the rodent results require an extrapolation based on a scaling assumption. The DHS (1985) has provided guidelines for scaling such that--in the absence of strong arguments to the contrary--dose rate is scaled according to the two-thirds power of body weight. Thus, the current analysis uses

$$q_1^*\ \text{human} = q_1^*\ \text{rodent} \quad (I_H / I_R) \times (W_R / W_H)^{2/3} \qquad (8\text{-}4)$$

where I_R and I_H are the inhalation rates of rodents and humans, respectively, and W_R and W_H are the body weights of rodents and humans, respectively, where q_1^* is expressed in units of $(ppm)^{-1}$. Table 8.2 displays the values of UCL on

data for LAS in female rats at exposures not greater than 250 ppm (10 groups), which is $q_1^*(h) = 7.7 \times 10^{-5}$ ppb^{-1} (not shown in the table). This result, when multiplied by the ratio of risk for all observed human cancer to observed liver cancer in humans gives 13×10^{-5} ppb^{-1}. This value also allows in humans for all cancers in the probably more susceptible female. Considering the uncertainties involved, these two results are remarkably similar to each other and to the best estimate just discussed. We have not attempted adjustments for the increased susceptibility due to early age of exposure, however, DHS staff believe that such an adjustment would elevate the risk estimate derived from the human date. That is, lifetime exposure is likely to be of greater risk to humans than adult exposure as occurred in the occupational study.

Using data from Maltoni and Lefemine (1975), the EPA (1984b) calculated a UCL on rodent unit risk of 6.8×10^{-6} ppb^{-1}. This is equivalent to a q_1^* of 1.8×10^{-5} ppb^{-1}. Figure 8-1 shows that this result is below the bottom of the present range, reflecting the use of only the earlier Maltoni et al. data, rather than the more recent results published in 1984, and the choice not to use a metabolic model. Note that the lower value of risk for BT-1,2, which are the earlier studies, is among the lowest of the present assessment. EPA has also calculated risks based on feeding studies. Using the later Maltoni et al (1980, 1981) data, EPA (1985b) calculated a human inhalation potency of 2.95×10^{-1} $(mg/kg\text{-}day)^{-1}$, equivalent to a human q_1^* of 11×10^{-5} ppb^{-1}. Figure 8-1 shows that this value is below the top of the present range. EPA has also calculated risks based on feeding studies. Assuming that dietary absorption has the same efficiency as inhalation absorption (both about 40%), the EPA (1984b) oral potency of 2.3 $(mg/kg\text{-}day)^{-1}$ is equivalent to q_1^* of 1.7×10^{-3} ppb^{-1}. This result is approximately 9-fold greater than the top of the range presented in Table 8-3.

In a more recent risk assessment, Chen and Blancato (1989) have used metabolized dose in a multistage model to estimate cancer risk from the Maltoni et al. (1984) data on liver angiosarcoma, experiments BT-1 and BT-15. Their result of 2.3×10^{-5} ppb^{-1} for the UCL on lifetime unit risk actually appears to be for females and not for males as indicated in their report. In Tables 5, 10, and 13 for the Maltoni inhalation data, the males and females were reversed. This value compares to the risk of 18×10^{-5} ppb^{-1} calculated for the DHS analysis. The lower risk estimate of Chen and Blancato (1989) appears to be due to their higher calculated dose rate. Chen and Blancato (1989) used a daily dose rate, which is not clearly documented in the study, but appears to be 8-fold higher than estimates based upon calculation methods used in the current DHS analysis.

Zapponi et al. (1988) have reported that using different bioassays has little effect on unit risks that result from fitting the multistage model. They used the Michaelis-Menten function to establish metabolized exposure, and found $K_m = 950$ ppm (in current terms) for the BT-1 experiment in comparison to the $K_m = 336$ ppm used in the current analysis. For that experiment the UCL on unit risk was 2.5×10^{-5} when adjusted for rat lifetime exposure, which is similar to the estimate for BT-1,2 in the current analysis of 1.9×10^{-5}.

Brown and Hoel (1986) used a time-variable form of the multistage model to determine how well the model was able to predict incidence in appropriate experiments. Their result indicates that the model performed very well for

the rat (F-344) data, adequately for the B6C3F1 mice data and marginally for the Swiss mice and hamster data. Models with 3 to 7 stages produced the fits, and a strong effect of the first stage was apparent. A separate approach explored statistically for effect of age at first exposure, detecting a significant reduction in susceptibility with increasing age of first exposure.

All these estimates are subject to substantial uncertainties, as have been discussed on the scientific literature (DHS, 1986, and EPA, 1984a). The available information does not suggest that there is a threshold for vinyl chloride's carcinogenic effect, though this remains uncertain. The multistage model is the best choice based on the plausible mechanism of vinyl chloride carcinogenicity. Nevertheless, our incomplete understanding of cancer makes this choice subject to uncertainty. Furthermore, the present approach uses other assumptions that are designed to be somewhat health protective in the absence of precise knowledge. One of the most important of these is the extrapolation from humans to animals on the basis of surface area in accordance with DHS guidelines (1985). This approach may overpredict or underpredict human risk.

In spite of such uncertainties and the potential differences in exposure duration, oncogenic sensitivity of different species, age of exposure, sex, and levels of exposure and in spite of the uncertainties in the human data, the estimated unit risk values for the human epidemiologic data and those calculated from animal inhalation data are remarkably consistent with one another.

Because many of the tumors associated with vinyl chloride exposure (particularly LAS) exhibit a long latency period, exposure at an early age would produce a greater risk. The average latency period for the development of LAS in one study of occupationally exposed vinyl chloride workers was determined to be 22.1 years (Stafford, 1983). Drew et al. (1983) demonstrated that in rats, mice and hamsters, the highest incidence of neoplasms was observed when vinyl chloride exposure was started early in life. Exposures early in life may produce up to a 10-fold greater incidence in tumors compared to exposures late in life.

Because of these considerations, this assessment concludes that it is necessary that the best estimate coincide with the top of the range of estimates of human unit risk extrapolated from rodents. This approach provides adequately health protective estimates of human unit risks, which represent the 95% upper confidence limits for risk calculations.

TABLE 8.1 SUMMARY DESCRIPTION OF RODENT EXPERIMENTS CONSIDERED IN RISK ANALYSES

Experiment	Strain[a]/Species, Sex	Exposures[b] ppm	Exposures[b] (no.)	Effective[c] LDE (ppm)	Weight (kg)	Inhalation rate (m^3/day)
Maltoni et al.						
BT-1,2	sd/rat, female	0-500	(10)	0-10.4	.275	.190
	sd/rat, male[d]	0-500	(10)	0-10.4	.425	.254
BT-9,15	sd/rat, female	0-50	(6)	0-2.6	.400	.244
	sd/rat, male	0-50	(6)	0-2.6	.600	.320
Bi et al.	wi/rat, male	0-3000	(4)	0-48.6	.300	.200
Drew et al.	fi/rat, female	0-100	(5)	0-13.7	.300	.200
	bc/mouse, female[d]	0-50	(3)	0-5.8	.030	.039
	sw/mouse, female	0-50	(4)	0-5.8	.030	.039
	gs/hamster, female[d]	0-200	(4)	0-5.8	.092	.086

[a]sd = Sprague-Dawley, wi = Wistar, fi = Fischer-344, sw = CD1 Swiss, bc = B6C3F1, gs = golden Syrian.

[b]Range of exposures for all groups used in the analysis. Number of groups used is in parentheses.

[c]Range of exposures expressed as effective lifetime daily exposure, using Equation 8-1 and the lifetime adjustments of the text.

[d]Did not achieve an adequate fit of the multistage model for any tumor.

TABLE 8.2 RISKS OF CARCINOGENICITY FROM VINYL CHLORIDE EXPOSURE ESTIMATED FROM RODENT DATA

Experiment	Strain[a]/Species, Sex	Tumor[b]	Coefficients[c] /stages	Ratio[d] $\frac{q_1^*(r)}{q_1(r)}$	Rodent UCL $q_1^*(r)$ 10^{-5} ppb^{-1}	Human UCL[e] $q_1^*(h)$ 10^{-5} ppb^{-1}
Maltoni et al.						
BT-1,2	sd/rat, female	LAS	1,2	2.3	1.9	4.9
(≤500 ppm)	sd/rat, female	mammary	0,1	1.7	1.4	3.7
BT-9,15	sd/rat, female	LAS	1,2	1.9	6.7	18.
	sd/rat, male	LAS	1/1	2.5	2.5	6.5
Bi et al.	wi/rat, male	LAS	1,2	1.9	5.0	13.
	wi/rat, male	lung angiosarcoma	1,2	2.8	1.7	4.5
Drew et al.	fi/rat, female	LAS	0,1,2	2.1	3.2	8.4
	fi/rat, female	hepatocellular carcinoma	0,1,2	2.0	1.7	4.4
	fi/rat, female	mammary	0,1	1.7	1.6	4.2
	sw/mouse, female	lung	0,1	1.8	6.9	20.

[a]See Table 8.1 note a

[b]LAS = liver angiosarcoma

[c]Number to the right of the slash indicates degree that is chosen by the user for polynomial in the multistage model. Remaining numbers indicate subscripts of non-zero coefficients of the polynomial for the maximum likelihood estimate, following Equation 8-6.

[d]Ratio of unit risks: the 95% UCL to the maximum likelihood estimate.

[e]Determined by multiplying by the scaling factor on rodent dose.

TABLE 8.3 RANK ORDERING OF ESTIMATES OF HUMAN RISK BY CATEGORY

Rank	Experiment	Strain[a]/Species, Sex	Tumor[b]	Individuals[c]	Unit Risk, UCL q_1^*(h) ppb^{-1}
1	Drew	sw/mouse, female	lung carcinoma	228	20×10^{-5}
2	BT-9,15	sd/rat, female	LAS	380	18×10^{-5}
3	Bi	wi/rat, male	LAS	78	13×10^{-5}
4	Drew	fi/rat,female	LAS	353	8.4×10^{-5}
5	BT-9,15	sd/rat, male	LAS	298	6.5×10^{-5}
6	BT-1,2	sd/rat, female	LAS	313	4.9×10^{-5}
7	Waxweiler	oc/human, male	liver + brain + lung	1294	4.5×10^{-5}
8	Bi	wi/rat,male	lung angiosarcoma	78	4.5×10^{-5}
9	Drew	fi/rat, female	hepatocellular carcinoma	353	4.4×10^{-5}
10	Drew	fi/rat, female	mammary	354	4.2×10^{-5}
11	BT-1,2	sd/rat, female	mammary	394	3.7×10^{-5}
12	Waxweiler	oc/human, male	liver	1294	2.5×10^{-5}

[a]oc = occupational cohort. See Table 8.1 for other abbreviations.

[b]LAS = liver angiosarcoma.

[c]Number of all individuals entered in the analysis, exposed and unexposed.

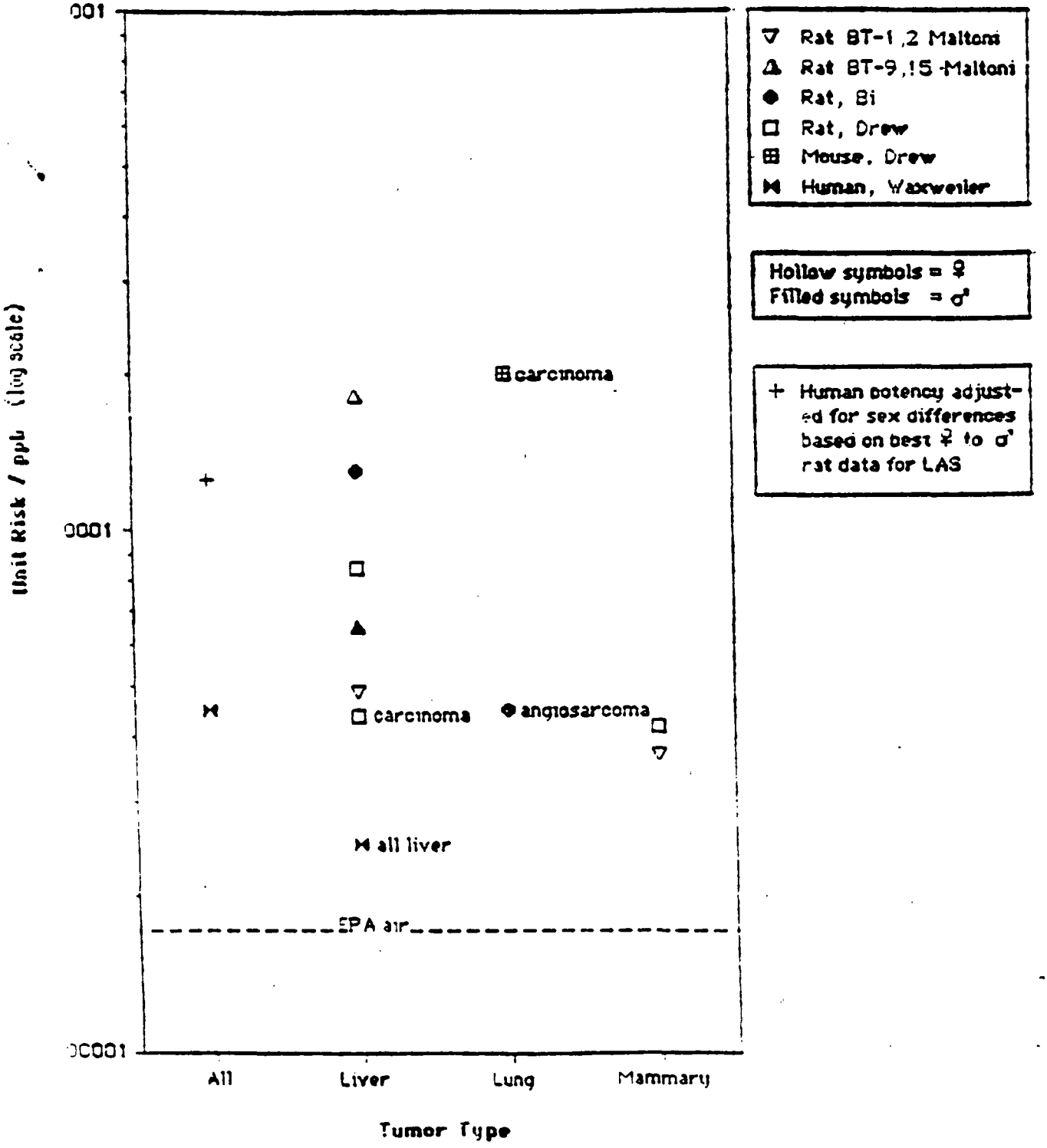


Figure 8-1. Upper Confidence Limits on Unit Risk to Humans from Lifetime Exposure to Vinyl Chloride. Estimates were derived from the indicated studies in Table 8-2. Liver tumors are angiosarcomas unless otherwise indicated.

9.0. CONCLUSIONS

9.1 Acute Toxicity

Vinyl chloride has a relatively low degree of acute toxicity in experimental animals; two-hour inhalation LD_{50} values are greater than 200,000 ppm in several species. Human exposure for longer than five minutes to concentrations of 8000 ppm or more may lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis and death. Several human deaths have been attributed to occupational exposure at very high levels of vinyl chloride. Autopsies of these patients revealed congestion of the liver, spleen and kidneys.

9.2 Subchronic and Chronic Toxicity

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 (Veltman et al., 1975). Spirtas et al. (1975) measured the frequency of eight symptoms commonly reported by workers exposed to vinyl chloride (including dizziness, headaches and nausea) and observed a dose-response relationship using exposure levels estimated from job classifications. These symptoms were observed at exposure levels even below 50 ppm.

9.3 Pharmacokinetics

Approximately 42% (but up to 71%) of an inhaled dose of vinyl chloride was absorbed by both man and rats. Oral exposure results in more complete absorption. Radiolabeled vinyl chloride metabolites have been detected in a range of tissues, suggesting thorough distribution. Most of the metabolized vinyl chloride is excreted by the kidney, often as glutathione conjugates. Unmetabolized vinyl chloride is eliminated primarily by pulmonary excretion.

Both alcohol dehydrogenase and cytochrome P-450 are involved in the metabolism of vinyl chloride. The evidence suggests that reactive metabolites may be responsible for the toxic effects of vinyl chloride, with the most likely candidates thought to be chloroethylene oxide and chloroacetaldehyde.

The rate of metabolism of vinyl chloride appears to depend upon the level of exposure, with higher levels being incompletely metabolized. The saturation of the metabolizing enzymes becomes substantial in monkeys above exposures of 100 ppm, and in the absence of better data this value may be extrapolated to humans.

9.4 Reproductive Toxicity

No teratogenic or embryotoxic effects were observed in mice, rats or rabbits exposed to vinyl chloride at maternally toxic doses during gestation. A recent study has suggested that vinyl chloride can cross the placental barrier of exposed pregnant female rats and cause liver cancer and angiosarcoma in the offspring. Epidemiologic studies have suggested a possible increased rate of fetal deaths in women whose husbands were occupationally exposed to vinyl chloride. However, additional studies have

concluded that there was no association between vinyl chloride exposure and fetal deaths or birth defects.

9.5 Mutagenicity

Vinyl chloride has been identified as a mutagen in bacteria, yeast and animal systems, both with and without addition of an exogenous metabolic activation system. Chloroacetaldehyde and chloroethylene oxide, the putative toxic metabolites of vinyl chloride, were also mutagenic. Levels of chromosomal aberrations and sister chromatid exchanges were higher in workers exposed to vinyl chloride (20 to 150 ppm) than for unexposed control groups. Workers exposed to less than 15 ppm showed no differences in chromosome breaks or aberrations from controls.

9.6 Carcinogenicity

Both experimental animal studies and epidemiological studies of worker populations have demonstrated that vinyl chloride is carcinogenic.

The International Agency for Research on Cancer (IARC) reviewed the literature on vinyl chloride mutagenicity and carcinogenicity and concluded that vinyl chloride is a proven human carcinogen (IARC, 1979) and placed vinyl chloride in its carcinogenicity group 1. Substances assigned to this category have demonstrated sufficient evidence to support a causal association between exposure and cancer in humans.

IARC noted that, "...several independent but mutually confirmatory studies have shown that exposure to vinyl chloride results in an increased carcinogenic risk in humans, involving the liver, brain, lung and hemolymphopoietic systems in man." They also noted in "two proportionate mortality studies ... there appeared to be an increased proportion of cancer of the digestive system in both sexes and possibly of the urinary system and of the breast in woman," and "there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans" (IARC, 1979).

The Environmental Protection Agency (EPA, 1984b) has likewise reviewed the data and also concluded that vinyl chloride is a proven human carcinogen. The EPA placed vinyl chloride in its group A as a proven human carcinogen.

Although both EPA and the National Academy of Science have concluded that there were inadequate exposure data to base a quantitative carcinogenic risk assessment on epidemiological studies, the present risk assessment includes an analysis of an occupational study of Waxweiler et al. (1976), using a retrospective estimate of exposure (Barnes, 1976; Paddle 1986) that was converted to an effective exposure on the basis of a pharmacodynamic model which takes account of the metabolic conversion.

The animal studies demonstrated a relationship between tumor formation and the sex and age of the animal at first exposure. Fetuses, newborns, younger animals, and females exhibited the highest carcinogenic sensitivity (Drew et al., 1983). In the epidemiological studies of vinyl chloride workers, who were predominantly male, the average age at first exposure was 29.7 years. Thus, to protect all members of the general population, it is more appropriate to base risk assessment calculations on the animal inhalation studies, which because of their use of more sensitive categories, the young and females, reflect a wider range of population sensitivity.

The staff of the Department of Health Services conclude that:

1. Vinyl chloride is mutagenic and is a proven animal and human carcinogen.

2. Because vinyl chloride is genotoxic and there is no experimental evidence that vinyl chloride has a carcinogenic threshold, it should not be considered to have one. Animal evidence has demonstrated that vinyl chloride is carcinogenic at a lifetime daily equivalent exposure of 0.06 ppm. Potential human residential exposures may be only from six to 60-fold lower than those in the animal studies.

3. Vinyl chloride has been demonstrated to cause a number of malignant tumor types in animals, including angiosarcoma of both the liver and lung, hepatocellular carcinomas, several different lung tumors, brain tumors, and other types of cancers. Vinyl chloride has been shown to cause liver angiosarcoma in humans and epidemiological evidence suggests that vinyl chloride may induce lung, breast, and brain tumors. Vinyl chloride has been demonstrated to be multisite carcinogen, and this risk assessment performed by the staff of DHS reflects this finding.

4. Quantitative risk assessments of the relevant animal inhalation studies of vinyl chloride using the linearized multistage model have suggested a range of potential human unit risks from 4×10^{-5}/ppb to 20×10^{-5}/ppb (Table 8.3). The human unit risk from occupational vinyl chloride exposure for males has been estimated herein to be 4.5×10^{-5} ppb^{-1} for cancer at all sites and to be 2.5×10^{-5} ppb^{-1} for liver cancer alone. Thus, although the human risk estimates are based on a historical reconstruction of occupational exposures, the results overlap the range estimated from animal studies.

5. The California Air Resources Board has monitored vinyl chloride emissions from the BKK landfill in West Covina and the OII landfill in Monterey Park. Estimates of peak concentrations for maximally exposed receptors range from 2 to 10 ppb at the BKK landfill and 0.6 to 9 ppb at the OII site. The Air Resources Board has estimated that between 17,000 and 131,000 individuals may be exposed to 1 ppb at the BKK site. The present assessment predicts that there is only a 5% chance that a lifetime exposure of 131,000 residents to 1 ppb would result in more than 3 to 26 excess cancer cases, and there is a 95% chance that there would be less cases.

REFERENCES

Adkins B Jr, Van Stee EW, Simmons JE, Eustis SL (1986). Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 17:311-22.

Anderson D, Hodge MCE and Purchase IFH (1977) Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice. Environ Health Perspect 21:77-78.

Anderson D and Richardson CR (1981) Issues relevant to the assessment of chemically induced chromosome damage in vivo and their relationship to chemical mutagenesis. Mutat Res 90:261-272.

Anderson MW, Hoel DG, Kaplan NL (1980) A general scheme for the incorporation of pharmacokinetics in low-dose risk estimation for chemical carcinogenesis: example -- vinyl chloride. Toxicol Appl Pharmacol 55:154-161.

Barbin A, Laib RJ, Bartsch B (1985). Lack of miscoding properties of 7-(2-oxoethyl)guanine, the major vinyl chloride-DNA adduct. Cancer Res 45:2440-2444.

Barbin A, Bartsch H (1986). Mutagenic and promutagenic properties of DNA adducts formed by vinyl chloride metabolites. In: The Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis. IARC Sci Publ (70):345-58.

Barbin A, Bartsch H (1989). Nucleophilic selectivity as a determinant of carcinogenic potency (TD50) in rodents: A comparison of mono- and bi-functional alkylating agents and vinyl chloride metabolites. Mut Res 215 95-106.

Barbin A, Bereziat J-C, Croisy A, O'Neill Ik, Bartsch H (1990). Nucleophilic selectivity and reaction kinetics of chloroethylene oxide assessed by the 4-(p-nitrobenzyl)pyridine assay and proton NMR spectroscopy. Chem-Biol Interact 73:261-278.

Bardin CW, Taketo T, Gunsalus GL, Koide SS and Mather JP (1982) The detection of agents that have toxic effects on the testis and male reproductive tract. In: The Banbury Report, Vol. 11: Environmental Factors in Human Growth and Development, pp. 337-355.

Barlow SM and Sullivan FM (eds.) (1982) Reproductive Hazards of Industrial Chemicals, Academic Press, London, pp. 566-582.

Barnes AW (1976) Vinyl chloride and the production of PVC. Proc Roy Soc Med 69:278-281.

Bartsch H, Malaveille C and Montesano R (1975) Human, rat and mouse liver-mediated mutagenicity of vinyl chloride in S. typhimurium strains. Int J Cancer 15:429-437.

Bartsch H and Montesano R (1975) Mutagenic and carcinogenic effects of vinyl chloride. Mutat Res 32:93-114.

Basalaev AV, Vazine AN and Kochetkov AG (1972) On the pathogenesis of changes developing due to a long-term exposure to the effect of vinyl chloride. Gig Tr Prof Zabol 16:24-27. Cited in EPA, 1984.

Basler A and Rohrborn G (1980) Vinyl chloride: an example for evaluating mutagenic effects in mammals in vivo after exposure to inhalation. Arch Toxicol 45:1-7.

Beaumont JJ and Breslow NE (1981) Power consideration in epidemiologic studies of vinyl chloride workers. Am J Epidemiol 114:723-734.

Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Masina A, Pirastu R, Reggiani A, Vigotti MA (1987). A cohort study on vinyl chloride manufacturers in Italy: Study design and preliminary results. Cancer Lett 35:253-61.

Bertazzi PA, Villa A, Foa V, Saia B, Fabbri L, Mapp C, Mercer C, Manno M, Marchi M, Mariani F and Bottasso F (1979). An epidemiological study of vinyl chloride exposed workers in Italy. Arg Hig Rada Toksikol 30:403-409 (Suppl).

Bi W, Wang Y, Huang M and Meng D (1985) Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Safety 10:281-289.

Biology Data Book (1974) P. L. Altman and D. S. Dittmer, Eds. Published by the Federation of American Societies for Experimental Biology, Bethesda, MD. Volume III, p. 1741.

Bolt HM (1986). Metabolic activation of vinyl chloride, formation of nucleic acid adducts and relevance to carcinogenesis. In: The Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis. IARC Sci Publ (70):261-8.

Bolt HM (1988), Bartsch H, Barbin A. Roles of etheno-DNA adducts in tumorigenicity of olefins. Crit Rev Toxicol 18:299-310.

Bolt HM, Kappus H, Buchter A and Bolt W (1976) Original Investigations. Disposition of (1,2-^{14}C) vinyl chloride in the rat. Arch Toxicol 35:153-162.

Bolt HM, Laib RJ, Kappus H and Buchter A (1977) Pharmacokinetics of vinyl chloride in the rat. Toxicol 7:179-188.

Bolt HM, Filser JG and Buchter A (1981) Inhalation pharmacokinetics based on gas uptake studies. III. A pharmacokinetic assessment in man of "peak concentrations" of vinyl chloride. Arch Toxicol 48:213-228.

Bolt HM, Laib RJ, Peter H, Ottenwalder H (1986). DNA adducts of halogenated hydrocarbons. J Cancer Res Clin Oncol 112:92-6.

Brady JF, Dechun L, Ishizaki H, Lee M, Ning SM, Xiao F, and Yang CS (1989) Induction of cytochrome P450IIE1 and P450IIB1 by secondary ketones and the role of P450IIE1 in chloroform metabolism. Toxicol Appl Pharm 100:453-450.

Brown KG, Hoel DG (1986). Statistical modeling of animal bioassay data with variable dosing regimens: example--vinyl chloride. Risk Anal 6:155-66.

Buchter A, Bolt HM, Kappus H and Bolt W (1977) Die gewebsverteilung von 1,2-^{14}C-vinylchlorid bei der ratte. Int Arch Occup Environ Health 39:27-32.

Buchter A, Bolt HM, Filser JG, Goergens HW, Laib RJ and Bolt W (1978) Pharmakokinetik und karzinogenese von vinyl chloride. Arbeitsmedizinische Risikobeurteilung. Verh Dtsch Ges Arbeitsmedizin (Gentner, Stuttgart) 18: 111-124. (cited in Bolt et al, 1981).

Buchter A (1979) Erarbeitung einer speziellen arbeitsmedizinischen Uberwachungsuntersuchung in korrelation zur individvellen Vinylchlorid-Exposition. Forschungsbericht des Landes Nordrhein-Westfalen. Fachgruppe Medizin, Nr. 2813, Westdeutscher Verlag, Opladen. (cited in Bolt et al., 1981).

Buchter A, Filser JG, Peter H and Bolt HM (1980) Pharmacokinetics of vinyl chloride in the Rhesus monkey. Toxicol Lett 6:33-36.

Buffler PA, Wood S, Eifler C, Suarez L and Kilian DJ (1979) Mortality experience of workers in vinyl chloride monomer production plant. J Occup Med 21:195-202.

Byren D, Engholm G, Englund A and Westerholm P (1976) Mortality and cancer morbidity in a group of Swedish VCM and PCV workers. Environ Health Perspect 17:167-170.

California Department of Health Services (CDHS, 1985) Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale. California Department of Health Services, Health and Welfare Agency, Sacramento, CA.

California Health and Safety Code (1988) Chapter 3.5: Toxic air contaminants; section 39650. In: California Air Pollution Control Laws, Calfornia Air Resources Board, Sacramento, CA.

Caputo A, Viola PL and Bigotti A (1974) Oncogenicity of vinyl chloride at low concentrations in rats and rabbits. Int Res Commun 2:1582.

Chen CW, Blancato JN (1989). Incorporation of biological information in cancer risk assessment: example--vinyl chloride. Cell Biol Toxicol 5:417-44.

Ciroussel F, Barbin A, Eberle G, Bartsch H (1990). Investigations on the relationship between DNA ethenobase adduct levels in several organs of vinyl chloride-exposed rats and cancer susceptibility. Biochem Pharmacol 39:1109-13.

Clemmesen J (1982) Mutagenicity and teratogenicity of vinyl chloride monomer (VCM). Epidemiologic evidence. Mutat Res 98:97-100.

Cooper WC (1981) Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972. Environ Health Perspect 41:101-106.

Creech JL Jr., and Johnson MN (1974) Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16:150-151.

Dahar, WS, Bond, GG, McLaren, EA, Sabel, FL, Lipps, TE and Cook, RR (1988) Update to vinyl chloride mortality study. J Occup Med 30:648-649.

Danziger H (1960) Accidental poisoning by vinyl chloride: Report of two cases. Can Med Assoc J 82:828-830.

Doll R (1988) Effects of exposure to vinyl chloride: An assessment of evidence. Scand J Work Environ Health 14:61-78.

Drevon C, Kuroki T and Montesano R (1977) Microsome mediated mutagenesis of a Chinese hamster cell line by various chemicals (abstract). In: 2nd International Conference on Environmental Mutagens, Edinburgh, 1977, p. 150.

Drew RT, Boorman GA, Haseman JK, McConnell EE, Busey WM and Moore JA (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol Appl Pharmacol 68:120-130.

Drodzdowicz BZ and Huang PC (1977) Lack of mutagenicity of vinyl chloride in two strains of Neurospora crassa. Mutat Res 48:43-50.

Du JT, Tseng MT and Tamburro CH (1982) The effect of repeated vinyl chloride exposure on rat hepatic metabolizing enzymes. Toxicol Appl Pharmacol 62:1-10.

Duck BW, Carter JT and Coombes EJ (1975) Mortality study of workers in a polyvinyl-chloride production plant. Lancet II:1197-1199.

Duprat P, Fabry JP, Gradiski D and Magadur JL (1977) Metabolic approach to industrial poisoning: blood kinetics and distribution of ^{14}C vinyl-chloride monomer (VCM). Acta Pharmacol Toxicol Suppl 41:142-143.

Duverger M, Lambotte E, Malvoisin E, deMeester C, Pancelet F and Mercier M (1981) Metabolic activation and mutagenicity of vinylic monomers (vinyl chloride, styrene, acrylonitrile, butadiene). Toxicol Eur Res 3:131-140.

Duverger-Van Bogaert M, Lambotte-Vandepaer M, deMeester C, Mercier M and Pancelet F (1982) Vinyl chloride and acrylonitrile: activation mechanism and mutagenicity. Toxicologie Experimentale 4:35-37.

Eberle G, Barbin A, Laib RJ, Ciroussel F, Thomale J, Bartsch H, Rajewsky MF (1989). $1,N^6$-etheno-2'-deoxyadenosine and $3,N^4$-etheno-2'-deoxycytidine detected by monoclonal antibodies in lung and liver DNA of rats exposed to vinyl chloride. Carcinogenesis 10:209-12.

Edmonds, LD, Falk H and Nissim JE (1975) Congenital malformations and vinyl chloride. Lancet II:1098.

Edmonds LD, Anderson CE, Flynt JW Jr and James LM (1978) Congenital central nervous system malformations and vinyl chloride monomer exposure. A community study. Teratology 17:137-142.

Environmental Protection Agency (EPA) (1984a) Techniques for the Assessment of the Carcinogenic Risk to the U.S. Population Due to Exposure from Selected Volatile Organic Compounds from Drinking Water via the Ingestion Inhalation and Dermal Routes. Office of Drinking Water, Washington, D.C. PB84-213941.

Environmental Protection Agency (EPA) (1984b) Health Effects Assessment for Vinyl Chloride. Office of Health and Environmental Assessment, Cincinnati, Ohio. EPA 540/1-86-036.

Environmental Protection Agency (EPA) (1985a). Drinking Water Criteria Document for Vinyl Chloride. Office of Drinking Water, Washington, D.C. NTIS PB86-118320.

Environmental Protection Agency (EPA) (1985b). Health and Environmental Effects Profile for Chloroethene. Environmental Criteria and Assessment Office. Cincinnati, Ohio. ECAO-CIN-P155.

Environmental Protection Agency (EPA) (1985c) Addendum to the Health Assessment Document for Dichloromethane (Methylene Chloride). Updated Carcinogenicity Assessment of Dichloromethane (Methylene Chloride). EPA 600-8-82/004F.

Equitable Environmental Health, Inc. (EEH) (1978) Epidemiological study of vinyl chloride workers. Prepared for Manufacturing Chemists Assoc.

Fabricant JD and Legator MS (1981) Mutagenicity studies of vinyl chloride. Environ. Health Perspect 41:189-193.

Feron VJ, Kruysse A and Til HP (1979a) One year time-sequence inhalation toxicity study of vinyl chloride in rats. I. Growth, mortality, hematology, clinical chemistry and organ weights. Toxicology 13:25-28.

Feron VJ, Spit BJ, Ammel HR and Kroes R. (1979b) One-year time-sequence inhalation toxicity study of vinyl chloride in rats. III. Morphological changes in the liver. Toxicology 13:145-154.

Feron VJ, Hendriksen CFM, Speek AJ, Til HP and Spit BJ (1981) Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet Toxicol 19:317-333.

Filser JG and Bolt HM (1979) Pharmacokinetics of halogenated ethylenes in rats. Arch Toxicol 42:123-136.

Forman D, Bennett B, Stafford J and Doll R (1985) Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases. Br J Ind Med 42:750-3.

Fox AJ and Collier PF (1977) Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34:1-10.

Fucic A, Horvat D, Dimitrovic B (1990). Localization of breaks induced by vinyl chloride in the human chromosomes of lymphocytes. Mutat Res 243:95-9.

Funes-Cravioto F, Yakovienko KN, Kuleshov NP, Zhurkov VS, (1974). Localization of chemically induced breaks in chromosomes of human leucocytes. Mut Res 23:87-105.

Gamble J, Liu S, McMichael AJ and Waxweiler RJ (1976) Effect of occupational and nonoccupational factors on the respiratory system of vinyl chloride workers. J Occup Med 18:659-670.

Gargas ML, Andersen ME, Clewell HJ III (1986). A physiologically based simulation approach for determining metabolic constants from gas uptake data. Toxicol Appl Pharmacol 86:341-352.

Gargas ML, Seybold PG, Andersen ME (1988). Modeling the tissue solubilities and metabolic rate constant V_{max} of halogenated methanes, ethanes and ethylenes. Symposium on quantitative toxicology held at the 17th Conference on Toxicology, Dayton, Ohio, USA, Nov 3-5, 1987. Toxicol Lett 43:235-256.

Garro AJ, Guttenplan JB and Milvy P (1976) Vinyl chloride dependent mutagenesis: effects of liver extracts and free radicals. Mutat Res 38:81-88.

Gehring PJ, Watanabe PG, Park CN (1978) Resolution of a dose-response toxicity data for chemicals requiring metabolic activation: example -- vinyl chloride. Toxicol Appl Pharmacol 44:581-591.

Gehring PJ, Watanabe PG, Park CN (1979) Risk of angiosarcoma in workers exposed to vinyl chloride as predicted from rat studies. Toxicol Appl Pharmacol 49:15-21.

Green T and Hathway DE (1975) The biological fate in rats of vinyl chloride in relation to its oncogencity. Chem-Biol Interact 11:545-562.

Green T and Hathway DE (1977) The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. Chem-Biol Interact 17:137-150.

Greim H, Bonse G, Radwau Z, Reichert D and Heuschler D (1975) Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of a metabolic oxirane formation. Biochem. Pharmacol 24:2013-2017.

Groth DH, Coate WB, Ulland BM and Hornung RW (1981) Effects of aging on the induction of angiosarcoma. Environ Health Perspect 41:53-57.

Guengerich FP and Strickland TW (1977) Metabolism of vinyl chloride: destruction of the heme of highly purified liver microsomal cytochrome P-450 by a metabolite. Mol Pharmacol 13:993-1004.

Guengerich FP and Watanabe PG (1979) Metabolism of [^{14}C]- and [^{36}Cl]-labeled vinyl chloride in vivo and in vitro. Biochem Pharmacol 28:589-596.

Hagmar L, Akesson B, Nielsen J, Andersson C, Linden K, Attewell R, Moller T (1990) Mortality and cancer morbidity in workers exposed to low levels of vinyl chloride monomer at a polyvinyl chloride processing plant. Am J Ind Med 17:553-65.

Hansteen IL, Hillestad L, Thiis-Evensen E and Heldaas SS (1978) Effects of vinyl chloride in man. A cytogenetic follow-up study. Mutat Res 51:271-278.

Harris EA and Adams WGF (1967) Acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride. Brit Med J 3:712-714.

Hatch GG, Mamay PD, Christensen CC, Casto BC, Langenbach R and Nesnow S. (1981) In vitro transformation of hamster embryo cells exposed to gaseous or volatile chlorinated hydrocarbons. Proc Am Assoc Cancer Res 22:119 (abstract).

Heath CW Jr, Falk H and Creech JL Jr (1975) Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers. Ann NY Acad Sci 246:231-236.

Hefner RE Jr, Watanabe PG and Gehring PJ (1975a) Preliminary studies on the fate of inhaled vinyl chloride monomer (VCM) in rats. Environ Health Perspect 11:85-95.

Hefner RE Jr, Watanabe PG and Gehring PJ (1975b) Experimental Studies. Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. Ann NY Acad Sci 246:135-148.

Hefner RE Jr, Watanabe PG and Gehring PJ (1975c) Percutaneous absorption of vinyl chloride. Toxicol Appl Pharmacol 34:529-532.

Heger M, Muller G and Norpoth K (1982) Untersuchunger zur beziehung zwischen vinylchlorid (VCM)-aufnahme und metabolitenausscheidung bei 15 VCM-exponierten. II. Messunger zur ausscheidung des VCM-metaboliten thiodiglykosaure im harn. Int Arch Occup Environ Health 50:187-196.

Hehir RM, McNamara BP, McLaughlin J, Willigan DA, Bierbower CT and Hardisty JF (1981) Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ Health Perspect 41:63-72.

Heidelberger C, Freeman AE, Pierta RJ, Sivak A, Bertram JS, Casto BC, Dunkel VC, Francis MW, Kakunaga T, Little JB and Schectman LM (1983) Cell transformation by chemical agents--a review and analysis of the literature. Mutat Res 114:283-285.

Heldaas SS, Langard SL and Anderson A (1984) Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br J Ind Med 41:25-30.

Heldaas SS, Andersen AA, Langard S (1987) Incidence of cancer among vinyl chloride and polyvinyl chloride workers: further evidence for an association with malignant melanoma. Br J Ind Med 44:278-280.

Hemminki K and Vineis P (1985) Extrapolation of the evidence on the teratogenicity of chemicals between humans and experimental animals: chemicals other than drugs. Teratogen Carcinogen Mutagen 5:251-318.

Hong CB, Winston JM, Thornburg LP, Lee CC and Woods JS (1981) Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent to exposure. J Toxicol Environ Health 7:909-924.

Hopkins J (1979) Vinyl Chloride. Part 1: Metabolism. Food Cosmet Toxicol 17:403-412.

Huberman E, Bartsch H and Sachs L (1975) Mutation induction in Chinese hamster V-79 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloroacetaldehyde. Int J Cancer 16:639-644.

Infante PF (1976) Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann Ny Acad Sci 271:49-57.

International Agency for Research on Cancer (IARC) (1979) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans: Volume 19, Some Monomers, Plastics and Synthetic Elastomers, and Acrolein. International Agency for Research on Cancer, Lyon, France, pp. 377-438.

International Agency for Research on Cancer (IARC) (1987) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Supplement 6, Lyon, France, pp. 566-569.

Jacobsen JS, Perkins, CP, Callahan JT, Sambamurti K, Humayun MZ (1989). Mechanisms of mutagenesis by chloroacetaldehyde. Genetics 121:213-222.

Jacobsen JS, Humayun MZ (1990) Mechanisms of mutagenesis by the vinyl chloride metabolite chloroacetaldehyde. Effect of gene-targeted in vitro adduction of M13 DNA on DNA template activity in vivo and in vitro. Biochemistry 29:496-504.

Jenssen D and Ramel C (1980) The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat Res 75:191-202.

John JA, Smith FA, Leong BKJ and Schwetz BA (1977) The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA and Schwetz BA (1981) Vinyl chloride: inhalation teratology study in mice, rats and rabbits. Environ Health Perspect 41:171-177.

Jones J (1974) Worker exposure to vinyl chloride during production and fabrication of vinyl chloride and polyvinyl chloride. NIOSH Report Contract CDC-99-74-59, pp. 2-161.

Jones RD, Smith DM, Thomas PG (1988) A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. Scand J Work Environ Health 14:153-160.

Kalmaz EE and Kalmaz GD (1984) Carcinogenicity and epidemiological profile analysis of vinyl chloride and polyvinyl chloride. Regul Toxicol Pharmacol 4:13-27.

Keplinger ML, Goode JW, Gordon DE and Calandra JC (1975) Interim results of exposure of rats, hamsters, and mice to vinyl chloride. Ann NY Acad Sci 246:219-224.

Krahn DF (1979) Utilization of the CHO/HGPRT system: metabolic activation and method for testing gases. In: Hsie, A. W., O'Neill, J. P., and McElkeny, I. K. (eds.). Mammalian Cell Mutagenesis: The Maturation of Test Systems, Banbury Report No. 2, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp. 251-261.

Krajewski J, Dobecki M and Gromiec J (1980) Retention of vinyl chloride in the human lung. Br J Ind Med 37:373-374.

Krewski D, Murdoch DJ, Withey JR (1987) The application of pharmacokinetic data in carcinogenic risk assessment. In: Gillette JR, Jollow D, cohair, Subcommittee on Pharmacokinetics and Risk Assessment, NRC, Pharmacokinetics in Risk Assessment, Drinking Water and Health, Vol. 8. National Academy Press, Washington, DC. pp 441-468.

Kucerova M, Polivkova Z and Batora J (1979) Comparative evaluation of the frequency of chromosomal aberrations and the SCE numbers in peripheral lymphocytes of workers occupationally exposed to vinyl chloride monomer. Mutat Res 67:97-100.

Kuzmack AM and McGaughy RE (1975) Quantitative Risk Assessment for Community Exposure to Vinyl Chloride, U.S. Environmental Protection Agency, Washington, D.C.

Laib RJ and Bolt HM (1977) Formation of imidazole derivatives of nucleic acid bases (DNA and RNA) by metabolites of vinyl chloride in vivo and in vitro. In: Proceedings of the 4th Meeting of the European Association for Cancer Research, Lyon, France, p. 84.

Laib RJ, Klein KP, Bolt HM (1985a). The rat liver foci bioassay: I. Age-dependence of induction by vinyl chloride of ATPase-deficient foci. Carcinogenesis 6:65-68.

Laib RJ, Pellio T, Wunschel UM, Zimmermann N, Bolt HM (1985b). The rat liver foci bioassay: II. Investigations on the dose-dependent induction of ATPase-deficient foci by vinyl chloride at very low doses. Carcinogenesis 6:69-72.

Laib RJ, Doerjer G, Bolt HM (1985c). Detection of N2,3-ethenoguanine in liver-DNA hydrolysates of young rats after exposure of the animals to 14C-vinyl chloride. J Cancer Res Clin Oncol. 109:A7 Abstract No. Biol2.

Laib RJ, Bolt HM, Cartier R, Bartsch H (1989) Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol Lett 45:231-9.

LaPlanche A, Clavel F, Contassot J-C, Lanouziere C (1987). Exposure to vinyl chloride monomer: report on a cohort study. Br J Ind Med 44:711-715.

Lee CC, Bhandari JC, Winston JM, House WB, Peters PJ, Dixon RL and Woods JS (1977) Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ Health Perspect 21:25-32.

Lee CC, Bhandari JC, Winston JM and House WB (1978) Carcinogenicity of vinyl chloride and vinylidene chloride. J Toxicol Environ Health 4:15-30.

Lelbach WK and Marsteller HJ (1981) Vinyl-chloride associated disease. In: Advances in Internal Medicine and Pediatrics, Springer-Verlag, Berlin.

Leonard A, Decat G, Leonard ED, Leferver MJ, Decuyper LJ and Nicaise C (1977) Cytogenetic investigations on lymphocytes from workers exposed to vinyl chloride. J Toxicol Environ Health 2:1135-1141.

Lester D, Greenberg CA and Adams WR (1963) Effects of single and repeated exposure of humans and rats to vinyl chloride. J Am Ind Hyg Assoc 24:265-275.

Lilis R (1981) Review of the pulmonary effects of poly(vinyl chloride) exposure. Environ Health Perspect 41:167-169.

Lilis R, Anderson H, Nicholson WJ, Daum S, Fischbein AS and Selikoff IJ (1975) Prevalence of disease among vinyl chloride and polyvinyl chloride workers. Ann NY Acad Sci 246:23-41.

Loprieno N, Barale R, Baroncelli S, Bauer C, Bronzetti G, Camelii A, Cerciangani G, Corsi C and Gervasi-Turcki G (1976) Evaluation of the genetic effects induced by vinyl chloride monomer under mammalian metabolic activation studies in vitro and in vivo. Mutat Res 40:85-96.

Maier P, Schawalder HP (1988) Hepatocarcinogens induce gene mutations in rats in fibroblast-like cells from a subcutaneous granulation tissue. Carcinogenesis 9:1363-8.

Maltoni C and Lefemine G (1975) Carcinogenicity assays of vinyl chloride: current results. Ann NY Acad Sci 246:195-224.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D (1981). Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. Environ. Health Perspect. 41:3-29.

Maltoni C, Lefemine G, Ciliberti A, Cotti G and Caretti D (1984) Experimental Research on Vinyl Chloride Carcinogenesis. In: Maltoni C, Mehlman MA (eds.) Archives of Research on Industrial Carcinogenesis, Vol. II. Princeton Scientific Publishers, Inc., Princeton, New Jersey.

Marsteller HJ and Lelbach WK (1975) Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 246:95-134.

Masuda Y (1979) Long term mortality study of vinyl chloride and polyvinyl chloride workers in a Japanese plant. Arh Hig Rada Toksikol 30:403-409 (Suppl).

McCann J, Simmon V, Streitwieser D and Ames BN (1975) Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene chloride), chloroethanol (ethylene chlorohydrin), vinyl chloride, and cyclophosphamide. Proc Natl Acad Sci USA 72:3190-3193.

Miller A, Teirstein AS, Chuang M, Selikoff IJ and Warshaw R (1975) Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. Ann NY Acad Sci 246:42-52.

Mirkova E, Minailova A and Noska M. (1978) Embryotic and teratogenic action of vinyl chloride. Khigiena i Zdraveopazvane 23:440-443.

Mohn GR (1981) Mutagenicity of selected chemicals in Escherichia coli test systems. In: de Serres, F. J., and Shelby, M. D. (eds.) Comparative Chemical Mutagenesis, Environmental Science Research, Volume 24, Plenum Press, New York, pp. 69-108.

Monson RR, Peters JM and Johnson MN (1974) Proportional mortality among vinyl-chloride workers. Lancet pp. 397-398.

Muller G, Norpoth K, Kusters E, Herweg K and Versin E (1978) Determination of thiodiglycolic acid in urine specimens of vinyl chloride exposed workers. Int Arch Occup Environ Health 41:199-205.

Nakamura J (1983) A mortality study of vinyl chloride workers in Japan. J UOEH 5:49-57 (Suppl).

Nicholson WJ, Hammond EC, Seidman H and Selikoff IJ (1975) Mortality experience of a cohort of vinyl chloride-polyvinyl chloride workers. Ann NY Acad Sci 246:225-230.

Ott MG, Langner RR and Holder BB (1975) Vinyl chloride exposure in a controlled industrial environment. Arch Environ Health 30:333-339.

Perrard MH (1985) Mutagenicity and toxicity of chloroethylene oxide and chloroacetaldehyde. Experientia 41:676-677.

Peter S and Ungvary G (1980) Lack of mutagenic effect of vinyl chloride monomer in the mammalian spot test. Mutat Res 77:193-196.

Picciano DJ, Flake RE, Gay PC and Kilian DJ (1977) Vinyl chloride cytogenetics. J Occup Med 19:527-530.

Pirastu R, Comba P, Reggiani A, Foa V, Masina A, Maltoni C (1990) Mortality from liver disease among Italian vinyl chloride monomer/polyvinyl chloride manufacturers. Am J Ind Med 17:155-61.

Probst GS, McMahon RE, Hill CE, Thompson CZ, Epp JK and Neal SB (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: a comparison with bacterial mutagenicity using 218 compounds. Environ Mutagen 3:11-32.

Prodan L, Suciu I, Pislaru V, Ilea E and Pascu L (1975a) Experimental acute toxicity of vinyl chloride (monochloro-ethene). Ann NY Acad Sci 246:154-158.

Prodan L, Suciu I, Pislaru V, Ilea E and Pascu L (1975b) Experimental chronic poisoning with vinyl chloride. Ann. NY Acad. Sci 246:159-163.

Purchase IFH, Richardson CR and Anderson D (1975) Chromosomal and dominant lethal effects of vinyl chloride. Lancet, August 30, 1975.

Purchase IF, Stafford J and Paddle GM (1987) Vinyl chloride: An assessment of the risk of occupational exposure. Food Chem Toxicol 25:187-202.

Radike MJ, Stemmer KL and Bingham E (1981) Effect of ethanol on vinyl chloride carcinogenesis. Environ Health Perspect 41:59-62.

Radike MJ, Warkany J, Stemmer K, and Bingham E (1988) Perinatal carcinogenesis induced by inhaled vinyl chloride. Toxicologist 8:166 (abstract 660).

Rinsky RA, Ott G, Ward E, Greenberg H, Halperin W and Leet T (1988) Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am J. Ind Hyg 13:429-438.

Rosenkranz HS (1981) Mutagenicity of selected chemicals in Escherichia coli DNA repair deficient assays. In: deSerres, F. J., and Shelby, M. D. (eds.), Comparative Chemical Mutagenesis, Environmental Science Research, Volume 24, Plenum Press, New York, pp. 5-18.

Rossner P, Sram RJ, Novakova J and Lambl V (1980) Cytogenetic analysis in workers occupationally exposed to vinyl chloride. Mutat Res 73:425-427.

Selikoff IJ and Hammond EC (eds.) (1975) Toxicity of vinyl chloride-polyvinyl chloride, Ann NY Acad Sci 246.

Short RD, Minor JC, Winston JM and Lee CC (1977) A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. J Toxicol 3:965-968.

Singer B, Grunberger D (1983). Molecular Biology of Mutagens and Carcinogens. Plenum Press, NY p.92-94.

Singer B, Spengler SJ (1986). Replication and transcription of polynucleotides containing ethenocytosine, ethenoadenine and their hydrated intermediates. In: The Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis. IARC Sci Publ (70):359-371.

Singer B, Spengler SJ, Chavez F, Kusmierek JT (1987) The vinyl chloride-derived nucleoside, N2,3-ethenoguanosine, is a highly efficient mutagen in transcription. Carcinogenesis 8(5):745-7.

Singer B, Spengler SJ (1988) DNA polymerase I and AMV reverse transcriptase recognition of etheno bases in templates. Symposium on mechanisms and consequences of DNA damage processing. Held at the 17th annual UCLA symposia on molecular and cellular biology, Taos, NM, USA, January 24-30, 1988. J Cell Biochem Suppl (12 Part A):352 Abstract No E465.

Smith AH, Waxweiler RJ and Tyroler HA (1980) Epidemiologic investigation of occupational carcinogenesis using a serially additive expected dose model. Am J Epidemiol 112:787-797.

Smulevich VB, Fedotova IV and Filatova VS (1988) Increasing evidence of the rise of cancer in workers exposed to vinyl choride. Br J Ind Med 45:93-97.

Sokal JA, Baranski B and Majka J (1980) Experimental studies on the chornic effects of vinyl chloride in rats. J Hyg Epidemiol Microbiol Immunol 24:285-294.

Spengler S and Singer B (1981) Transcriptional errors and ambiguity resulting from the presence of $1,N^6$-ethenoadenosine or $3,N^4$-ethenocytidine in polyribonucleotides. Nucleic Acids Res 9:365-373.

Spirtas R, McMichael AJ, Garuble J and VanErt M (1975) The association of vinyl chloride with morbidity symptoms. Am Ind Hyg Assoc J 16:779-789.

Spirtas R and Kaminski R (1978) Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. Update of the NIOSH Register. J Occup Med 20:427-429.

Stafford J (1983) Liver angiosarcoma case registry, ICI. (cited in Maltoni et al., 1984).

Stanford Research Institute (SRI) (1983) Vinyl chloride. In: Monographs on Organic Air Pollutants, Final Report, prepared by SRI International for the National Cancer Institute, contract No. NO1-CP-26004-02, pp. 375-395.

Styles JA (1980) Studies on the detection of carcinogens using a mammalian cell transformation assay with liver homogenate activation. In: Norpoth KH and Garner RC (eds.), Short Term Test Systems for Detecting Carcinogens, Springer-Verlag, New York, pp. 226-238.

Suciu I, Prodan L, Ilea E, Paduraru A and Pascu L (1975) Clinical manifestations in vinyl chloride poisoning. Ann NY Acad Sci 246:53-69.

Suskov II and Sazonova LA (1982) Cytogenetic effects of epoxy, phenolformaldehyde and polyvinylchloride resins in man. Mutat Res 104:137-140.

Suzuki Y (1980) Non-neoplastic effects of vinyl chloride in mouse lung. Environ Res 21:235-253.

Suzuki Y (1981a) Electron microscopic observations of hepatic and subcutaneous hemangiosarcomas induced in mice exposed to vinyl chloride monomer. Am J Ind Med 2:103-117.

Suzuki Y (1981b) Neoplastic and nonneoplastic effects of vinyl chloride in mouse lung. Environ Health Perspect 41:31-52.

Symons MJ and Taulbee JD (1981) Practical considerations for approximating relative risk by the standard mortality ratio. J Occup Med 23:413-416.

Tabershaw IR and Gaffey WR (1974) Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med 16:509-518.

Tassignon JP (1980) Methodologie du traitement des donn'es de l'etude du Profeseur Maltoni. Report to the XX Meeting of "Le Club de Canc'rogen'se chimique" (Institut der Radium-Fondation Curie, Paris, 1979). Publications Essestielles, pp. 113-125.

Testa B and Jenner P (1981) Inhibitors of cytochrome P-450s and their mechanism of action. Drug Metab Rev 12:1-117.

Theriault G and Allard P (1981) Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. J Occup Med 23:671-676.

Theriault G, Iturra H and Gingras S (1983) Evaluation of the association between birth defects and exposure to ambient vinyl chloride. Teratology 27:359-370.

Thomas LB and Popper H (1975) Pathology of angiosarcoma of the liver among vinyl chloride-polyvinyl chloride workers. Ann NY Acad Sci 246:268-277.

Til HP, Immel HR and Feron VJ (1983) Lifespan Oral Carcinogenicity Study of Vinyl Chloride in Rats. Prepared by the Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research (CIVO Institute TNO) Report No. V 83.285/291099.

Torkelson MS, Oyen F and Rowe VK (1961) The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. J Am Ind Hyg Assoc 22:354-361.

Torkelson TR and Rowe VK (1981) Halogenated aliphatic hydrocarbons containing chlorine bromine and iodine. In: Patty's Industrial Hygiene and Toxicology, 3rd Revised Edition, vol. 2B, Chapter 48, pp. 3433-3601.

Tu AS, Murray TA, Hatch KM, Sivak A and Milman HA (1985) In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28:85-92.

Ungvary G, Hudik A, Tratui E, Lorincz M and Folly G (1978) Effects of vinyl chloride exposure alone and in combination with Trypan Blue--applied systematically during all thirds of pregnancy on the fetuses of CFy rats. Toxicology 11:45-54.

Van Duuren BL (1988) Direct-acting alkylating and acylating agents: DNA adduct formation, structure-activity, and carcinogenesis. Maltoni, C. and I. J. Selikoff (ed.). Annals of the New York Academy of Sciences, vol. 534. Living in a Chemical World: Occupational and Environmental Significance of Industrial Carcinogens; international conference, Bologna, Italy, October 6-10, 1985. New York Academy of Sciences: New York, NY, pp. 620-634

Veltman G, Lange CE, Juhe S, Stein G and Bachner U (1975) Clinical manifestations and course of vinyl chloride disease. Part I. Toxicological investigation of vinyl chloride-polyvinyl chloride. Ann NY Acad Sci 246:7-17.

Verburgt FG and Vogel E (1977) Vinyl chloride mutagenesis in Drosophila melanogaster. Mutat Res 48:327-336.

Viola PL, Bigotti A and Caputo A (1971) Oncogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res 31:516-522.

Wagoner JK, Infante PF (1980) A review of the methodological approaches in the assessment of an association between vinyl chloride exposure and reproductive hazards. In Infante PF, Legator MS (1980) "Proceedings of a Workshop on Methodology for Assessing Reproductive Hazards in the Work- place "NIOSH-DHHS Publication No. 81-100, Washington, DC, pp. 43-49.

Walles SA, Holmberg B, Svensson K, Osterman-Golkar S, Sigvardsson K, Lindblom K (1988) Induction of single-strand breaks in liver DNA of mice after inhalation of vinyl chloride. In: Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention. IARC Sci Publ (89):227-31.

Ward AM, Udnoon S, Watkins J, Walker AE and Darke CS (1976) Immunological mechanisms in the pathogenesis of vinyl chloride disease. Br Med J 1:936-938.

Watanabe PG, McGowan GR, Madrid EO and Gehring PJ (1976a) Fate of (^{14}C)vinyl chloride following inhalation exposure in rats. Toxicol Appl Pharmacol 37:49-59.

Watanabe PG, McGowan GR and Gehring PJ (1976b) Fate of (^{14}C)vinyl chloride after single oral administration in rats. Toxicol Appl Pharmacol 36:339-352.

Watanabe PG, Zempel JA and Gehring PJ (1978a) Comparison of the fate of vinyl chloride following single and repeated exposure in rats. Toxicol Appl Pharmacol 44:391-399.

Watanabe PG, Zempel JA, Pegg DG and Gehring PJ (1978b) Hepatic macromolecular binding following exposure to vinyl chloride. Toxicol Appl Pharmacol 44:571-579.

Waxweiler RJ, Stringer W, Wagoner JKC, Falk H and Jones J (1976) Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271:40-48.

Weber H, Reinl W and Greiser E (1981) German investigation on morbidity and mortaility of workers exposed to vinyl chloride. Environ Health Perspect 41:95-99.

Wilson WH, McCormick WE and Tatum CF (1967) Occupational acroosteolysis: report of 31 cases. J Am Med Assoc 201:83-87.

Withey JR (1976) Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J Toxicol Environ Health 1:381-394.

Wong O, Whorton MD, Ragland D, Klassen C, Samuels D, Chaxton K (1986) An update of an epidemiological study of vinyl chloride workers 1942-82. Final report to the Chemical Manufacturers Association. Environ Health Assoc, Oakland, CA.

Woo YT, Lai DY, Arcos JC and Argus MF (1985) Chemical Induction of Cancer, Structural Bases and Biological Mechanisms, volume IIIB, Aliphatic and Polyhalogenated Carcinogens. Academic Press, Inc., pp. 3-129.

Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P, Halperin W (1989) Cohort and case-control analyses of workers exposed to vinyl chloride: an update. J. Occup Med 31:518-523.

Zapponi GA, Bucchi AR, Lupi C (1988). Reproducibility of low-dose extrapolation procedure: comparison of estimates obtained using different rodent species and strains. Biomed Environ Sci 1:160-70.

Zuccato E, Marcuci F and Mussiui E (1980) The role of respiration in vinyl chloride excretion in rats. Toxicol Lett 5:213-217.

Appendix A

Abstracts of Maltoni et al. (1984) Bioassays

Intraperitoneal Administration

Rats: Groups of 30 male and 30 female 13-week-old Sprague-Dawley rats received an intraperitoneal injection of 4.25 mg vinyl chloride in olive oil on 1, 2, 3, or 4 occasions over a two-month period and observed for the duration of their lives (145 weeks). One nephroblastoma and one subcutaneous angiosarcoma were found. No difference in survival or body weight was observed between test animals and controls. This experiment was considered inadequate for the determination of the carcinogenic potential of vinyl chloride because of the unconventional dosing protocol used (Experiment BT12, Maltoni et al., 1984).

Subcutaneous Administration

Rats: In a separate study, a group of 75 male and female Sprague-Dawley rats was administered a single subcutaneous injection of 4.5 mg vinyl chloride in 1 ml olive oil at 21 weeks of age and observed for the remainder of their lifetime (145 weeks after injection). Body weight and survival were not significantly different between controls and treated animals. One nephroblastoma in a treated male was observed (Experiment BT13, Maltoni et al., 1984). The insufficient protocol prevents any assessment of the carcinogenicity of vinyl chloride from this experiment.

Transplacental Exposure

Rats: Groups of pregnant female Sprague-Dawley rats were exposed from day 12 to day 18 of gestation to 6,000 or 10,000 ppm vinyl chloride. The females and offspring were observed for their lifetimes (143 weeks after start of experiment). Survival of the offspring was poor after week 95 of the experiment. Several animals from both groups exposed in utero had mammary tumors, zymbal gland carcinoma, leukemias and nephroblastomas; no hepatic angiosarcomas or hepatomas were reported. No results from control animals were reported, thus statistical evaluation of these results is not possible. Only a few tumors were found in the female breeders (Experiment BT5, Maltoni et al., 1984; IARC, 1979).

Transplacental-Inhalation Exposure

Rats: Groups of 12-week-old pregnant Sprague-Dawley rats were exposed to either 0 or 2,500 ppm vinyl chloride four hours/day, five days/week for seven weeks, then seven hours/day for 69 weeks, after which time all animals died. One group of offspring was first exposed transplacentally from day 12 of gestation, then exposed by inhalation after birth using the same protocol. A second group of offspring was also exposed transplacentally from day 12 of gestation but was exposed by inhalation four hours/day, five days/week for seven weeks, then seven hours/day, five days/week for eight weeks. Vinyl chloride was toxic at all concentrations tested: all animals exposed to vinyl chloride for 76 weeks died by that time, whereas the control animals survived for up to 150 weeks. The poor survival of treated animals almost certainly diminished the number of observed tumors, especially tumors with long latency periods, such as liver angiosarcomas. An increased incidence of zymbal gland tumors (8/54), liver angiosarcomas (27/54), hepatomas (5/54), and

neuroblastomas (32/54) were reported for the breeding females exposed to vinyl chloride, compared to 1/60, 0,60, 0/60, 1/60, respectively, in the controls.

In the male offspring exposed to vinyl chloride for 76 weeks, 9/63 had zymbal gland carcinomas, 36/63 had liver angiosarcomas, 27/63 had hepatomas, and 31/63 had neuroblastomas, compared to 2/158, 0/158, 1/158, and 0/158, respectively, in the controls. In the female offspring exposed to vinyl chloride for 76 weeks, 6/64, 28/64, 38/63, and 28/64 were reported for these above tumors respectively compared to zero tumor incidence in the controls. The incidence of these same tumors in the male offspring exposed to vinyl chloride for only 15 weeks was 7/59, 24/59, 42/59, and 7/59 for the same tumors respectively, compared to 2/158, 0/158, 1/158, and 0/158, respectively, in the controls. In female offspring exposed for only 15 weeks, the incidence was 2/60, 28/60, 43/60, and 11/60 for the same tumors, respectively, compared to a zero incidence of these tumors in controls. These studies (BT4001, BT4006) were cited by Maltoni and colleagues (1984) as an example of transplacentally-induced-tumorigenesis, but was, in effect, an investigation of the increased sensitivity of young experimental animals to the toxic effects of vinyl chloride. The tumor incidence in breeders and offspring exposed to vinyl chloride for 76 weeks did not appear to differ significantly, nor did the increased tumor incidence in offspring exposed to vinyl chloride for 15 weeks appear to differ substantially from the tumor incidence in exposed breeders. However, no explicit statistical comparison of these parameters was made in the report (Maltoni et al., 1984; Experiments BT4001, BT4006).

Inhalation Exposure

Hamsters: Groups of 30 male Syrian golden hamsters were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm vinyl chloride, four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age. The hamsters were then observed for their lifespan (109 weeks). Two liver angiosarcomas were observed in the group exposed to 500 ppm vinyl chloride and one liver angiosarcoma was observed in the group exposed to 6,000 ppm. The increased incidence of forestomach epithelial tumors in hamsters exposed to 500 ppm or more of vinyl chloride appeared to be biologically significant but no statistics were reported (Experiment BT8, Maltoni et al., 1984).

Appendix B

Cancer Risk Estimates for

Vinyl Chloride

Based on Human Data

Introduction

Epidemiological data from many studies provide strong evidence that vinyl chloride is a human carcinogen. See Tables B-1 and B-2. As with the evaluation of toxic effects of many other substances, the main problem that occurs in using the epidemiological data for quantitative predictions of effects of vinyl chloride is the lack of suitable exposure data. For vinyl chloride, some indirect exposure estimates are available.

The quantitative risk assessment developed in this appendix uses cancer incidence data from one study, Waxweiler et al (1976). The industry-wide estimates of exposure by Barnes et al (1976) furnish the data for estimating year-by-year exposures of the known worker population in the Waxweiler study. The analysis uses these atmospheric exposures to estimate values of the metabolized exposure at the tissue, based on the satuation (Michaelis-Menton) model of formation of an active carcinogen. The calculations provide risk per unit of metabolized exposure, which closely approximates atmospheric exposure at concentrations below 10 ppm.

Mortality data

Of the many occupational studies that have been reported, the cohort study reported by Waxweiler et al (1976) contains the most thoroughly documented information for risk assessment purposes. That study selected a cohort of polyvinyl chloride (PVC) workers who had worked for at least five years between 1942 and 1973 and who had commenced work at least ten years before follow-up was completed. Follow-up for mortality was to the end of 1973.

Among the cohort of 1294 workers, only 7 were lost to follow up. There were 136 deaths during the follow-up period, of which 35 were due to cancer. Eleven of these cancer deaths were due to angiosarcoma of the liver, more than any other study, and three were due to billiary cancer. The standardized mortality ratio (SMR) for billiary and liver cancer was 1155, for brain cancer, 329, and for lung cancer, 156. All of these values represent statistically significant increases. It is apparent from Table B-2 that the SMRs from Waxweiler et al. are consistent with some of the other studies. The cumulative risk of liver, lung and brain cancer following vinyl chloride exposure is, however, greatest in the Waxweiler et al. (1976) report. Thus, cancer risks to vinyl chloride workers are unlikely to be substantially underestimated by a risk assessment based on this study.

Exposure Data

As in many retrospective cohorts, individual exposure data were not available (Waxweiler et al., 1976). However, several reports have attempted to reconstruct the magnitude of exposure among vinyl chloride workers since the 1940's (Ott et al., 1975; Jones, 1974; Paddle, 1986). Table B-3 summarizes proposed estimates of exposure for several countries.

Most of the specific exposure data available for the United States derive from measurements at a single plant operated by Dow Chemical Company (Jones, 1974). Although exposures for some job classes were quite high, most

exposures were less than proposed international levels during commensurate time periods because Dow Chemical Company responded to early reports of vinyl chloride toxicity in animal studies by creating an in-house standard of 50 ppm (Ott et al., 1975; Paddle, 1986). This standard was well below industry-wide acceptable limits during the 1960's and early 1970's and probably well below the average exposure at other vinyl chloride polymerization plants. Dow Chemical Company had not reported any cases of angiosarcoma of the liver to 1985 (Forman et al., 1985).

The exposure estimates presented by Barnes (1976) and summarized in Table B-3 of this appendix are likely to describe the average exposures for the Waxweiler et al. cohort, which spanned the years, 1942-1973. Barnes did not substantiate his exposure estimates but simply stated, "the general consensus of opinion throughout the world, today, is that average atmospheric exposure for polymerization workers between 1940 and 1970 might have been of the following order" (Barnes, 1976). The Barnes estimates approach the existing standards during the corresponding time periods. The current analysis used those Barnes estimates, which are expected to be within a factor of five of the actual values experienced by these workers.

Some work histories started before the first time period provided by Barnes (January 1, 1945). The present analysis counted those histories separately and assigned exposures prior to 1945 a concentration of 1000 ppm, which is equal to Barnes' estimates of concentration in the first ten years, on the assumption that exposure during early process days (pre-1945) was the same as that during the 1945-1955 exposure period.

Recorded deaths due to angiosarcoma of the liver occurred between 1964 and 1973. The present analysis examined work histories to identify the person-time in each calendar year for the cohort which had at least five years of employment and who began work (and thus vinyl chloride exposure) prior to 1964. The analysis incorporated these restrictions to correspond to the same restrictions used by Waxweiler and co-workers (1976) in generating their SMR values. Thus, both the exposure and the SMR values correspond to those workers with at least five years of exposure and at least a ten-year latency period from first exposure.

Relationship of Risk to Exposure

This development of a relationship of risk to exposure considers a cohort of individuals, each subcohort of which is exposed at a constant rate to a particular chemical during each time period of one calendar year. The rates of exposure may differ among subcohorts and time periods. The development here makes no distinction according to age.

The model assumes proportionality between excess risk and the metabolized exposure, a measure of the amount of vinyl chloride ever bound to macromocules in the course of an individual life time (Gehring et al 1977, Anderson et al 1980). Thus, the excess risk due to a lifetime daily equivalent metabolized exposure, Y_{ij}, of subcohort i during time period j is assumed to be given by

$$P_{ij} = QY_{ij}T_j/T, \qquad \text{(B-1)}$$

where P_{ij} = excess probability of cancer in subcohort i due to exposure during time period j.
Q = the lifetime unit risk, a coefficient of proportionality, independent of subcohort and period,
Y_{ij} = metabolized exposure for subcohort i during time period j, defined in Equation B-3 and representing adduct formation,
T_j = time of exposure during time period j,
T = general population lifetime (life expectancy).

This analysis uses a metabolic model of formation of active carcinogen because occupational exposures experienced in the older studies are well above the saturation level for adduct formation for all species in which the kinetics have been determined. The analysis assumes that Michaelis-Menton kinetics govern the rate at which adducts form in target tissue due to a reactive metabolite (Gehring, 1977). That rate is given by

$$F_{ij} = aV_mX_{ij}/(K_m + X_{ij}), \qquad \text{(B-2)}$$

where Fij = rate of adduct formation in subcohort i due exposure during time period j
a = proportionality constant
Vm = maximum velocity of the reaction,

K_m = Michaelis saturation constant,
X_{ij} = atmospheric exposure.

Instead of using the target dose rates F_{ij} in the subsequent analysis, it is convenient to use the proportional quantity, the metabolized exposure, defined as,

$$Y_{ij} = K_mF_{ij}/aV_m = K_m\ X_{ij}/(K_m + X_{ij}). \qquad \text{(B-3)}$$

See Figure B-1 for monkey data used to estimate K_m = 150 ppm. The analysis uses this value for humans.

The metabolized exposure has the convenient property of becoming essentially equal to (atmospheric) exposure for values of exposure sufficiently below the saturation level K_m (less than 1% error for exposure less than 1% of saturation level). Strictly speaking, Y_{ij} is the difference in metabolized exposure between the study population and the comparison population used in calculating relative risk. However, the exposure of the comparison population is usually negligible when contrasted to that of the exposed study population. The exposed study population also usually experiences the background population exposure. In the case of occupational exposures, estimation of workplace exposures effectively gives an estimate of the difference between the worker cohort exposure and the exposure of the comparison population.

In order to estimate the unit risk Q, the analysis continues by equating the modeling prediction of Equation B-1 to the risk of excess cancers in subcohort i due to the life time daily equivalent to the exposure in time period j.

$$P_{ij} = (A_{ij} - E_{ij})/N_{ij}, \quad \text{(B-4)}$$

where A_{ij} = specific (liver in this case) cancer deaths that occurred in subcohort i due to life time daily equivalent to the exposure in time period j,
E_{ij} = number of specific cancers expected to occur in the lifetime of those N_{ij} workers, based on experience in the general population,
N_{ij} = number of individuals in subcohort i during time period j.

Equating the expressions for P_{ij} in Equations B-1 and B-4, then multiplying by N_{ij} and summing over the indices i and j yields an equation for Q in terms of overall quantities that were observed or reconstructed.

$$Q\ \Sigma_{ij}N_{ij}Y_{ij}T_j/T = \Sigma_{ij}(A_{ij} - E_{ij}). \quad \text{(B-5)}$$

Dividing by the sum on the left-hand side,

$$Q = (A-E)/NY(T_y/T), \quad \text{(B-6)}$$

where Σ_{ij} = summation over i,j
$A = \Sigma_{ij}A_{ij}$, overall observed cancer deaths,
$E = \Sigma_{ij}E_{ij}$, overall expected cancer deaths,
$N = \Sigma_{ij}N_{ij}$, overall person-years exposed,
$Y = \Sigma_{ij}N_{ij}Y_{ij}/N$ overall average exposure intensity, (B-7)
T_y = actual time of exposure during each time period of one year.

Equation B-6 takes a convenient form by using an expression for relative risk, which is the SMR divided by 100.

$$Q = (R-1)(S/D)H/Y(T_y/T)N, \quad \text{(B-8)}$$

where R = A/E = relative risk,
E = STH = SH/D = expected number of deaths in the lifetime of individuals from the general population matched to those in the overall cohort,," to the definatin of E,
S = yearly background rate of this specific cancer in the general population,
H = number of individuals in the cohort,
T = 1/D = 70 years for humans,
D = probability of death in the general population per year.

The actual computations had available estimates of only the overall exposures for each time period. The analysis first proceeds by assuming that each of these estimated exposures represents the population-weighted average for that time period, so that

$$Y_{ij} = Y_j.$$

On this assumption Equation B-7 becomes the single summation,

$$Y = \Sigma_j N_j Y_j / N, \qquad \text{(B-9)}$$

where $N_j = \Sigma_i N_{ij}$, the number of individuals exposed in time period j.

The analysis next determines the effect of a distribution of subjects and exposures. In the absence of data on distributions of the number of subjects, N_{ij}, in each subcohort experiencing atmospheric exposure X_{ij} within each time period j, calculations for a uniform distribution indicate how much the actual value of Y in Equation B-7 may differ from that calculated in Equation B-9, assuming all the N_j values of X_{ij} are at one exposure level, X_j, the time-period mean. The uniform distribution is that in which, for each year (j), the number of persons exposed at each level is uniformly distributed over the exposure range from 0 to $2X_j$. With that distribution an integration produces the expression for metabolized exposure during the year, for use in Equation (B-9).

$$Y_j = (K_m/2X_j)\,[2X_j - K_m \mathrm{Ln}(1+2X_j/K_m)], \qquad \text{(B-10)}$$

where Ln is the natural logarithm of the designated argument.

A numerical exploration for Km = 150 ppm shows that the expression in Equation (B-9) is between 0.89 and 0.92 of that using the case, $X_{ij} = X_j$ in Equation B-3, over the range of exposures 100-1000 ppm. This range covers that of the study Waxweiller et al. (1976). So for each year the analysis of that study will use 0.9 times the average metabolized exposure Y_j for the year based on Barnes estimates for X_j. Therefore, the analysis multiplied 0.9 by the value of overall metabolized exposure obtained in Equation (B-9) using a single average value of metabolized exposure for each year.

Table B-4 provides quantities needed to estimate the average metabolized exposure Y in Equation B-8.

$$\Sigma_j N_j Y_j = 1.72 \times 10^6 \text{ ppm-persons}$$
$$N = \Sigma_j N_j = 1.44 \times 10^4 \text{ persons}$$

Thus the modified Equation B-7 gives the overall average metabolized exposure,

$$Y = 0.9 \times 1.72 \times 10^6 \text{ ppm} / 1.44 \times 10^4 = 108 \text{ ppm}$$

In the Waxweiler study the time during each year spent working furnishes

$$T_y = (8\text{hr}/24\text{hr})(5\text{days}/7\text{days})(46 \text{ weeks}/52\text{weeks}) \text{ yr} = 0.211 \text{ yr}$$

for all years. Equation B-8 requires this quantity.

Risk Calculations for Liver Cancer

The remaining quantity needed to obtain unit risk in Equation B-8 is the background mortality ratio S/D. The present analysis used information on deaths in the general population during the same time period as the study. Between 1960 and 1979, 67,782 deaths from liver cancer occurred among white males in the United States (International Classification of Diseases -(ICD)

codes 155,156). The total number of deaths among the same group was approximately 18,297,297. Thus, one in approximately 270 deaths was the background from liver cancer, S/D.

Finally the analysis estimates unit risk for liver cancer per person by using Equation B-8. The numerator contains the added lifetime risk of liver cancer per person, which is the excess relative risk, 10.55, times the background rate of one liver cancer death per 270 deaths to all causes or 0.039. The denominator contains the lifetime equivalent of exposure during one calendar year: the average metabolized exposure, 108 ppm, times 0.211 years of exposure divided by 70 years of life expectancy. The equation then calls for multiplying the resulting quantity by the ratio, person-years of exposure to cohort size or N/H, which is the average number of years of exposure, 11.3 years, in order to obtain the lifetime daily equivalent of average metabolized exposures.

The expected unit risk Q, then, is the lifetime added risk per person divided by the lifetime daily equivalent of average metabolized exposure, 3.6 ppm.

$$Q = (11.55-1)(1/270)\ 1294/108\ ppm\ (0.211/70)\ 14442$$
$$= 0.039/3.6\ ppm = 1.1 \times 10^{-2}\ ppm^{-1}$$

Cancer Risk Scenarios Including Brain and Lung Cancer as Well as Liver Cancer

This analysis adopts the same approach for brain cancer and lung cancer. The next sections discuss evidence for the relationship of these cancers to vinyl chloride exposure. In the absence of evidence to the contrary, the analysis assumed that the latency period is the same as for angiosarcoma of the liver. The number of deaths from brain cancer (ICD codes 191 & 192) between 1960 and 1979 in the United States was 79,847 (1/229 of deaths), and for lung cancer (ICD codes 160-163, 165) 978,504 (1/18.7 of deaths). Applying the same procedure indicated above, (R-1)S/D for the added brain cancer lifetime risk was one in 100 and, for lung cancer, was one in 33.4. Substituting these ratios in Equation B-8 yields the most likely values, given in Table B-6.

While it is clear that exposure to vinyl chloride causes angiosarcoma of the liver, the causal relationship to brain and lung cancer is not so well-defined. One review suggested that there was a consistent relationship to brain cancer in occupational studies, but not to lung cancer (Beaumont and Breslow, 1981). However, it would seem appropriate to consider lung cancer in the risk assessment along with liver and brain cancer, since this is consistent with a conservative approach and the relationship with lung cancer cannot be rejected out of hand. In fact, the report referenced above focused on statistical power independent of the degree of exposure experienced by the various cohorts reviewed. The lung cancer findings become more consistent when considered in conjunction with the liver cancer excess experienced by each cohort. Since excesses of liver cancer can be used as a surrogate indicator of exposure, this suggests that some studies not finding an excess of lung cancer may have been a result of relatively low exposures.

A more recent large study presents evidence against a relationship between lung cancer and vinyl chloride exposure (Wong et al., 1986). This

study considered deaths between 1942 and 1982 inclusive for a cohort of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride.

The SMR for liver cancer was 641, for brain cancer was 180, but for lung cancer was only 95.8. Most of the liver and brain cancer excess was in two of the 37 plants forming the cohort. Unfortunately, lung cancer SMRs were not presented for these two plants. In spite of this, the study provides evidence against a vinyl chloride-lung cancer association. However, without lung cancer data for the two plants with the highest liver and brain cancer excesses, it would seem inadvisable to exclude lung cancer from the risk assessment.

Confidence Limits for the Lifetime Risk Estimates

Confidence limits for the risk estimates are calculated by combining the risks for tumor development for each site (by summing observed and expected values for each site) and then calculating the 95% confidence limits of that single point estimate assuming a Poisson distribution. The 95% confidence interval for the liver cancer SMR is (467-2404). To estimate the upper 95% confidence limit for the excess risk estimate, the upper limit of excess risk (24.04 - 1 = 23.04) is multiplied by the lifetime risk for the average person of dying from liver cancer (1/270). Therefore, the upper 95% confidence limit for the added risk due to vinyl chloride exposure is 23.04 x 1/270 = 0.085 or 1/11.7.

The same sort of calculation estimates the upper 95% confidence limit based on liver cancer and brain cancer combined. In this case, the combined observed and expected values for liver and brain cancer (7+3)/(0.6+0.9) results in 95% confidence interval for the SMR of (319 - 1226). Thus, the upper 95% confidence limit for the excess risk estimate is (12.26-1)(1/270+1/229), or 1/11.0.

For liver cancer, brain cancer, and lung cancer combined, the observed to expected ratio is 22/9.2 and the 95% confidence interval for the SMR is (149 - 362). Using the same strategy, the upper 95% confidence limit for the estimate of added risk is (3.62 - 1)(1/270 + 1/229 + 1/18.7), or 1/6.20.

Extrapolation of Risk to Low Dose Exposure

There are many models for extrapolating risks to low exposures. The method of analysis employed here gives only one exposure point and therefore limits the models that may be used. A linear extrapolation of excess risk was chosen as the most appropriate for this analysis. This approach is very close to a one-hit model extrapolation. In turn, the one-hit model extrapolation is very close to a multistage extrapolation with linearization as recommended by the U.S. Environmental Protection Agency (EPA) Carcinogen Assessment Group for use with animal data. Thus, a simple linear extrapolation would provide similar results to the more complex multistage model approach that could have been used with more extensive data.

Equation B-1 provides the formula for downward extrapolation in the current analysis. The values of Q for each case come from use of Equation B-8. The numerator contains the

most likely value or the 95% confidence limits of (R-1)S/D for the cancer sites considered. Table B-6 provides the results for the three cancer sites.

Assumptions and Uncertainties

The confidence limits that were calculated for the risk estimates measure only the uncertainty related to the SMR statistics for workers and do not measure the uncertainty of the risk assessment process overall. This risk assessment is based on specific assumptions which, if incorrect, affect the assessment by either overstating or understating the true risk. These assumptions are listed below.

1. Assumptions are made concerning the exposure estimates. This can affect the accuracy of the risk estimates in either direction.

2. The relationship between excess relative risk and lifetime average exposure rate is assumed to be linear. If the relationship is better described by a supralinear curve, then a linear assumption will understate the risk. Conversely, if the relationship is better described by a sublinear curve, then a linear assumption will overstate the risk.

3. It was assumed that cancer risks were dependent on cumulative exposure and not on exposure rate. A given cumulative exposure achieved as an adult is assumed to carry the cancer risk equal to the same cumulative exposure starting at birth.

4. It was assumed that relative risk was dependent only on cumulative exposure and not on age.

5. Based on the pattern of excess exposure for this cohort (Smith et al., 1980), it was assumed that the dose accumulated five years prior to death was not relevant to causation of cancer.

6. The SMRs used were calculated using United States general population cancer rates. If national cancer rates were higher than local rates, the value of the SMR is underestimated, and vice versa.

7. It is assumed that lung cancer and brain cancer are causally associated with vinyl chloride exposure and that the dose accumulated in the five years immediately prior to death was not relevant to causation of cancer. If these cancers are not associated with exposure to vinyl chloride, then the true risk is overstated by including them in the analysis.

8. It is assumed that the effect of a given cumulative exposure is the same in men and women.

Conclusions

This risk assessment analysis suggests that a lifetime daily equivalent exposure to 3.6 ppm of vinyl chloride may result in an added lifetime cancer risk of 1/25.6 for liver cancer, 1/100 for brain cancer, and

1/33.4 for lung cancer, assuming each cancer is related to vinyl chloride exposure.

If one adopts a linear extrapolation approach, one would conclude that a lifetime exposure to one part per billion of vinyl chloride has a 95% upper confidence limit of 4.5×10^{-5} risk of cancer, if all these cancers are related to such exposure. In the most likely case that only liver and brain cancer are related to exposure, a lifetime to one part per billion has a 95% upper confidence limit of 2.6 x 10-5 risk of cancer.

1ppb = 4.5×10^{-5}

2.6×10^{-5}

2

Figure B-1
Rate of Adduct Formation from Exposure of Rhesus Monkeys to Vinyl Chloride
(Data points after Buchter, et al., 1980)

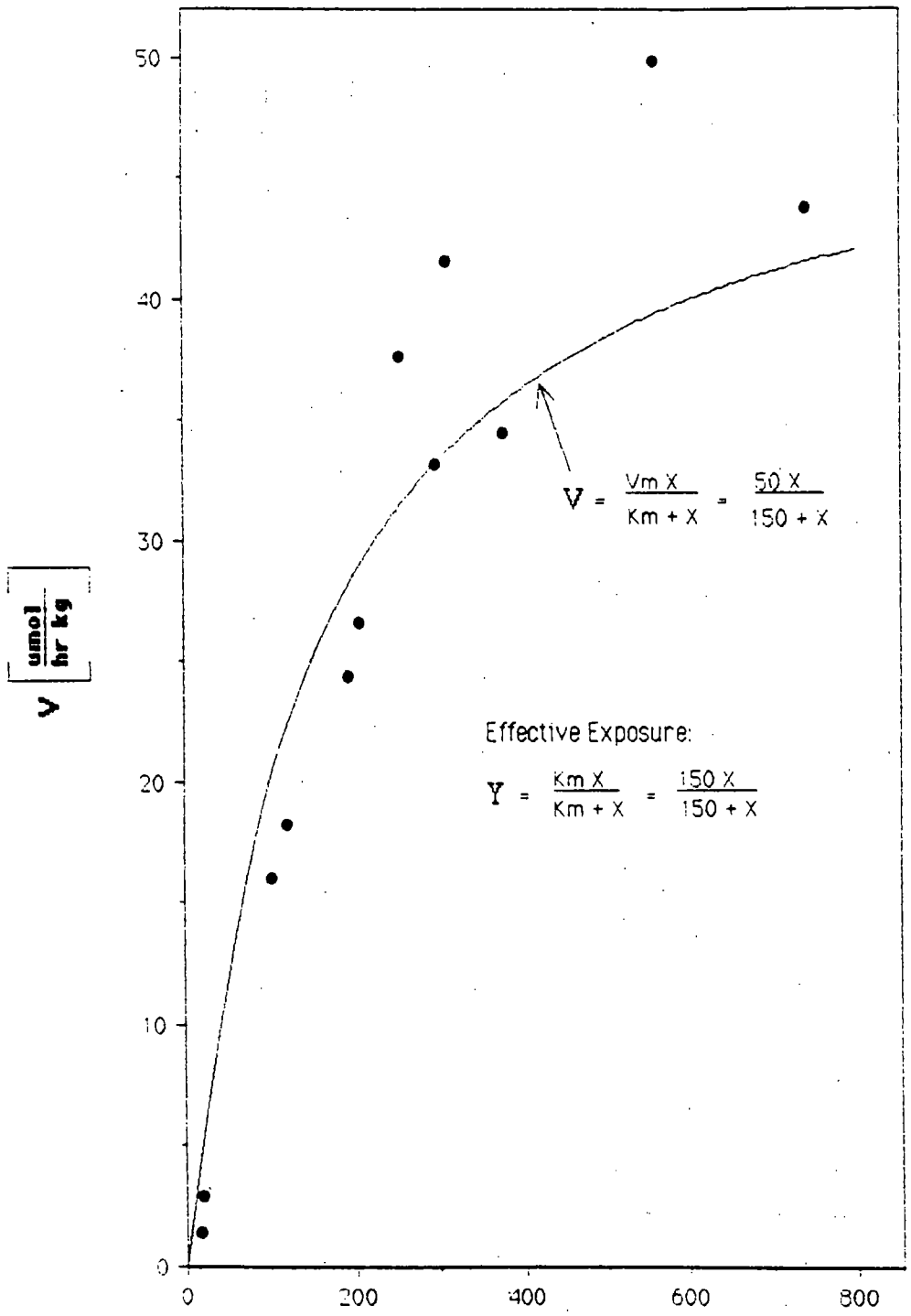


TABLE B-1

COHORT CHARACTERISTICS OF SELECTED VINYL CHLORIDE STUDIES

Author	Cohort Size	Total No. of Deaths	Number of Cancer Deaths	Range of Exposure Duration Minimum	Maximum	Longest Follow-up	Notes on Follow-up	Place of Company Involved
Byren et al., 1976	750	58	11	>0 yr 15% > 10 yrs		1940's - 1974	97%	Sweden
Cooper, 1981++	10173	707	139	> 1 yr	23 yrs	1940's - 1972	95%	37 Plants United St.
Duck et al., 1975	2120	136	35	>0 yr	> 15 yrs	1948 - 1974	99.6%	South Wal
Fox et al., 1977	7561	393	115	>0 yr 23% > 10 yrs, 8% > 20 yrs		1940 - 1974	99.1%	Great Brit
Heldaas et al., 1984	454	50	23	> 1 yr 35% > 5 yrs		1953 - 1979		
Monson et al., 1974++	*	161	41			1946 - 1974	99.2%	Louisvill Kentucky
Nicholson et al., 1975	257	24	9	----------(not given)-------		1947 - 1973		New York
Obershaw et al., 1974++	8384	352	79	> 1 yr	> 30 yrs	1930's - 1972	85%	33 Plants United St
Okamura, 1983	4524	209	37	> 1 yr	> 15 yrs	1950 - 1975		Japan
Theriault et al., 1981	451	59	20	> 5 yrs	> 30 yrs	1943 - 1974	81% > 15 yrs. 23% > 29 yrs	Canada
Waxweiler et al., 1976++	1287	136	35	> 5 yrs	27 yrs	1940's - 1973	99.5%	4 Plants I United Sta
Weber et al., 1981	7021	414	94	>0 yr	> 10 yrs	1940's - 1974	90%	West Germa
Wong et al., 1986++	10173	1536	359	>1 yr	30 yrs	1942 - 1982	92%	United Sta

*Proportional mortality study

++Overlapping cohorts of Goodrich company workers

TABLE 8-2

STANDARD MORTALITY RATIOS (AND 90% CONFIDENCE INTERVALS)
FOR SELECTED VINYL CHLORIDE STUDIES

Author	Liver				Number of Liver Angiosarcomas	Lung				Brain (CNS)			
	O	E	SMR	90% C.I.		O	E	SMR	90% C.I.	O	E	SMR	90% C.I.
Byren et al., 1976	liver and pancreas 4	0.97	413	(140.3, 982.9)	2	3	1.78	168	(45.5, 435.1)	2	0.33	612	(104.6, 1904.5)
Cooper, 1981*	digestive 29	40.8	75	(50.8, 96.9)	8	respiratory 25	23.9	107	(72.7, 146.1)	12	5.9	203	(117.3, 329.5)
Duck et al., 1975	digestive 11	11.09	99	(55.6, 164.2)	0	16	15.5	103	(64.7, 156.8)	-	-	-	- -
Fox et al., 1977	4				2	46	51.23	89.8	(69.2, 114.8)	2	3.66	54.6	(9.4, 171.2)
Heldaas et al., 1984	1	?			1	5	2.84	180	(69.2, 370.0)	-	-	-	- -
Monson et al., 1975*	biliary and liver 8	0.7	1100	(568.3, 2061.5)	5	13	7.9	160	(97.3, 261.6)	5	1.2	420	(163.8, 875.6)
Nicholson et al., 1975	3	0.12	2500	(675.2, 6454.2)	3	0	1.1	0		1	0.1	1000	(39.5, 4728.4)
Tabershaw et al., 1974*	digestive 19	21.67	94	(57.4, 128.6)	6	respiratory 25	23.93	112	(72.6, 145.9)	-	-	-	- -
Nakamura, 1983	6	2.54	236	(102.7, 466.0)	1	2	2.33	86	(14.8, 269.7)	-	-	-	- -
Theriault et al., 1981	digestive 14	5.4	259	(156.7, 405.3)	8	respiratory 2	5.78	34.6	(6.0, 108.7)	0	0.6	0	
Wagueller et al., 1976*	biliary & liver 7	0.6	1155	(547.0, 2190.6)	11 **	respiratory 12	7.7	156	(89.9, 252.5)	3	0.9	329	(90.0, 860.6)
Weber et al., 1981	12	0.79	1523	(876.3, 2460.7)	4	-	-	-	-	2	1.23	162	(28.1, 518.0)
Wong et al., 1986*	liver and biliary 37	5.77	641.2	(478.2, 843.6)	[15]	115	122	94.2	(80.3, 110)	23	12.76	180	(123.2, 255.4)

*Overlapping cohorts of Goodrich company workers.

**All confirmed cases, irrespective of meeting the five-year exposure and ten-year latency criteria of this cohort study

90% C.I. = 90% confidence interval

TABLE B-3

HISTORIC EXPOSURE LEVELS (ppm): VINYL CHLORIDE

Standards	U.K. Bornes	Location Author Year	USA Ott	USA Ott	USA Barrete et al	USA Kramer & Hutchler	USA Cook et al	USSR Filatova & Grunsberg	Lefevre et al	Romania Suciu et al	Hungary Anghelescu et al	Greece Gitelos	Sweden Byren & Hulberg
	1000	1950				Avg TWA in 1950-155 ppm							
		1951											
		1952	range TWA 5-385 ppm										
AC = 00 ppm		1953		most jobs < 80 ppm				(Pub.1957) reactor area avg: 38-310 ppm range: 15 ppm- 16,000 ppm (16K-peak) precip. & centrifuge: 8 - 3050 ppm drying ovens: 4 - 15 ppm					
		1954											
		1955	peaks = 4000			TWA range for 1950-1965: 10-300 ppm							
		1956											
	400-500	1957		one job class = 135-825									
		1958											
		1959											
		1960											
		1961	TWA range = 5-240 ppm										
		1962											
		1963											
CGIH = 0 ppm		1964											
	300-400	1965				Avg. TWA in 1965-30 ppm		1965: highest measure = 115 ppm and 75% measures were > MAC of 12 ppm	500 ppm @ scrapers' hands				
		1966											
		1967											
		1968			(Pub.1969) TWA range: 5-200 ppm					(Pub. 1967) "levels ranged as high as 2.2 ppm"	(Pub. 1969) 43-213 ppm		
		1969					(Pub.1970) reac.area: 50-100 ppm						
		1970											
SHA = 500		1971										(Pub. 1971) peak value= 10,000 ppm	(Pub. 1974) range in reactor area: 18-20 ppm
SHA = 200		1972			peaks > 1000 ppm		peaks: 600-1000 ppm @ scrapers' hands						
	150	1973											
SHA = 50		1974											
SHA = 1	5	1975											

MAC = Maximum Allowable Concentration
ACGIH = American Conference of Government Industrial Hygienists
OSHA = Occupational Safety and Health Administration
TWA = time weighted average (in ppm) based on an eight-hour day
ppm = part per million
range TWA = highest and lowest TWA reported
avg TWA = average TWA for that period
peaks = highest concentration reported (ppm). There is little documentation regarding frequency or duration of peaks
reactor area = work area around and within the vessel where polymerization took place
scraper' hands = after polymerization; workers entered vessel to scrape any buildup of polymer off the reactor vessel walls; measurements represented this exposure
precipitor, centrifuge and drying ovens = post polymerization work areas

TABLE B-4

EFFECTIVE EXPOSURE FOR WAXWEILER ET AL. (1976)

Year	Index	Workers[a]	Exposure (ppm) Estimate[b]	Exposure (ppm) Metabolized[c]	Product person-ppm[d]
		N_j	X_j	Y_j	N_jY_j
1942	1	71	1000	130	9261
1943	2	152	1000	130	19826
1944	3	191	1000	130	24913
1945	4	244	1000	130	31826
1946	5	344	1000	130	44870
1947	6	438	1000	130	57130
1948	7	538	1000	130	70174
1949	8	553	1000	130	72130
1950	9	597	1000	130	77870
1951	10	651	1000	130	84913
1952	11	681	1000	130	88826
1953	12	734	1000	130	95739
1954	13	757	1000	130	98739
1955	14	826	500	115	95308
1956	15	876	480	114	100114
1957	16	879	460	113	99428
1958	17	767	440	112	85800
1959	18	850	420	111	93947
1960	19	837	400	109	91309
1961	20	813	390	108	88075
1962	21	858	380	108	92275
1963	22	889	370	107	94884
1964	23	896	360	106	94871
	Total	14442	Weighted Average	119	

[a]Number of workers exposed.
[b]Estimates of exposure after Barnes, by linear interpolation.
[c]Metabolized exposure by modified Michaelis-Menton Equation B-2. K_m = 150 ppm.
[d]Product of number of workers times metabolized exposure.

TABLE B-5

HISTORICAL EVOLUTION OF OCCUPATIONAL EXPOSURE LIMITS[1], [2]

Year	Authority	Vinyl Chloride Limit (ppm)
1954	MAC[3]	500
1962	ACGIH[3]	500
1971	OSHA[3]	500
1972	OSHA	200
1974	OSHA	50 - temporary emergency standard over an eight hour period
Late 1974	OSHA	Proposed non detectable limit
April 1975	OSHA	1 - averaged over eight hour period with a maximum of five for 15 minutes

[1]From G. Paddle Correspondence (1986).

[2]As a point of interest, this table presents a summary of historical occupational standards for vinyl chloride.

[3]MAC - Maximum Allowable Concentration;
ACGIH - American Conference of Government Industrial Hygienists;
OSHA - Occupational Safety and Health Administration

TABLE B-6

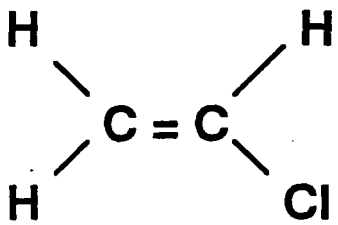
VINYL CHLORIDE UNIT RISK COEFFICIENTS FOR WAXWEILER ET AL (1976)

Cancer Site	Maximum Likelihood Estimate	Lower 95% Limit	Upper 95% Limit
Liver	1.1×10^{-5}	0.38×10^{-5}	2.5×10^{-5}
Liver and Brain	1.4×10^{-5}	0.49×10^{-5}	2.6×10^{-5}
Liver, Lung and Brain	2.2×10^{-5}	0.84×10^{-5}	4.5×10^{-5}

TECHNICAL SUPPORT DOCUMENT

PART C

PROPOSED IDENTIFICATION OF



VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California
Air Resources Board
Stationary Source Division

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PART C

STAFF RESPONSES TO PUBLIC COMMENTS ON THE VINYL CHLORIDE REPORT

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

October 1990

PART C

TABLE OF CONTENTS

I. COMMENTS RECEIVED

DRAFT

The Goodyear Tire & Rubber Company

Akron, Ohio 44316-0001

CORPORATE ENGINEERING

September 1, 1989

Air Resources Board
Toxic Air Contaminant Identification Branch
P.O. Box 2815
Sacramento, California 95812
ATTN: Vinyl Chloride
Mr. Robert Barham, Chief

Dear Mr Barham:

The following comments are offered in response to the "Report to the Air Resources Board on Vinyl Chloride - Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant".

Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants.

In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to and as reliable as the method outlined in the report should be permitted.

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An adequate review of the medical studies of the effect of exposure to vinyl chloride can not be satisfactorily completed before the end of the first comment period. Therefore, a request is being made for an extension of the initial comment period.

If you have questions, please call the writer at 216-796-2698.

Sincerely,

C A See

C A See
Environmental Engineer
Corp Environmental Engineering

CAS:cas

BFGoodrich

DRAFT

The BFGoodrich Company
3925 Embassy Parkway
Akron, Ohio 44313

September 6, 1989

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

Comments on Technical Support Document:
Proposed Identification of Vinyl
Chloride as a Toxic Air Contaminant
Part A and Part B Reports

Dear Mr. Barham:

The BFGoodrich Company welcomes this opportunity to comment on the above-captioned documents and we would like to commend CARB for accurately assembling and summarizing the extensive data describing vinyl chloride's uses, emissions, physical properties and exposure in California.

We have only two comments for your consideration. First, the primary deficiency of the CARB document on identifying VCM as an air toxic from landfills is that it fails to note these important epidemiology studies:

1) Doll, Sir R., (1988) "Effects of Exposure to Vinyl Chloride: An Assessment of the Evidence", Scandinavian Journal of Work, Environment, and Health, 14(2):61-78.

DRAFT

2) Wu, W.; Steenland, K.; Brown, D.; Wells, V.; Jones, J.; Schulte, P. and Halperin, W. "Cohort and Case-Control Analyses of Workers Exposed to Vinyl Chloride — An Update". NIOSH Report Draft, October, 1988.

3) Wong, O.; Whorton, M.D.; Ragland, D.; Klassen, C.; Samuels, D. and Chaxton, K. "Final Report — An Update of an Epidemiology Study of Vinyl Chloride Workers, 1942-1982". Prepared for Chemical Manufacturer's Association, October 17, 1986.

The second area of concern with the CARB document is more an issue of semantics; nevertheless, we offer it for your consideration. The PART A Report at pages A-1, A-17 and A-27 accurately states the following facts, but we would like to see clarifying phrases added or sentences reordered as described below.

Page A-1 to A-2

* PVC is fabricated for use in several products of which many are used by the construction industry. In California, the identified sources of vinyl chloride emissions are landfills, PVC production and fabrication facilities, and sewage treatment plants, not PVC fabricated products for consumer or construction industry use.

Page A-17 to A-18

* Plastic Materials and Consumer Products. Plastic products made of PVC and other vinyl chloride polymers are ubiquitous in most homes. Because vinyl chloride monomer can remain in the PVC resin for an extended period of time, an indirect source of indoor vinyl chloride emissions may come from the release of unreacted vinyl chloride monomer from these plastic products. However, emissions of unreacted vinyl chloride monomer have been substantially reduced due to improvements in monomer stripping technology (Wheeler, 1987). Thus, consumer products made of PVC resins no longer contain elevated residual levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride.

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In the past, residual vinyl chloride concentrations in PVC resins at the time of shipment, were as high as 2000 ppm. Curently, PVC resins contain about 10 ppm residual vinyl chloride at the time of shipment and may lose vinyl chloride at a rate of 20 to 50 percent per month during storage. In addition, most of the vinyl chloride will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products.

Page A-27

Landfill Emissions. Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emission from disposed wastes which contain vinyl chloride (i.e., chlorinated organic compounds); and and the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons.

It is hoped that by making the previously described suggested changes, the readers of Report A will more readily understand that the major source of VCM emissions in California in landfills is from chlorinated organic waste disposal, not from the disposal of PVC fabricated consumer and construction industry products.

Thank you for the opportunity to comment on the Part A and B Reports. Please feel free to call me at (216) 374-2962 should you have any questions on our proposed additions to these documents.

Sincerely,

Kathleen E. Stimler

Kathleen E. Stimler
Manager, Government Relations

6661W

The Vinyl Institute

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

September 8, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Vinyl Chloride
1102 Q Street
Sacramento, California 95812

Re: Draft Report on Vinyl Chloride

Dear Mr. Barham

On August 29th, the Vinyl Institute* received the preliminary draft report on vinyl chloride dated July 1989 being prepared by the California Air Resources Board (CARB). There has been, therefore, a limited amount of time for our membership to thoroughly review the documents prior to the comment deadline.

Nevertheless, after reviewing the document, there are at least two areas of discussion that are inadequately treated in the California Air Resources Board (CARB) document. Therefore, most of the comments will be spent on those two areas. They are the pharmacokinetic knowledge of vinyl chloride in the risk assessment approach and a total inadequate treatment of the large number of epidemiology studies in the published literature. These are very concisely dismissed by the Department of Health Services (DHS) as being unacceptable to be used in the risk assessment process for regulatory purposes.

* The Vinyl Institute is an operating division of the Society of the Plastics Industry, Inc. Its members include Air Products and Chemicals, Borden Chemicals & Plastics, Certain-Teed Corporation, Dow Chemical USA, BFGoodrich Company, Georgia Gulf Corporation, Occidental Chemical Corporation, PPG Industries, Shintech Inc., and Vista Chemical Company. Together, these companies account for more than 80% of the domestic production of both vinyl chloride and polyvinyl chloride.

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Point One: Pharmacokinetic Information. There are several publications in the literature not cited in the DHS document, that address the incorporation of pharmacokinetics in low dose risk estimation for chemical carcinogenesis. One such article was published as far back as 1980 in Toxicology and Applied Pharmacology, authored by Anderson, Hoel and Kaplan. That document demonstrates how to incorporate the pharmacokinetic information on vinyl chloride into a risk assessment approach for low dose risk estimation. There are numerous other publications on the pharmacokinetics of vinyl chloride as well. Another such document, published in 1981 in the Archives of Toxicology authored by Bolt, Filser and Buchter, demonstrates significant information that is relevant when extrapolating low level carcinogenic risk estimates from the existing data base. The DHS document fails to incorporate any of the established pharmacokinetic information in its treatment of theoretical risk for vinyl chloride.

A number of studies indicate that probably a reactive metabolite, not vinyl chloride per se is responsible for its toxicity. Although some inhaled vinyl chloride is excreted unchanged, depending on dose, a varying amount is metabolized. The metabolism of vinyl chloride has been the subject of numerous studies and it is currently thought that vinyl chloride 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. Gehring, et al. analyzed the metabolic and carcinogenic data from man and laboratory animals, and used several models to predict the incidence in man from the animal data. They found that all models over-predicted the risk to man unless corrections were made for the varying rates of metabolism and for the surface area differences of the different species.

Point Two: Epidemiology. There have been many published epidemiological investigations of occupational workers exposed to vinyl chloride at a variety of occupational exposure levels. Vinyl chloride may, in fact, be one of the most epidemiologically-studied industrial chemicals in the literature. To dismiss that data and relegate it only for comparative purposes to animal data 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 goes on to state that risk extrapolations based on the human data yield results they judge to be comparable. The practical aspect of responding to an order of magnitude or two in risk assessment can often be dramatic, therefore risk estimates that yield order of magnitude different estimates of risk are extremely important. When adequate or substantial human evidence exists, that data should be given preferential treatment in the risk assessment process.

Many of the epidemiology studies that have been in the published literature have been updated in the past year or two. One example is the study Update of Vinyl Chloride Mortality authored by Dahar, et al. which was updated as recently as 1988 and further demonstrated a decreasing cancer incidence rate in workers as the latency period has been expanded substantially. The person years in this one particular study has been expanded from only approximately 4,000 person years to over 17,000 person years, thus a substantial increase in sensitivity of the study, as only one example. The Chemical Manufacturers Association (CMA) Vinyl Chloride Panel-sponsored epidemiology study was updated as recently as 1986. It is a very comprehensive epidemiology study consisting of a cohort of over 10,000 workers employed at 37 different plants belonging to 17 different companies. That study identified at that time, over 1,536 deaths. These are only several examples of many epidemiology studies published on vinyl chloride and DHS's approach to dismiss human epidemiology evidence in their risk assessment is inadequate.

Many of the human epidemiological studies point out a statistically-significant association between an increase in lung, liver and brain cancer and exposure to vinyl chloride. For brain cancer, three out of five studies demonstrate statistically-significant findings, although the results were somewhat variable. Positive findings occurred in studies with the greatest statistical power. Most reasonable interpretation of the data is consistent with the causal association of vinyl chloride exposure and an excess of brain cancer, however, the relative risk calculation for brain cancer is much lower than that for liver cancer. 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. It is for these reasons, therefore, that the incidence rate on the angiosarcoma is the most suitable end-point for analysis of risk of exposure to vinyl chloride for a number of reasons:

1. 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.

2. Angiosarcoma has been demonstrated to occur both in animals and humans when exposed to vinyl chloride.

3. It is therefore demonstrated unlikely that any other carcinogenic result from vinyl chloride would incur lower exposures than those lowest exposures that would induce angiosarcoma. Recent publications entitled Vinyl Chloride, An Assessment of the Risk of Occupational Exposure, was published in 1987 in the Fundamentals of Chemical Toxicology Journal, Volume 25, pages 187 to 202, 1987, authored by

Purchase, et al. A very extensive evaluation of the available information at that time is included in this article, and a very comprehensive examination of risk assessment approaches to vinyl chloride is examined. We believe that this document demonstrates a much more studied and scientifically defensible approach to assessing risk of exposure to vinyl chloride.

In summary, there are at least twenty epidemiological studies which involve over 45,000 workers who have occupationally been exposed to vinyl chloride. To dismiss this body of epidemiological study in favor of basing risk assessment on animal data is questionable at best. In the paper by Purchase, et al., information that is precisely the issue being addressed by DHS is present. In addition, an epidemiological study of populations living in the vicinity of VCM production facilities had been conducted previously. This study, Barr, et al. 1982, suggests that 100 ppb represented the estimated dose representing a 1x10-6 lifetime risk in man. That value is similar to the highest estimates derived from the animal data when taking biotransformation data into account. The studies discussed in the paragraphs above, will be forwarded under separate cover.

Finally, the Vinyl Institute is extremely interested in reviewing the revised draft document before it is forwarded to the Scientific Review Panel. Please add our organization to your distribution list. Materials should be forwarded to:

Meredith N. Scheck
Assistant Director
The Vinyl Institute
155 Route 46 West
Wayne, New Jersey 07470

Thank you for your attention to this matter.

Sincerely yours,

Meredith N. Scheck

Meredith N. Scheck
Assistant Director

MNS/pmb
cc: Mr. Richard Forey
Substance Evaluation Section
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

The Vinyl Institute

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

September 12, 1989

Mr. Robert Barham, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
P.o. Box 2815
Sacramento, California 95812

Re: Draft Report on Vinyl Chloride

Dear Mr. Barham:

The enclosed article was referenced in comments submitted on September 8th by The Vinyl Institute on the Air Resources Board's Draft Report on Vinyl Chloride. I would appreciate it if this report is appended to those comments.

Sincerely yours,

Meredith N. Scheck
Assistant Director

MNS/pmb

enc.:
I.F.H. Purchase, J. Stafford and G. M. Paddle, "Vinyl Chloride: An Assessment of the Risk of Occupational Exposure", Fundamentals of Chemical Toxicology Journal, Vol. 25, No. 2, pp. 87-202 (1987).

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Vinyl Chloride - Risk Assessment

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Printed in Great Britain

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DRAFT

Review Section

VINYL CHLORIDE: AN ASSESSMENT OF THE RISK OF OCCUPATIONAL EXPOSURE*

I. F. H. PURCHASE
Central Toxicology Laboratory

J. STAFFORD
Plastics and Petrochemicals Division

and

G. M. PADDLE
Central Medical Group, Imperial Chemical Industries plc, Alderley Park, Macclesfield, Cheshire, England

(*Received* 14 *December* 1983; *revisions received* 13 *January* 1986)

Introduction

Vinyl chloride monomer (VCM), more properly named monochlorethane, is a colourless gas normally handled under pressure as a liquid which boils at −14°C at normal pressure. Discovered around 1835, VCM's commercialization did not begin until the 1930s and did not reach high volume until after 1945. Present manufacture is around 12×10^6 tonnes per annum, nearly all of which is used to make the polymer polyvinyl chloride (PVC).

Until the 1960s, VCM was regarded as a material of low human toxicity and the main concerns were related to the compound's narcotic effect. Indeed there are many reports of employees exposed to VCM monomer in polymer plants becoming dizzy and unconscious. Because VCM was considered to be relatively innocuous, it had a threshold limit value (TLV) of 500 ppm, 8-hr time-weighted average (TWA) for many years (ACGIH, 1974; Lester *et al.* 1963; Torkelson *et al.* 1961). Measurements of employee exposure were infrequent, since most measurement and warning systems were designed to ensure that plant atmospheres were beyond the explosive limits, fire and explosion being the main hazards of VCM. Retrospective estimates (Barnes, 1976) of typical TWA personal exposures (in ppm) for polymerization workers have been cited as: 1000 in 1945–1955, 400–500 in 1955–1960, 300–400 in 1960–1970, 150 in mid-1973 and 5 in 1975. However in some jobs, particularly in the cleaning of the autoclaves in which VCM is polymerized to PVC, very much higher exposures, in thousands of ppm, were undoubtedly experienced for short/medium periods, since in some plants operators became faint and unconscious from time to time.

The first clear indication of chronic health problems associated with VCM arose in the 1960s in men who entered VCM polymerization autoclaves to remove build-up of polymer from the walls. Some of these men developed acro-osteolysis (AOL: Cook *et al.* 1971; Harris & Adams, 1967; Suciu *et al.* 1963). Modification of working practices led to a reduction in the incidence of AOL cases in autoclave cleaners. Although AOL is occasionally seen in people not exposed to VCM (Meyerson & Meier, 1972; Wilson *et al.* 1967) it is a rare disease. In the late 1960s, studies in rats involving exposure to high concentrations of VCM for long periods (Viola, 1969) failed to produce AOL but showed an increase in the incidence of tumours at various sites.

Further studies (Maltoni *et al.* 1980 & 1981; Maltoni & Rondinella, 1980) showed the rare tumour angiosarcoma of the liver (ASL) in exposed rats, and confirmed VCM as an animal carcinogen. Three ASL cases in employees at a PVC polymerization plant (Creech & Johnson, 1974) confirmed VCM as a human carcinogen. Other known aetiological agents for ASL in man were thorium dioxide, arsenic and, possibly, anabolic steroids (Maltoni *et al.* 1980).

Since 1974, the health hazards of VCM have been the subject of many investigations, scientific papers, seminars and other presentations (Conference to Reevaluate the Toxicity of Vinyl Chloride Monomer, Poly(vinyl Chloride) and Structural Analogs, 1981; Gauvain, 1976; IARC Working Group, 1979; Selikoff, 1975; Szadkowski & Lehnert, 1982; US DHEW, 1980). The plethora of information (and misinformation) now available suggests that an objective historical case study of VCM would be of value.

Experimental and human data

Experimental studies

The principal effect seen in the acute and subacute studies is anaesthesia, which occurs at relatively high

*A longer version of this paper has been published in *Toxicological Risk Assessment*, edited by D. B. Clayson, D. Krewski and I. Munro and published by CRC Press, Inc., Boca Raton, FL (1985).

Abbreviations: AOL = acro-osteolysis; ASL = angiosarcoma of the liver; PVC = polyvinyl chloride; TLV = threshold limit value; TWA = time-weighted average; VCM = vinyl chloride monomer.

Table 1. Lowest concentrations or doses at which a significant excess of various tumour types was observed in rat carcinogenesis studies

Tumour	Concn (ppm)	Dose (mg/kg)
Forestomach papilloma	30,000	
Zymbal-gland carcinoma	10,000	
Neuroblastoma	10,000	
Nephroblastoma	250 (female)	
	100 (male)	
Liver angiosarcoma	200	50 (male)
	50	16.65 (female)
Mammary-gland adenocarcinoma	5 (female)	

Data from Maltoni *et al.* (1981).

doses (7–10%) in both animals and man. The doses responsible for acute toxicity are about 1000-fold higher than the minimum dose for carcinogenicity and there is frequently no sign of overt organ toxicity prior to the development of the carcinogenic response.

VCM is mutagenic in a variety of test systems including *Salmonella typhimurium* (Rannug *et al.* 1976), Saccharomyces (Loprieno *et al.* 1977) and Drosophila (Verburgt & Vogel, 1977), usually with some form of mammalian microsomal metabolizing system to convert VCM into its active metabolites, chloroethylene oxide and chloroacetaldehyde. The data on the mutagenicity of VCM provide useful qualitative information on its mode of action and metabolism, but are not suitable for the quantitative estimation of risk to man.

The most useful experimental data are derived from long-term animal carcinogenicity studies. An extensive series of 17 studies (Maltoni *et al.* 1981) gives a useful database for risk assessment. Other studies (Feron *et al.* 1981; Lee *et al.* 1978) tend to confirm the findings of Maltoni.

Carcinogenic effects were observed in mice, rats, and hamsters. A complication in the selection of these data for risk assessment is the variety of tumour types observed (Table 1). Some of these occurred at very high exposure levels, but mammary adenocarcinoma in females and ASL in both sexes of both rats and mice occurred at 50 ppm or less, exposures similar to those believed to have occurred on manufacturing plants (Barnes, 1976).

Epidemiological studies

Several major epidemiological studies on workers exposed to VCM have been reported (Table 2). The main organs that have been associated with higher incidences of cancer in workers exposed to VCM are the liver, lung and brain. Increases in the standardized mortality ratios of cancers in the buccal cavity and pharynx, of lymphomas and of cancers of the lymphatic and cardiovascular systems have been reported in one or two studies. The analysis of cancer of the respiratory system is often confounded by smoking, making quantitative analysis of the contribution of VCM difficult. The excess of liver cancers is due to an excess of ASL in many of the studies.

An analysis of the statistical power of various studies for association between VCM exposure and cancer of the lung, liver and brain (Beaumont & Breslow, 1981) concluded that the results for liver were consistent with an aetiological role for VCM. For brain cancer, where three out of five studies had statistically significant findings, the results were more variable; positive findings occurring in the studies with the greatest statistical power. The most reasonable interpretation was that the data were consistent with a causal association between VCM exposure and an excess of brain cancer. Infante (1981), in reaching the same conclusion, points out that the relative risk for brain cancer is much lower than that for liver cancer. Only two out of eight studies on lung cancer (Beaumont & Breslow, 1981) yielded statistically significant results and, because studies with a high power were negative, a causal association was considered unlikely.

ASL is the most suitable endpoint for analysis of the risk of exposure to VCM for a number of reasons. It is a rare cancer in unexposed populations, making attribution to VCM exposure on the basis of work history a reasonable approach. ASL occurs in both animals and humans exposed to VCM and it is unlikely that any other carcinogenic effect of VCM will be found to occur at lower exposures than the lowest exposures that induce ASL. For these reasons, most work on the quantitative risk assessment of chronic exposure to VCM has used ASL as the endpoint to study.

Case register

The availability of data from a comprehensive case register of ASL cases with a history of occupational exposure to VCM provides an opportunity to identify risk factors for the induction of ASL.

Persons potentially exposed to vinyl chloride

Current manufacture and use of VCM and PVC results in the potential exposure of four groups of the population. The highest exposure category covers the workers involved in the manufacture of VCM, its polymerization to PVC and certain other industrial uses of VCM. Within this group, certain occupations, particularly autoclave cleaning, involve higher potential exposure than others, although all groups would now be expected to have exposures complying with hygiene standards of 1–5 ppm.

The next category covers those exposed as a result of using the PVC. Workers in the compounding and fabrication of PVC products are exposed to residual VCM released from PVC on heating (but PVC does not decompose to VCM when heated). In general the exposure levels for these workers are very low in comparison to those for PVC polymerization workers (from 10 to 100 times lower).

Consumers who eat food and drink beverages that have been packed in PVC may ingest unreacted VCM

which has migrated into the food or beverage. Since 1974, the amount of VCM in PVC has been reduced to less than 1 mg/kg with the result that the maximum human daily intake of VCM in food and drink is 0.1 μg/day (Ministry of Agriculture, Fisheries & Food, 1978).

The fourth group with potential exposure to VCM are those who live in the vicinity of VCM or PVC manufacturing or fabricating factories. The levels in ambient air around a factory are very low (in the parts per 10^9 range) but much larger population groups, which include all age groups, are involved.

For the workers in VCM manufacture and PVC polymerization and fabrication, the route of exposure is by inhalation. Much of the animal carcinogenicity data are based on inhalation exposure and the human epidemiology is predominantly of populations exposed occupationally by inhalation. Thus an assessment of the risk factors and the quantitative risk of inhalation exposure is the main objective. For the consumer exposed to VCM via food and beverages the route is by ingestion. Relatively few experimental studies have used oral administration and only one study used a comparable exposure pattern (Feron *et al.* 1981). Similarly there are no specific epidemiological data on oral ingestion. Risk assessment for exposure via the oral route must rely on the existing animal data and on extrapolation from epidemiological and experimental studies of inhalation exposure.

Risk assessment from experimental animal data

Assumptions

In carrying out a risk assessment on the basis of animal data, a number of assumptions have to be made. The first of these relates to the overall dosimetry. Experimental animals are exposed to concentrations of vinyl chloride or dosed with amounts of vinyl chloride that allow an estimate of the amount to which they have been exposed. It is possible to calculate a correction factor for these quantities so that they are applicable to man. However, rats and mice live for relatively short periods of time (up to 2 years) during which they develop cancers of a type similar to those seen in man. The latent period for the same tumours in man may be between 20 and 40 years. It is therefore assumed that the lifetime of man is equivalent to the lifetime of an experimental animal species even though the chronological time is substantially different.

Strictly speaking, mathematical extrapolation of risk on the basis of experimental animal data provides an estimate of the risk at low doses to the experimental animal under consideration. A variety of factors, particularly inherent biological susceptibility and differences in metabolism, render the extrapolation of the data from animals directly to man subject to numerous errors. It is at this point that scientific judgement is required to decide whether these data are applicable to the human situation.

Metabolism

In rats, VCM has been shown to be metabolized extensively, producing a range of excretion products. After administration by gavage or inhalation, part of the dose is exhaled unchanged and the remainder is excreted or retained in the carcass. A general scheme

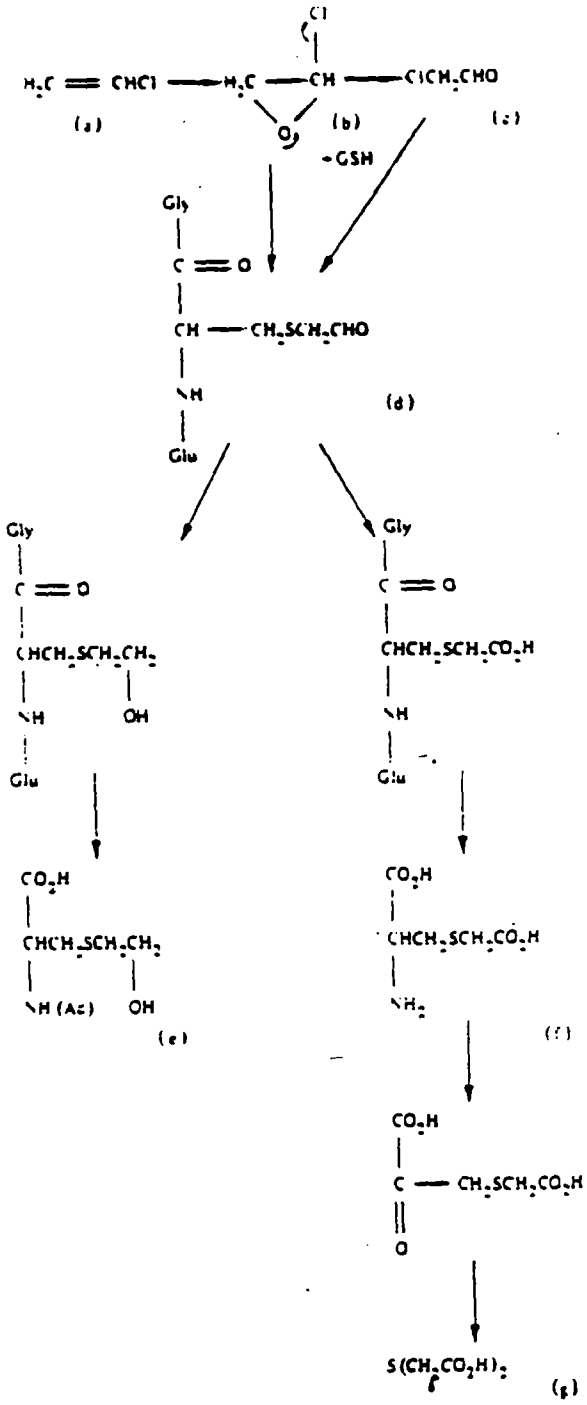

Fig. 1. Scheme showing the metabolism of vinyl chloride monomer (VCM) in rats to *S*-containing metabolites. VCM (a) is converted to chloroethylene oxide (b) which is transformed spontaneously to chloroacetaldehyde (c). These two metabolites are mutagenic and hence are considered to be the proximate carcinogens. The urinary excretion products *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (e) *S*-(carboxymethyl)-cysteine (f) and thiodiglycollic acid (g) are derived from these mutagenic metabolites via (d). Gly and Glu are the glycine and glutamate residues of glutathione. [After Green & Hathway (1977)].

Table 2. Epidemiological studies of cancer associated with exposure to vinyl chloride monomer

Reference	No. in study* (% follow up)	Sites (or tumours) with changes in SMR: Increase	No increase	Comments
Monson *et al.* (1974)	7	Brain Lung Liver, including ASL		
Tabershaw & Gaffey (1974)	8384 (85%)	Buccal cavity and pharynx Respiratory system Unknown site Lymphoma Angiosarcoma		Significant SMR not significant but increases with exposure and time
			Genital Digestive organs Urinary tract Leukaemia	
Duck *et al.* (1975)	2120	None		Some criticism of conduct of study
Nicholson *et al.* (1975)	257 (99%)	ASL		
Ott *et al.* (1975)	594 (99%)	All tumours?		Arsenicals involved
Byren *et al.* (1976)	771 (97%)	Liver/pancreas		Significant increase (2 ASL)
		Cerebral? Cardiovascular		Increase not significant
ORC (1976)	10,171 (95%)	Digestive tract		PMR study
Reinl & Weber, 1976; Reinl *et al.* 1978; Weber *et al.* 1981	11,028 (90%)	Malignant liver Lymphatic system GI tract	Brain	Related to duration of exposure
Waxweiler *et al.* (1976)	1151	Brain Respiratory tract Lymphatic system ASL		Mixed exposure, not VCM related
Fox & Collier (1977)	7409 (99%)	Primary liver ASL		Not significant Significant
			Stomach Brain Lymphatic and haemopoietic system	
Fletzel-Heyme *et al.* (1978)	1618 (95%)	Colon/stomach Prostatic hyperplasia		
Bertazzi *et al.* (1979)	5441 (86%)	All tumours		
Buffler *et al.* (1979)	464 (100%)	Respiratory system		
Chiazze & Ference (1981)	3847	Digestive system		PMR study of female and male fabricators
Chiazze *et al.* (1980)			Breast	Increase in PMR not confirmed by case-controlled study
Beaumont & Breslow (1981)		Liver Brain	Respiratory tract	Review of nine studies

Cooper (1981)	10,171 (93%)	Brain	Buccal cavity and pharynx Respiratory tract Digestive system Brain Lung		Follow up of Tabershaw and Gaffey's study. No increase in incidence of brain cancer with increase in exposure	
Theriault & Allard (1981)	1310 (97%)	Liver	Liver	No ASL		
Filatova *et al.* (1982)	3212 (100%)	Lymphatic and haemopoietic systems				
Theriault (1982)	1310 (97%)	Digestive system (liver)	Lung	Lung SMR = 42.6		

ASL = Angiosarcoma of the liver SMR = Standardized mortality rate PMR = Proportional mortality rate

*With percentage follow-up in brackets.

of VCM metabolism in rats is given in Fig. 1. On the basis of this scheme the highly reactive intermediates in the metabolic process (particularly chloroethylene oxide) react with cellular macromolecules, including DNA to produce the critical lesions leading to mutation or the induction of cancer.

Studies on the quantitative aspect of VCM metabolism have shown that there is a dose dependency in the rate of metabolism. After administration of ^{14}C-labelled VCM by gavage at doses between 0.5 and 100 mg kg to Wistar rats, the amount of ^{14}C excreted in the urine and faeces and retained in the carcass was estimated over 72 hours (Watanabe & Gehring, 1976). As the dose of VCM was increased, the proportion exhaled increased and that excreted in the urine and faeces decreased (Fig. 2). The proportion retained in the carcass also decreased. The same general trend occurred after administration by inhalation, although the magnitude of the differences in retention and excretion was less (Watanabe & Gehring, 1976).

Studies of the amount of non-volatile material retained in the carcasses of rats exposed to various levels of ^{14}C-labelled VCM for 6 hours demonstrated that the metabolism of VCM appeared to be in accordance with Michaelis–Menten kinetics (Gehring *et al.* 1978). The constants for maximum velocity of metabolism (V_m in μg metabolized 6 hr) and the Michaelis constant (K_m in μg VCM litre air) according to the formula:

$$V = \frac{V_m S}{K_m - S}$$

(where V = velocity of metabolism in μg 6 hr and S = concentration of VCM being inhaled) were $V_m = 8558\ \mu$g metabolized 6 hr and $K_m = 560\ \mu$g VCM litre air. Thus there was a considerable change in the ratio of administered dose to metabolized dose as the exposure concentration increased (Table 3). At the higher doses a smaller proportion of VCM was metabolized than at low doses.

Review of earlier calculations of risk

There have been a number of attempts to calculate the risk of ASL development on the basis of extrapolation from experimental data. These have been reviewed by Barr (1982) and an adaptation of his data is presented in Table 4.

The introduction of biotransformation data into the estimation of risk increased the level of exposure calculated to cause a 10^{-6} lifetime risk, from parts per billion to in excess of one part per million. A further refinement of the technique using DNA binding as the measure of dosimetry (Anderson *et al.* 1980) provided a similar estimate of the exposure.

A variety of mathematical models can be used for extrapolating below the experimental dose range, and it is not possible to select from amongst these mathematical models on the basis of goodness of fit to experimental data. Attempts to do so have shown that most of the models fit the data equally well (Gehring *et al.* 1979). It is equally difficult to select amongst the models on the basis of the assumed mechanism of action of VCM. Thus a comparison of the lifetime risks calculated using the Armitage–Doll

Table 3. Vinyl chloride dose and incidence of hepatic angiosarcomas in Sprague–Dawley rats exposed on 5 days wk for 52 wk*

Conc. (ppm)†	Amount metabolized: µg 4 hr	µg (total)	Angiosarcoma incidence (%): Male	Female	Mean	Expmt no.
30,000	5647	1.47×10^6	16.6	43.3	30.0	BT 6‡
10,000	5521	1.44×10^6	10.0	13.3	11.7	BT 1
6000	5403	1.41×10^6	10.3	33.3	22.0	BT 1
2500	5030	1.3×10^6	20.0	23.3	21.7	BT 1
500	3413	8.8×10^5	0	20.0	10.0	BT 1
250	2435	6.3×10^5	3.4	6.7	5.1	BT 1
200	2129	5.5×10^5	11.7	8.3	10.0	BT 2
150	1761	4.6×10^5	1.7	8.3	5.0	BT 2
100	1309	3.4×10^5	0	1.7	0.8	BT 2
50	739	1.9×10^5	1.1	7.2	4.2	BR 1, 9
25	395	1.0×10^5	1.7	6.7	4.2	BT 15
10	169	4.4×10^4	0	1.7	0.8	BT 15
5	84	2.2×10^4	0	0	0	BT 15
1	17	4.4×10^3	0	0	0	BT 15
0	0	0	0	0	0	BT 1, 2, 9, 15

*After Mahoney *et al.* (1981).
†Experiment BT 6 ended after only 68 wk, while the rest were all approximately 140 wk; therefore the percentage of tumours in BT 6 is probably low relative to the rest because of the short latency period available.

multistage model by the Food Safety Council (1980) and by Gaylor & Kodell (1980) showed that for the same 10^{-6} lifetime risk, the Food Safety Council estimated the dose as 2×10^{-2} ppm whereas Gaylor & Kodell estimated the dose as 5×10^{-4} ppm. The difference between these two estimates was due to alternative assumptions on the value of the expansion of the exponential term used.

In general, calculations based on the amount of material metabolized or on human data have produced exposure values of about 1 ppm for a 10^{-6} lifetime risk. All the other studies have produced exposure values in the ppb range. A large variable appears to be the selection of the mathematical model applied to the experimental data.

In the following section two models are used to calculate the exposure for a 10^{-6} risk from a variety of experimental animal data applying the correction for metabolism used by Gehring *et al.* (1979).

Calculation of exposure for 10^{-6} risk

A summary of the crude ASL incidence rates for inhalation studies in Sprague–Dawley rats is given in Table 3. Similar data for Wistar rats exposed by

Table 4. Summary of quantitative risk assessments for vinyl chloride monomer*

Reference	Species	Exposure for 10^{-6} lifetime risk (ppb†)	Comments
		By inhalation	
Schneiderman *et al.* (1975)	Rat	73	Probit (slope = 1, Mantel)
		119	Logit (slope = 3.45)
		2	Logit (slope = 2.3, one-hit)
Kuzmack & McGaughy (1975)	Rat, man	14	Linear through zero
		140–1400	Log-probit
Gehring *et al.* (1979)	Rat, man	> 1000	Biotransformation data included
			Linear or log-probit
	Rat	< 10–> 1000	Depends on mathematical model used
Food Safety Council (1980)	Rat	20	One-hit
		20	Armitage–Doll
		2.1×10^{-4}	Weibull
		3.9×10^{-3}	Multi-hit
Anderson *et al.* (1980)	Rat, man	> 1000	DNA binding used for dosimetry
Gaylor & Kodell (1980)	Rat	0.7	Upper 97.5% confidence limit of linear model
		0.5	Armitage–Doll
Carlborg (1981)	Rat	2.5×10^{-3}	Weibull
Barr (1982)	Man	> 100	Derived from Barr's negative epidemiology
This paper (Table 9)	Rat	0.025–9.16	Log-probit
	Mouse	2×10^{-15}	
	Man	0.63–90	Log-probit including biotransformation data for man
	Rat	2×10^{-3}–2×10^{-6}	Weibull
	Mouse	6×10^{-43}	
	Man	0.067–6.14	Weibull including biotransformation for man
		By ingestion	
EPA (1980)	Rat	4 µg/day	Food or water
NAS (1980)	Rat	3×10^{-3} mg/kg/day	Water
Crump & Guess (1980)	Man	0.7 µg/day	Applying worker data to water
	Rat	0.5 µg/day	Upper 95% confidence limits

*After Barr (1982).
†Except where stated otherwise.

inhalation (Table 5) for rats exposed orally (Table 6) and for mice exposed by inhalation (Table 7) are also presented. Data from experiments with various exposure periods of short duration are given in Table 8. For calculating the amounts of the dose metabolized in rats in the inhalation experiments, the constants calculated (Gehring *et al.* 1978) have been applied. For Wistar rats, the K_m and V_m values derived for Sprague–Dawley rats have been used. These estimates of metabolized dose have been included in the tables.

For the experiment in which VCM was given by gavage, the data from Fig. 2 were used to estimate the amount of VCM exhaled unchanged. As the $t_{\frac{1}{2}}$ for exhalation of VCM was 14 minutes, these data based on a 72-hour period give a good estimate of the fraction of VCM exhaled in the 24 hours between doses. It has been assumed that the VCM not exhaled was metabolized, an assumption similar to the one used for estimating metabolized dose in the inhalation experiments. Green & Hathway (1975 & 1977) showed that VCM administered by gavage to Wistar rats was exhaled and metabolized in a similar manner to that in the Sprague–Dawley rats, and the V_m and K_m values derived for Sprague–Dawley rats have been used. In the experiments by Feron *et al.* (1981), who used Wistar rats, the same assumptions about V_m and K_m have been made. The quantity of VCM administered has been dealt with as if it had been administered by gavage.

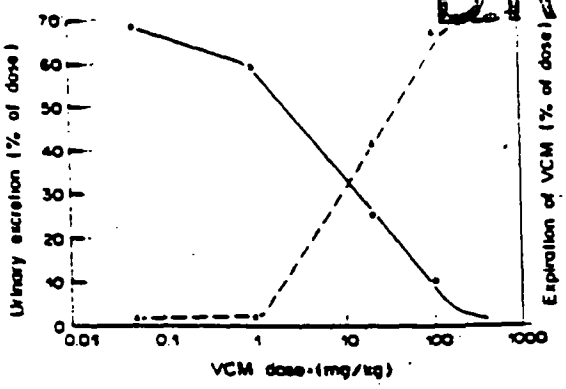

Fig. 2. Summary of dose-dependent urinary and pulmonary excretion of vinyl chloride monomer (VCM). Urinary excretion (●) represents metabolites of VCM, while pulmonary elimination (▲) is unchanged VCM. [After Watanabe & Gehring (1976)].

For mice, the data have been combined in Table 7. The estimation of the dose metabolized in mice has been calculated using values for V_m that have been adjusted on the basis that, for a chemical requiring metabolism to its active form, the quantity metabolized will be proportional to the body surface area and must be expressed in terms of metabolized dose/kg body mass. This technique has also been used by Gehring *et al.* (1978) for estimating the dose metabolized by man.

Table 5. Vinyl chloride dose and incidence of hepatic angiosarcoma in male Wistar rats exposed on 5 days/wk for 52 wk

Concn (ppm)	Amount metabolized		Angiosarcoma incidence (%)	Expmt no.
	µg/4 hr	µg (total)		
10,000	5521	1.4×10^6	29.6	BT 7
6000	5403	1.4×10^6	11.5	BT 7
2500	5030	1.3×10^6	12.0	BT 7
500	3413	8.8×10^5	10.7	BT 7
250	2435	6.3×10^5	3.7	BT 7
50	739	1.9×10^5	0	BT 7
1	17	4.4×10^3	0	BT 17
0	0	0	0	BT 7, 17

Table 6. Vinyl chloride (VCM) dose and incidence of hepatic angiosarcoma in rats given VCM by gavage or ingestion

Dose (mg/kg)	Amount exhaled* (% of dose)	Amount metabolized		Angiosarcoma incidence (%)			Expmt no.
		µg/dose†	µg (total)	Male	Female	Mean	
50‡	50	6250	1.6×10^6	20	22.5	21.2	BT 11
16.65	35	2705	7.0×10^5	10	15.1	12.5	BT 11
3.33	10	750	2.0×10^5	0	0	0	BT 11
1.0	2	3245	7.26×10^5	1.3	2.7	2.0	BT 27§
0.3	1.7	74	2.16×10^5	0	1.4	0.7	BT 27
0.03	1.4	7.4	2.16×10^3	0	0	0	BT 27
0	—	0	0	0	0	0	BT 11, 27
300‖	80	15,000	6.2×10^6	49	53	51	Feron *et al.* (1981)
14.1¶	32	2290	1.65×10^6	49	16	32	
5.0	16.5	1040	7.25×10^5	10	4	7	
1.7	2	420	2.9×10^5	0	0	0	
0	69	0	0	0	0	0	

*Calculated from data derived from Watanabe & Gehring (1976) presented in Fig. 2.
†Assuming a 250-g rat.
‡Sprague–Dawley rats dosed by gavage with VCM in corn oil 5 times/wk for 52 wk.
§BT27 dosed for 59 wk.
‖Wistar rats used as controls by Feron *et al.* (1981) and dosed for 83 wk.
¶Wistar rats receiving a diet containing VCM dissolved in PVC.

Table 5. Vinyl chloride dose and incidence of hepatic angiosarcoma in mice

Concn (ppm)	Amount metabolized: µg/4 hr	µg (total)	Angiosarcoma incidence (%) Male	Female	Mean	Expmt no
10,000	11,245	1.7×10^6	3.8	30	17.8	BT 4*
6000	11,007	1.7×10^6	6.7	36.7	21.7	BT 4
2500	10,246	1.5×10^6	20.7	33.3	27.1	BT 4
1000	8699	3.4×10^6	39.4	50.0	44.7	Lee *et al.*†
500	6952	1.0×10^6	20.0	26.7	23.3	BT 4
250	4959	7.4×10^5	30.0	30.0	30.0	BT 4
250	4959	7.4×10^5	24.0	47.0	36.5	Lee *et al.*†
50	1506	2.2×10^5	3.3	0	1.7	BT 4
1	1506	5.9×10^5	10.3	0	5.2	Lee *et al.*†
0	0	0	0	0	0	BT 4 & Lee *et al.*

*Swiss mice, 81-wk experiment; dosed for 30 wk.
†CD, mice, 52-wk experiment; 6 hr day exposure (Lee *et al.* 1978). These results have not been included in the calculations for Table 9 because the experimental design incorporated interim kills.

Thus:

$$V_e \text{ (mouse)} = V_e \text{ (rat)} \times \frac{0.011 \text{ m}^2}{0.045 \text{ m}^2}$$

$$= 5706 \ \mu\text{g/4 hr} \times \frac{0.011}{0.045}$$

$$= 1395 \ \mu\text{g/4 hr}$$

The values of 0.045 m^2 and 0.011 m^2 are the body surface area of a rat and a mouse, respectively. Since toxicity is a function of the concentration of the toxic metabolite in the tissue, the amount transformed must be normalized for mass to estimate an equivalent response. Thus V_e must be adjusted on the basis of the body weights of a rat (0.25 kg) and a mouse (0.03 kg) by dividing by 0.03/0.25 = 0.12.

The V_e for the mouse on a mass-equivalent basis is therefore:

$$\frac{1395}{0.12} = 11625 \ \mu\text{g/4 hr}$$

This value of V_e has been used in calculating the total amount of VCM metabolized (Table 7).

From the variety of models (or mathematical extrapolation techniques) used for low-dose risk extrapolation (Table 4), an arbitrary choice of models has been made to test the robustness of the extrapolation from the different animal studies.

A log-probit analysis of the dose that would be expected to produce a lifetime risk of ASL of 10^{-4} is presented in Table 9. This calculation can be carried out on the basis of the concentration inhaled, the daily dose metabolized or the total quantity metabolized during the whole experiment. There is a wide variation in the estimated dose depending on the database used for the calculation. The largest variation between doses derived from the rat experiments is 360-fold (0.025 ppb c. 9.1 ppb) when exposure in ppb is considered, but this decreases to 100-fold for other estimates of dose. The results from mice are substantially lower when expressed in ppb (2×10^{-12} ppb) but the difference is less for other expressions of dose.

Similar calculations of the dose expected to give a 10^{-4} lifetime risk of ASL have been based on a Weibull analysis (Table 9). This is a more 'conservative' mathematical model and the estimates of dose are accordingly lower. The variation in estimates of dose is, if anything, larger than that observed with the log-probit analysis (for example, a 10^{-5} difference between the S values derived from Wistar and Sprague–Dawley rats). The doses for mice are so much lower than those calculated for rats or man that the assumptions used in their calculation must be suspect.

A further calculation to derive the human dose likely to produce a risk of 10^{-4} is given in Table 9 (S calculated for man). These calculations are based on a V_e for man of 1675 µg/8 hr based on corrections for body surface area and mass. The values are substan-

Table 6. Vinyl chloride (VCM) dose and hepatic angiosarcoma incidence in Sprague–Dawley rats exposed to VCM by inhalation

Concn (ppm)	Schedule*	No. of doses	Amount metabolized: µg/4 hr	µg (total)	Angiosarcoma incidence (%) Male	Female	Mean	Expmt no.
10,000	I	260	5521	1.4×10^6	10	13.3	11.7	BT 1
10,000	II	85	5521	4.7×10^5	0	0	0	BT 3
10,000	III	25	5521	1.4×10^5	1.7	0	0.8	BT 10
10,000	IV	100	1379	1.4×10^5	1.7	0	0.8	BT 10
10,000	V	25	5521	1.4×10^5	0	1.7	0.8	BT 10
6000	I	260	5403	1.4×10^6	10.3	33.3	22.0	BT 1
6000	II	85	5403	4.6×10^5	0	3.3	1.7	BT 3
6000	III	25	5403	1.4×10^5	0	0	0	BT 10
6000	IV	100	1350	1.4×10^5	3.4	1.7	2.5	BT 10
6000	V	25	5403	1.4×10^5	0	1.7	0.8	BT 10

*After Mahoni *et al.* (1981).
†Schedules: I—4 hr/day, 5 days/wk for 52 wk; II—4 hr/day, 5 days/wk for 17 wk; III—4 hr/day, 5 days/wk for 5 wk; IV—1 hr/day, 4 days/wk for 25 wk; V—4 hr/day, 1 day/wk for 25 wk.
‡Amount metabolized (v) in 4 hour derived from the formula: $V\ (\mu g/hr) = V_m \times S\ K_m - S$ where V_m is 4/6 of the 6 hr value.

Table 9. Quantitative risk estimations derived from available animal carcinogenicity data and expressed as the amount or concentration of vinyl chloride calculated to give a lifetime risk of ASL of 10^{-5} either on the basis of log-probit analysis or a Weibull distribution

Table no.	Experimental data	Exposure for rodents (S ppb*)	Amount metabolized in 6 hr by rodents (V μg/6 hr)	Total amount metabolized by rodents (TM mg)	Exposure (ppb) calculated from V (S calculated for man)†
		Log-probit analysis‡			
4	S D rats, inhalation	0.025	1.21	0.305	0.61
5	Wistar rats, male only, inhalation	9.16	139	39.1	90
6	Rats, ingestion – Wistar	3×10^{-5} mg/kg	0.69 mg/dose	2.27	
	– S D	9×10^{-4} mg/kg	2.19 mg/dose	0.2	--
	– both§	6×10^{-4} mg/kg	1.70 mg/dose	0.88	
7‖	Mice, inhalation	2×10^{-11}	0.60	0.0063	0.03
4, 5	Wistar and S D rats combined, inhalation	0.038	1.41	0.35	0.72
8	S D rats, short-term inhalation	--	0.004	2.86	--
		Weibull distribution‖			
4	S D rats, inhalation	2×10^{-8}	0.011	0.0032	0.067
5	Wistar rats, male only, inhalation	2×10^{-1}	15.7	3.68	8.14
6	Rats, ingestion – Wistar	9×10^{-10} mg/kg	3×10^{-6} mg/dose	0.0002	
	– S D	4×10^{-6} mg/kg	0.33 mg/dose	0.003	
	– both§	2×10^{-6} mg/kg	0.005 mg/dose	0.0015	
7‖	Mice, inhalation	6×10^{-11}	2×10^{-9}	2×10^{-9}	1×10^{-9}
4, 5	Wistar and S D rats combined, inhalation	6×10^{-8}	0.0172	0.0042	0.009
8	S D rats, short-term inhalation	--	3×10^{-6}	0.19	

ASL = Angiosarcoma of the liver S D = Sprague Dawley

*Except where stated otherwise.
†Exposure calculated from V (in column 3) using the formula: S = V × 8640/1675 = V, where V_m for man is 1675 μg/8 hr.
‡Estimated using minimum likelihood.
§Wistar and S D rats combined
‖Study B1 4 only

tially higher than those calculated for the rat and mouse and there is still a range of over 100-fold in the estimates derived from the different rodent experiments. When this amount of variability occurs in the extrapolation of the risk of low-dose exposure to VCM based solely on different experiments in the same species the reliability and hence the utility of these procedures is open to question.

The general relationship between the dose administered and the incidence of angiosarcomas derived from 52-week exposure does not apply to exposures of shorter duration (Table 8). In all experiments a total metabolized dose in excess of 5×10^2 μg was required to produce an incidence of angiosarcoma in excess of 1–2%. This relationship was seen in both rats and mice and in experiments in which VCM was administered by gavage or by inhalation. In long-term inhalation studies, a total metabolized dose of 5×10^2 μg is equivalent to about 200 ppm administered over 52 weeks and represents a practical threshold for this series of experiments.

In conclusion there is a wide variation in the estimates of dose for a 10^{-6} lifetime risk. This variation is due to the type of mathematical model that is applied to the assumptions that are made and to the particular experiment that is used to provide data for the extrapolation. A high level of confidence cannot be placed on low-dose extrapolations when variables that would not be expected to alter the expression of risk have a profound effect on the estimated risk. In addition, the interspecies extrapolation from experimental animals to man is largely intuitive. It is clear that estimates of risk should take into account all available data, including epidemiology, to provide a degree of reliability.

Risk assessment from human studies

Register of ASL cases

Since 1974, lists of reported ASL cases attributable to VCM exposure in the VCM/PVC industry have been kept by NIOSH (Spirtas & Kaminski, 1978), by IARC and by the VCM Committee of the Association of Plastics Manufacturers in Europe (APME). Details of 99 cases in the APME register at the end of 1982 have been analysed by country and by manufacturing company and plant. The cases have been recorded from all major VCM/PVC manufacturing countries (Table 10), but the incidence has not necessarily been in proportion to the PVC production capacity now or prior to 1962. In the absence of data on the number of workers employed, production capacity is the only available indication of the numbers of people potentially exposed.

The majority of the ASL cases are PVC autoclave cleaners or men who have worked in or around autoclaves. There are ASL cases among men who manufactured VCM and a few cases were involved both with monomer and with polymer production. Only one case suffered from both acro-osteolysis and ASL. The ASL cases tended to occur in larger numbers in some plants than in others (Table 11). Of the total of 39 ASL cases recorded in North America, 34 have occurred at four PVC plants, while over 40

Table 11. Clustering of ASL cases in individual PVC plants

Plant no.*	Country		No. of ASL cases
	Western Europe		
1	West Germany		10
2	West Germany		4
3	West Germany		2
4	West Germany		2
1	France		5
2	France		5
3	France		2
1	UK		5
2	UK		2
1	Sweden		5
		Total...	42
	North America		
1	Canada		10
1	USA		11
2	USA		9
3	USA		4
		Total...	34
	Rest of World		
1	Japan		2
1	Yugoslavia		4
1	Czechoslovakia		2
		Total...	8

*For the purposes of this case study, it is not necessary to identify the precise ownership and location of these plants.

Table 10. Distribution of ASL cases by country

Country	No. of ASL cases	PVC production nameplate capacity (kilotonnes/yr) 1952	1962	1972
USA	29	193	704	2090
West Germany	21	22	260	1155
France	14	11	176	627
Canada	10	5	22	88
UK	7	27	177	502
Sweden	5	3	20	105
Yugoslavia	4	3	8	60
Italy	3	9	212	778
Czechoslovakia	2	1	25	48
Japan	2	12	384	1699
Belgium	1	3	25	195
Norway	1	2	20	65
Total...	99			
Western Europe	52	82	951	3950
North America	39	198	726	2178
Rest of World	8	51	709	3334
Total...	99	331	2386	9462

ASL = Angiosarcoma of the liver

Table 12. ASL case numbers by year of death and geographical location (excluding IT01*)

Year of death	ASL cases in: Western Europe	North America	Rest of world	Key publications
1955		C1		
6				
7		C2		
8				
9				
1960				
1		US8		
2		C3		
3				
4		US5	Cz2	
5				
6				
7	F1			
8		C4, C5, US4, US7, US10		
9	G1	US12, US16		
1970	Sw1	US11		Viola.
1	G2	C6, US2		
2	N1, Sw2, UK1, It2	C7		
3	G3§	C8, US1, US3, US23	Y1, Y2, Cz1	Maltoni
4	G4, G5, UK3	C9, US13		Creech & Johnson
5	F2, F3, G6, G7, G8, It3	US6, US9, US18, US26	Jap1	
6	B1, F4, F5, F6, F7, Sw3	US19, US20, US22	Jap2, Y3	
7	F8, F9, G10, G11, G12, Sw4	C10, US21, US24§		
8	F10, F11, G9, G13, G15, G16, G17	US27, US28	Y4	
9	F12, F13, UK4, UK5, G18			
1980	UK6, UK7, G19, Sw5, G20, G21	US17, US29, US30, US32		
1	It4, F14, UK8, G22			
2				
Total‡	52	38‡	6	

ASL = Angiosarcoma of the liver

*Italian case 01 was not a typical ASL: his primary tumour was probably of the pericardium. This man was engaged in extrusion of PVC sacks.

†B = Belgium, G = W. Germany, Sw = Sweden, C = Canada, It = Italy, UK = United Kingdom, Cz = Czechoslovakia, Jap = Japan, Y = Yugoslavia, F = France, N = Norway, US = USA. Thus G9 = case no. 9 in West Germany. Cases UK2, G14, US14, US15 and US25 were shown not to be associated with VCM exposure and hence withdrawn from the list.

‡Aerosol can filler.

§Cholangiosarcoma.

‡Does not include US31 (still alive).

North American PVC plants have not recorded an ASL case so far.

The average latent period between starting work in an occupation involving VCM exposure and death from ASL for the 99 cases is 21.9 years (in France, Sweden and the USA between 24 and 25 years, in Germany about 18 years). It is still too early to predict whether the annual number of ASL cases amongst VCM workers has reached a peak. ASL cases appeared earlier in North America than in Western Europe and while the occurrence is tending to decrease in North America (Table 12), it is still high in Western Europe.

On the basis of the data in this case register, it is possible to draw certain conclusions about risk factors associated with ASL. The large number of ASL cases in some factories and the absence of ASL cases in others of similar age indicates that variations in manufacturing practices between factories may be the cause. These variations may reflect both differences in the types of job carried out by individual workers and differences in engineering practices. The bulk of the cases have occurred, however, in highly exposed autoclave cleaners, with relatively few in other PVC or VCM production jobs. So far no well-authenticated cases have occurred in PVC compounding or fabrication where many more people have been exposed but to a much lower dose.

Prediction of future ASL cases as a consequence of pre-1974 exposure

The causal relationship between VCM and ASL is proved beyond doubt by the specificity of the tumour, the high relative incidence of that tumour in highly exposed workers, the consistency of the excess in different parts of the world, the time relationship between exposure and diagnosis and the dose-response relationship. An intensive analysis of the pre-1974 cohorts should establish the dose-response curve for ASL after VCM exposure and predict the likely outcome for the future.

It will be impossible to collect a complete data set on which to calculate risks of ASL for the whole world, but within a single company there may be closer definition of the cohort, the number of cases and the pattern of exposure. Using these data and averaging across the worldwide population exposed to VCM, it is possible to calculate the future incidence of ASL using relatively crude assumptions which can only be tested in time when the prediction can be judged against the final outcome.

Table 13. ASL case numbers by year of first exposure and geographical location (excluding IT01*)

Year of first exposure	ASL cases† in: Western Europe	North America	Rest of world	Key events
1939		US24‡		
40–				
1	Fr11	C3, US27		
2		US13, US29		
3	Fr14	C2, US19		
4	UK1	C1, C5, US5, US7, US28		
5	Sw2	C4, US3, US9		
6	Fr1, Fr3, Sw4	C7, C9, US8, US11, US21, US31§		
7	Sw3	C6, US22, US26		
8	Fr9	US1		
9	Fr12, Fr4	US12		
1950	Fr7, N1, UK8	US16	Y2, Cz2	
1	Sw1, UK5	US10, US32		
2	G3	US4		
3	G15, It3	C10	Jap1, Y1	
4	G7, G8, UK4, G19	US18	Y3	
5	G11, G16, G18	US2, US17, US20		
6	Fr10, G1			
7	Fr8, G4, It2, G2		Cz1	
8	Fr6, B1	US23	Jap2, Y4	
9	Fr2, It4			
1960	G5, G13			
1	G9, G10, G12, G17, G20, G22	C8		
2	G6, UK6, G21	US6		
3	Fr13, UK7			
4	Sw5	US30		
5	Fr5			
6	UK3			
7				
8				
9				
1970				Viola
1				
2				
3				Maltoni
Total...	52	39	8	

ASL = Angiosarcoma of the liver

*It01 is not consistent with other ASL cases: the primary tumour may have been of the pericardium. The man extruded PVC sacks.

†For explanatory key, see Table 12.

‡Cholangiosarcoma.

§US31 is still alive.

¶Aerosol can filler.

The data required are:

(1) Annual populations of employees classified by age;

(2) Annual exposure estimates for each person in (1);

(3) An exposure–response latency model for ASL induced by VCM.

The data under item (1) are available in the UK as a result of the data extracted from the relevant occupational records (Fox & Collier, 1977). Exposure data for item (2) are more difficult to obtain, but can be gleaned from the records that are used to define the occupational population. The problem of occupation changing, which occurred frequently, has been dealt with by using the principal employment category or the highest exposed employment category. The estimation of time-weighted average exposures for the least exposed employees is straightforward, as the exposures were essentially continuous and constant, but for autoclave cleaners, maintenance workers and laboratory workers, exposures could vary from zero to near narcotic levels. In the calculations described below, it has been possible to avoid using the exposure data directly by relying on the similarity in exposure levels in differing locations. The exposure–response–latency data indicated under item (3) can be derived from established cases.

The key data for these procedures are the set of cases worldwide, together with the descriptive data (Tables 12–14). It has been possible to calculate an incidence rate for each latency period for each exposure level for each age group (on the basis of the UK data and assuming that it is representative of the worldwide population) and to use these rates to derive a simple model of dose-response latency that can be applied to the population data. The broad conclusions are that most cases have a latency of about 20 years and cases will continue to occur for the next 10 years.

In the calculation used to estimate the future number of ASL cases (Table 15) an assumption has been made that when exposures were reduced to low levels, the future risk of ASL became negligible. Two dates at which the negligible risk levels were attained have been selected: 1964, when levels were reduced to hundreds of ppm, and 1974 when the levels were reduced to below 10 ppm following the discovery of

Table 14. Annual incidence of ASL cases (date of death) by geographical area

Year	No. of ASL cases dying in: Western Europe	North America	Rest of world	Annual total	Cumulative total	Key events
1955		1		1	1	
7		1		1	2	
1961		1		1	3	
2		1		1	4	
4		1	1	2	6	
7	1			1	7	
8		5		5	12	
9	1	2		3	15	
1970	1	1		2	17	Viola
1	1	2		3	20	
2	4	1		5	25	
3	1	4	3	8	33	Mahoney
4	3	2		5	38	Goodrich
5	6	4	1	11	49	
6	6	3	2	11	60	
7	6	3		9	69	
8	7	2	1	10	79	
9	5			5	84	
1980	6	4		10	94	
1	4	*		4	98	
2†	0	0	0	0		
Total	52‡	38*	8	98*	98*	

ASL = Angiosarcoma of the liver

*Does not include US31 (still alive in 1982).

†At time of compilation.

‡Includes G03 (aerosol can filler) but omits it01 (bag extruder).

the association between ASL and VCM exposure. A hypothetical exposed population of 100,000 has been used, but this is unimportant (see (a) below). An estimate of the age distribution within the hypothetical 'total' exposed population of 100,000 has been based on UK data (Fox & Collier, 1977). For persons already exposed during the whole of the various latent periods, the numbers with a latency of 30 years or more form only a small proportion of the total. The numbers of persons at risk in the future are calculated by advancing time in 5-year periods taking account of the age-dependent death rates in the population at large. Death rates for an intermediate year for the male population of England and Wales have been used in this calculation and the future cases (column 10) have been obtained by multiplication. The incidence figures for long latent periods (>25 years) are unreliable or non-existent but those for latencies of 15–25 years are fairly constant and values of 0.5 and 0.8 cases 1000 persons have been used for all latency periods over 15 years to calculate the expected number of cases for the 1964 and 1974 assumptions.

The calculation is unrealistic in many respects but the simplifications are unlikely to affect the estimate of future cases by more than a small factor. For example:

(a) The population size used for the calculation is probably larger than the exposed population, but the calculation depends on the ratio of "person-years to come" and "person-years experienced" and this ratio is the same for any population size.

(b) Exposure level has been ignored. The calculations are based on the overall risk to the cohort and although the incidence figures for sub-cohorts could be higher, the estimate of future cases will change very little. Similarly duration of exposure has been ignored.

Table 15. Hypothetical calculation of future ASL cases using two different assumptions about the date at which the levels became free of risk

Latency (yr)	Cases to date	Calculations assuming no risk after 1964: Persons at risk to date	5-yr incidence	Future persons at risk	Future cases	Calculations assuming no risk after 1974: Persons at risk to date	5-yr incidence	Future persons at risk	Future cases
1–5	0	100,000	0.00	0	0	100,000	0.00	0	0
6–10	1	98,250	0.01	0	0	94,500	0.01	3750	0
11–15	11	95,500	0.12	0	0	78,000	0.14	17,500	2
16–20	28	84,750	0.33	6750	2	46,500	0.60	45,000	27
21–25	28	61,400	0.46	24,550	11	28,750	0.97	57,200	57
26–30	18	36,750	0.49	41,750	20	18,750	0.96	59,750	57
31–35	6	21,250	0.28	48,100	13	10,850	0.55	58,500	32
36–40	6	6750	0.89	51,750	46	3500	1.71	55,000	94
41–45	0	600	?	45,750	?	310	?	46,350	?
46–50	0	0	?	34,500	?	0	?	34,500	?
51–	0	0	?	47,600	?	0	?	47,600	?
16–			0.50	300,750	150		0.80	403,560	323

For details of the assumptions and methods see text (pp. 197 & 198).

(c) The UK is not typical of the worldwide growth in the exposed population.
(d) No account has been taken of plant improvements occurring prior to 1964 and hence fewer cases may occur in, for example, the 1980–2000 period than are estimated from the 1940–1980 experience.

An assumption that the risk of ASL ceased in 1964 rather than in 1974 results in a considerable reduction in the estimate of future cases. For either assumption the number of new cases observed annually should soon begin to decline and the rate of decline will indicate which assumption is nearer to the truth.

There have been two other predictions of the number of cases of ASL likely to result from previous exposure to VCM. Nicholson *et al.* (1984) suggest that there will be a further 1500 cases of ASL, while Forman *et al.* (1986) conclude that a further 150–200 deaths might be expected over the next 30 years. Our estimates rely on a more sophisticated model than the latter estimate and on a larger data set than the former. Nevertheless, the conclusions of Forman *et al.* (1986) are similar to ours. Only the experience of the next few years will show which is the best estimate.

Summary and conclusions

There is little doubt that exposure to high levels of VCM as a consequence of occupation can result in an increased incidence of ASL. A review of 20 epidemiological studies involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver showed an increase in incidence in the majority of studies. For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity and pharynx, cardiovascular system and colon stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies. In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze *et al.* (1980), who did not confirm these findings in humans, are of importance.

The register of ASL cases now contains records of 99 persons with confirmed ASL and occupational exposure to VCM. The average latent period between first exposure to VCM and death from ASL is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of exposure are not available for the periods of most interest, the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of ASL. For example, ASL cases tended to occur in larger numbers in some plants than in others, a finding that can be explained most easily by differences in exposure patterns.

There is an extensive series of animal studies on the carcinogenicity of VCM. Some of these precede the epidemiological studies confirming the association between VCM exposure and ASL in man. ASL and neoplasms of a number of other organs have been induced in laboratory rodents by VCM. Estimation of the exposure levels likely to cause a lifetime risk of ASL of 10^{-6} on the basis of these data give extremely low levels (down to 3.9×10^{-7} ppb) which appear to be unrealistic estimates for man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolites chloroethylene oxide and chloroacetaldehyde. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response relationship. It has not been possible to estimate the rate of conversion in man, and hence extrapolation of these low-risk dose estimates is conjectural. The second part of the problem of extrapolation at low risk is the selection of the most suitable mathematical model for extrapolation. Using Maltoni's data from rats (Maltoni *et al.* 1981), there is a substantial range (up to 10^6) of low-risk dose estimates, depending on the mathematical model and the assumptions used in applying the models. Using the same (probit and log-dose) model and different sub-sets of experimental data, a large range of estimates is again obtained, even after correction for the non-linear kinetics of metabolism at high dose (which reduces this range to about 10^2). Larger differences are obtained with calculations using the Weibull analysis as a basis of low-dose estimation, suggesting that this is a problem with the use of mathematical models rather than one associated with the log-probit analysis. Although there was considerable variability in the dose-response relationship in the different experiments reported, in all cases a total metabolized dose of 5×10^5 μg (equivalent to inhalation of 200 ppm) was required to produce an elevation in ASL incidence. This dose represents a practical threshold in rodents. At this stage in their development, mathematical models for low-risk dose estimates are not sufficiently reliable or reproducible to engender confidence in their use.

Using negative epidemiological studies of populations living in the vicinity of VCM production facilities, an estimate of the dose for a 10^{-6} lifetime risk in man may be made (Barr, 1982). The value (100 ppb) is similar to the highest estimates derived from animal data and taking biotransformation data into account, is substantially larger than the lowest estimates, which are up to 10^{10} lower (3.9×10^{-7} ppb using a multi-hit model). The higher estimates are compatible with occupational experience and suggest that the current hygiene standard of around 1 ppm is sufficiently low to protect the health of VCM/PVC workers. The estimates also give a considerable safety factor for the general public consuming PVC-packed food and drink or living near VCM/PVC facilities.

It has been possible to provide a crude estimate of the number of cases of ASL that may occur in the future from exposure to VCM prior to 1974. Using the age structure of employees in one company, the total number of cases of ASL reported to date and the mortality pattern expected from a normal population, the possible future number of ASL cases has been estimated as in the region of 150–300.

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REFERENCES

ACGIH—American Conference of Governmental Industrial Hygienists (1974). Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1974. ACGIH, Cincinnati, OH.

Anderson M. W., Hoel D. G. & Kaplan N. L. (1980). A general scheme for the incorporation of pharmacokinetics in low-dose risk estimation for chemical carcinogenesis: example—vinyl chloride. *Toxic. appl. Pharmac.* 55, 154.

Barnes A. W. (1976). Vinyl chloride and the production of PVC. *Proc. R. Soc. Med.* 69, 277.

Barr J. T. (1982). Risk assessment for vinyl chloride in perspective. Presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, USA, June 1982.

Beaumont J. J. & Breslow N. E. (1981). Power considerations in epidemiologic studies of vinyl chloride workers. *Am. J. Epidem.* 114, 725.

Bertazzi P. A., Villa A., Foa V., Saia B., Febri L., Mapp C., Marcer C., Manno M., Marchi M. & Bottasso F. M. (1979). An epidemiological study of vinyl chloride exposed workers in Italy. *Archo higrada toxicol.* 30, 379.

Buffler P. A., Wood S., Eifler C., Suarez L. & Kilian D. J. (1979). Mortality experience of workers in a vinyl chloride monomer production plant. *J. occup. Med.* 21, 195.

Byren D., Enghol G., Englund A. & Westerholm P. (1976). Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. *Envir. Hlth Perspect.* 17, 167.

Carlborg F. W. (1981). Dose-response functions in carcinogenesis and the Weibull model. *Fd Cosmet. Toxicol.* 19, 255.

Chiazze L. & Ference L. D. (1981). Mortality among PVC-fabricating employees. *Envir. Hlth Perspect.* 41, 137.

Chiazze L., Warg O., Nichols W. E. & Ference L. D. (1980). Breast cancer mortality among PVC fabricators. *J. occup. Med.* 22, 677.

Conference to Reevaluate the Toxicity of Vinyl Chloride Monomer, Poly(vinyl Chloride) and Structural Analogs (1981). Conference sponsored by NIEHS NIOSH OSHA at NIH, Bethesda, March 1980. *Envir. Hlth Perspect.* 1981, 41, 1–231.

Cook W. A., Grever P. M., Dinman B. D. & Magnuson H. J. (1971). Occupational acro-osteolysis II. An industrial hygiene study. *Archs envir. Hlth* 22, 74.

Cooper W. C. (1981). Epidemiological study of vinyl chloride workers: mortality through December 31, 1972. *Envir. Hlth Perspect.* 41, 101.

Creech J. L. & Johnson M. N. (1974). Angiosarcoma of the liver in the manufacture of PVC. *J. occup. Med.* 16, 150.

Crump K. S. & Guess H. A. (1980). Drinking Water and Cancer. Report no. PB81-128167. NTIS, Washington.

Duck B. W., Carter J. T. & Combes E. J. (1975). Mortality study of workers in a polyvinyl chloride production plant. *Lancet* ii, 1197.

EPA (1980). Ambient Water Quality Criteria for Vinyl Chloride. Environmental Protection Agency Report, EPA 440/5-80-078 (October).

Feron V. J., Hendriksen C. F. M., Speek A. J., Til H. P. & Spit B. J. (1981). Lifespan oral toxicity study of vinyl chloride in rats. *Fd Cosmet. Toxicol.* 19, 317.

Filatova V. S., Antonyuzhenko V. A., Smulevich V. B., Fedotova I. V., Kryzhanovskaya N. A., Bochkareva T. V., Goryacheva L. A. & Bul-bulyan M. A. (1982). The blastomogenic hazard of vinyl chloride (a clinico-hygiene and epidemiological study). *Gig. Truda prof. Zabol.* 26 (1), 28.

Food Safety Council (1980). Proposed System for Food Safety Assessment: Final Report. FSC, Washington, DC. [Also in *Fd Cosmet. Toxicol.* 1980, 18, 711].

Forman D., Bennett B., Stafford J. & Doll R. (1986). Vinyl chloride and angiosarcoma of the liver—a report of the register of cases. *Br. J. ind. Med.* 42, 750.

Fox A. J. & Collier P. F. (1977). Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. *Br. J. ind. Med.* 34, 1.

Fretzel-Beyme R., Schmitz T. & Thiess A.M. (1978). Mortalitätsstudie bei VC PVC Arbeiterne der BASF Aktiengesellschaft, Ludwigshafen am Rhein. *Arbeitsmed. Sozialmed. Preventivmed.* 13, 218.

Gauvain S. (1976). Vinyl chloride. *Proc. R. Soc. Med.* 69, 275.

Gaylor D. W. & Kodell R. L. (1980). Linear interpolation algorithm for low-dose risk assessment of toxic substances. *J. envir. Path. Toxicol.* 4, 305.

Gehring P. J., Watanabe P. G. & Park C. N. (1978). Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example—vinyl chloride. *Toxic. appl. Pharmac.* 44, 581.

Gehring P. J., Watanabe P. G. & Park C. N. (1979). Risk of angiosarcoma in workers exposed to vinyl chloride as predicted from studies in rats. *Toxic. appl. Pharmac.* 49, 15.

Green T. & Hathway D. E. (1975). The biological fate in rats of vinyl chloride in relation to its oncogenicity. *Chemico-Biol. Interactions* 11, 545.

Green T. & Hathway D. E. (1977). The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. *Chemico-Biol. Interactions* 17, 137.

Harris D. K. & Adams W. G. F. (1967). Acro-osteolysis occurring in men engaged in the polymerisation of vinyl chloride. *Br. med. J.* 3, 712.

IARC Working Group (1979). *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Some Monomers, Plastics and Synthetic Elastomers and Acrolein*, p. 377. International Agency for Research on Cancer, Lyon.

Infante P. F. (1981). Observations of the site specific carcinogenicity of vinyl chloride to humans. *Envir. Hlth Perspect.* 41, 89.

Kuzmack A. M. & McGaughy (1975). Quantitative Risk Assessment for Community Exposure to Vinyl Chloride. US EPA Report, 5 December. EPA, Washington, DC.

Lee C. C., Bhandari J. C., Winston J. M., House W. B., Dixon R. C. & Woods J. S. (1978). Carcinogenicity of vinyl chloride and vinylidene chloride. *J. Toxic. envir. Hlth* 4, 15.

Lester D., Greenberg L. A. & Adams W. R. (1963). Effects of single and repeated exposures of humans and rats to vinyl chloride. *Am. ind. Hyg. Ass. J.* 24, 265.

Loprieno N., Bavale R., Baroncelli S., Barisch H., Brouzetti G., Gammellini A., Corsi C., Freza D., Nieri R., Leporini C., Rosellini D. & Rossi A. M. (1977). Induction of gene mutagens and gene conversions by vinyl chloride metabolites in yeast. *Cancer Res.* 36, 253.

Maltoni C., Lefemine G., Ciliberti A., Cotti G. & Carretti D. (1980). Epidémiologie animale et épidémiologie humane: le cas de chlorure de vinyl monomère. In *XXe Réunion de Club de Cancerogenèse Chimique*. ISBN 2.86315.007.3. p. 15. Publications Essentielles, Paris.

Maltoni C., Lefemine G., Ciliberti A., Cotti G. & Carretti D. (1981). Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. *Envir. Hlth Perspect.* 41, 3.

Maltoni C. & Rondinella R. (1980). Hepatic angiosarcoma in workers exposed to vinyl chloride in Italy. *Acta Oncologica* 1, 35 (in Italian).

Meyerson L. B. & Meier G. C. (1972). Cutaneous lesions in acro-osteolysis. *Archs Derm.* 106, 224.

Ministry of Agriculture Fisheries and Food (1978). Survey of Vinyl Chloride Content of Polyvinyl Chloride for Food Contact and of Foods. HMSO. London.

Monson R. R., Peters J. M. & Johnson M. N. (1974). Proportional mortality among vinyl chloride workers. *Lancet* ii, 397.

NAS (National Academy of Sciences) (1980). *Drinking Water and Health*. Vol. 3, p. 38. National Academy Press. Washington.

Nicholson W. J., Hammond E. C., Seidman H. & Selikoff I. J. (1975). Mortality experience of a cohort of vinyl chloride polyvinyl chloride workers. *Lancet* ii, 1197.

Nicholson W. J., Henneberger P. K. & Tarr D. (1984). Trends in cancer mortality among workers in the synthetic polymers industry. In *Industrial Hazards of Plastics and Synthetic Elastomers*: p. 65. Alan R. Liss. New York.

ORC (1976). Mortality data collected by ORC concerning the effects of vinyl chloride exposure in PVC fabrication. Cited by Barr (1982).

Ott M. G., Langner R. R. & Holder B. H. (1975). Vinyl chloride exposure in a controlled industrial environment. *Archs envir. Hlth* 30, 333.

Rannug V., Gothe R. & Wachtmeister C. A. (1976). The mutagenicity of chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride. *Chemico-Biol. Interactions* 21, 251.

Reinl W. & Weber H. (1976). Stand der epidemiologischen Forschung über die Vinylchlorid-krankheit. *Zentbl. Arb-Med. ArbSchutz* 26, 97.

Reinl W., Weber H. & Greiser E. (1978). Epidemiology study of the mortality of workers exposed to vinyl chloride in FRG. Paper presented at the 19th International Conference for Occupational Health, Dubrovnic, September.

Schneiderman M. A., Mantel N. & Brown C. C. (1975). From mouse to man—or how to get from the laboratory to Park Avenue and 59th Street. *Ann. N.Y. Acad. Sci.* 246, 237.

Selikoff I. J. (1975). Toxicity of vinyl chloride polyvinyl chloride. *Ann. N.Y. Acad. Sci.* 246.

Spirtas R. & Kaminsky R. (1978). Angiosarcoma of the liver in vinyl chloride polyvinyl chloride workers. *J. occup. Med.* 20, 427.

Suciu J., Dreyman I. & Valasku M. (1963). Contributions to the study of disease by vinyl chloride. *Med. Interna* 15, 967 (in Italian).

Szadkowski D. & Lehnert G. (1982). Vinylchlorid als Krankheitsursache: Eine Bibliographie. VKE. Frankfurt.

Tabershaw I. R. & Gaffey W. R. (1974). Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J. occup. Med.* 16, 509.

Theriault G. (1982). Cancer mortality of Canadian workers exposed to VCM: a three-year follow-up. *J. occup. Med.* 24, 730.

Theriault G. & Allard P. (1981). Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. *J. occup. Med.* 23, 671.

Torkelson T. R., Oyen F. & Rowe V. K. (1961). The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. *Am. ind. Hyg. Ass. J.* 22, 354.

US DHEW—Department of Health, Education and Welfare (1980). Selected abstracts on the carcinogenicity of VCM. DHEW. Washington, DC.

Verburgt F. G. & Vogel E. (1977). Vinyl chloride mutagenesis in *Drosophila melanogaster*. *Mutation Res.* 48, 327.

Viola P. L. (1969). Pathology of vinyl chloride. Proceedings of the 16th International Congress on Occupational Health, Tokyo.

Watanabe P. G. & Gehring P. J. (1976). Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. *Envir. Hlth Perspect.* 17, 145.

Waxweiler R. J., Stringer W., Wagoner J. K., Jones J., Falk H. & Carter C. (1976). Neoplastic risk among workers exposed to vinyl chloride. *Ann. N.Y. Acad. Sci.* 271, 40.

Weber H., Reinl W. & Grieser E. (1981). German investigations on morbidity and mortality of workers exposed to vinyl chloride. *Envir. Hlth Perspect.* 41, 95.

Wilson R. H., McCormick W. E., Tatum C. F. & Creech J. L. (1967). Occupational acro-osteolysis. *J. Am. med. Ass.* 201, 577.

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DRAFT

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STATEWIDE AIR POLLUTION RESEARCH CENTER

RIVERSIDE, CALIFORNIA 92521-0312

July 20, 1989

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

Dear Dr. Corey:

As promised in our telephone conversation of June 10, 1989, I enclose comments concerning the atmospheric chemistry of vinyl chloride, trichloroethene and tetrachloroethene (perchloroetnene). I hope that these comments are of use to you.

Yours sincerely,

Roger Atkinson

Roger Atkinson
Research Chemist

DRAFT

Comments Concerning the Atmospheric Chemistry of Vinyl Chloride

Roger Atkinson

A. Vinyl Chloride.

OH Radical Reaction.

In addition to the flash photolysis-resonance fluorescence data of Perry et al., Liu and coworkers (A. Liu, W. A. Mulac and C. D. Jonah, J. Phys. Chem., 93, 4092-4094, 1989) have used a pulsed radiolysis-resonance absorption method to determine absolute rate constants for the gas-phase reaction of the OH radical with vinyl chloride over the temperature range 313-1173 K in the presence of 1 atmosphere of argon diluent. The rate constants obtained by Liu et al. over the temperature range common to the Liu et al. and Perry et al. studies (313-423 K) are in good agreement with those of Perry and coworkers.

A product study of the gas-phase reaction of the OH radical with vinyl chloride, in the presence of NO_x, has recently been carried out by Tuazon et al. (E. C. Tuazon, R. Atkinson, S. M. Aschmann, M. A. Goodman and A. M. Winer, Int. J. Chem. Kinet., 20, 241-265, 1988) using long pathlength Fourier transform infrared (FT-IR) absorption spectroscopy to monitor the reactants and products in irradiated ethyl nitrite - NO - vinyl chloride - air mixtures in the presence and absence of ethane (used to scavenge any chlorine atoms produced from the OH radical reaction). The major products observed were formaldehyde (HCHO) and formyl chloride (HC(O)Cl), with the measured yields (corrected for secondary reactions of these products with the OH radical) being 0.96 and 0.83, respectively, in the presence of ethane and 0.89 and 0.80, respectively, in the absence of ethane. These product yield data show that HCHO plus HC(O)Cl account for essentially all of the vinyl chloride reacted, and that Cl atom production in this OH radical reaction with vinyl chloride is minor, at most. These data then agree with the reaction sequence shown on page A-46 of the vinyl chloride document.

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NO_3 Radical Reaction.

A rate constant for the gas-phase reaction of the NO_3 radical with vinyl chloride has recently been obtained, using a relative rate technique (R. Atkinson, S. M. Aschmann and M. A. Goodman, Int. J. Chem. Kinet., 19, 299-307, 1987). Combining the measured rate constant ratio at 298 ± 2 K of $k(NO_3 + \text{vinyl chloride})/k(NO_3 + \text{ethene}) = 2.08 \pm 0.09$ with the room temperature rate constant for the reaction of the NO_3 radical with ethene of 2.1×10^{-16} cm^3 $molecule^{-1}$ s^{-1} (R. Atkinson, S. M. Aschmann and J. N. Pitts, Jr., J. Phys. Chem., 92, 3454-3457, 1988) leads to a rate constant of

$$k(NO_3 + \text{vinyl chloride}) = 4.4 \times 10^{-16} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$$

at 298 ± 2 K.

Lifetime.

As noted, the lifetime of vinyl chloride in the troposphere is calculated by combining the measured rate constants for the gas-phase reactions with OH and NO_3 radicals and O_3 (and other gas-phase loss processes, if applicable) with measured or estimated ambient concentrations of OH and NO_3 radicals and O_3. Few, if any, reliable real-time measurements of ambient tropospheric OH radical concentrations exist to date. The most reliable global tropospheric OH radical concentration value is that derived from the ambient tropospheric concentrations and emission inventory of methylchloroform, leading to an annually and diurnally averaged global tropospheric concentration of 7.7×10^5 molecule cm^{-3} (Prinn et al., 1987). For the NO_3 radical, the measured lower tropospheric concentrations over continental areas range from <1 part-per-trillion (ppt) up to 430 ppt (see R. Atkinson, A. M. Winer and J. N. Pitts, Jr., Atmos. Environ., 20, 331-339, 1986). An average value of 10 ppt (2.4×10^8 molecule cm^{-3}) seems reasonable, with the recognition that this concentration is uncertain at any given time by a factor of ± 10.

Comments: - page 3

With these ambient OH and NO_3 radical concentrations, the calcula- lifetimes of vinyl chloride with respect to reaction with OH and NO_3 radicals are then 2.3 days and 220 days, respectively. Since the lifetime of vinyl chloride with respect to reaction with O_3 is (Table IV-2) ~50 days (using the rate data of Zhang et al. and Gay et al.), the OH radical reaction appears to be the dominant tropospheric loss process for vinyl chloride.

II. AIR RESOURCES BOARD STAFF RESPONSES TO COMMENTS ON PART A

DRAFT

A. Comments from the Goodyear Tire & Rubber Company

1. Comment: Clarification is requested concerning the relationship between the California 10 ppb ambient air quality standard for vinyl chloride and the 0.3 ug/day concentration of vinyl chloride which poses no significant risk to the population.

   Response: This comment is addressed in Part C, III. Department of Health Services Responses to Comments on Part B.

2. Comment: In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to, and as reliable as, the method outlined in the report should be permitted.

   Response: The ARB did not intend to imply that the sampling and analysis techniques described in the preliminary draft report on vinyl chloride should be the only method used by facilities testing for vinyl chloride.

B. Comments from the B.F. Goodrich Company

1. Comment: On page A-1 and A-2, the report should clarify that polyvinyl chloride (PVC) products used by consumers and the construction industry are not sources of vinyl chloride.

   Response: Page A-2 of the second draft report states that finished commercial PVC products are not expected to be significant sources of vinyl chloride due to current processing and shipping procedures. ARB staff can not conclude that these products have absolutely no vinyl chloride associated with them.

2. Comment: On page A-17 and A-18, the report should emphasize that consumer products of PVC no longer contain elevated residual levels of vinyl chloride monomer and are not expected to be important contributors to indoor levels of vinyl chloride.

   Response: The last sentence on page A-17 of the preliminary draft report states: "Thus, consumer products made of PVC resins no longer contain elevated levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride."

3. Comment: On page A-27 the ninth line from the top, the report should insert "i.e., chlorinated organic compounds" after, "which contain vinyl chloride".

   Response: The preliminary draft report states: "Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emissions from disposed wastes which

contain vinyl chloride; and 2) the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons." The "chlorinated organic compounds" referred to in the comment are addressed by the second mechanism.

C. Comments from Dr. Roger Atkinson of the Statewide Air Pollution Research Center at the University of California, Riverside:

1. Comment: The report (page A-44) should indicate that the results of the study of Liu and coworkers (A. Liu, W.A. Muloc, and C.D. Jonah, Journal of Physical Chemistry, 93, pp. 4092-4094, 1989) which determined absolute rate constants for the gas-phase reaction of the hydroxyl radical with vinyl chloride over the temperature range of 313 to 423° K agree with those of Perry and coworkers.

   Response: The second draft of the report reflects this additional information on page A-41.

2. Comment: The report (page A-44) should include the most reliable estimated average hydroxyl radical concentration of 7.7×10^5 molecules cm^{-3} derived by Prinn and coworkers (Prinn et al., 1987) through the use of the ambient tropospheric concentration and emission inventory of methyl chloroform.

   Response: This additional information is included on page A-41 in the second draft of the report.

3. Comment: The report (page A-46) should indicate that a study by Tuazon and coworkers (E.C. Tuazon, R. Atkinson, S.M. Aschmann, M.A. Goodman, and A.M. Winer, International Journal of Chemical Kinetics, 20, pp. 241-265, 1988) confirmed the study by Pitts and coworkers (Pitts et al., 1984) which demonstrated that the reaction of one molecule of vinyl chloride with hydroxyl radicals yields one molecule of formyl chloride.

   Response: This additional information is included on pages A-42 and A-43 in the second draft of the report.

4. Comment: The report (page A-47) should include new data (R. Atkinson, S.M. Aschmann and M.A. Goodman, International Journal of Chemical Kinetics, 19, pp. 299-307, 1987 and R. Atkinson, S.M. Aschmann and J.N. Pitts, Jr., Journal of Physical Chemistry, 92, pp. 3454-3457, 1988) concerning the rate constant of the gas-phase reaction of vinyl chloride and the nitrate radical.

   Response: This new data is included on pages A-43 and A-44 in the second draft of the report.

III. DEPARTMENT OF HEALTH SERVICES RESPONSES TO COMMENTS ON PART B

DRAFT

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 of 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.

Response to Comments: The Goodyear Tire and Rubber Company

Comment: "Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants." (sic)

Response: As pointed out at page A-1 of the risk assessment document, the Air Resources Board in 1978 adopted 10 ppb as the ambient air quality standard for vinyl chloride in California. That standard is not to be exceeded in air within the jurisdiction of the Air Resources Board.

The rate of intake of vinyl chloride which poses "no significant risk" under Health and Safety Code 25249.10 is 0.3 μg/day. DHS determined that intake rate to ensure that the estimated lifetime risk of cancer from intake of vinyl chloride by all routes is less than 10^{-5} or one chance in a hundred thousand, taking the carcinogenic potency of vinyl chloride to be 2.3/(mg/kg-day) in accordance with the U.S. EPA (1984) assessment based on a diet study. For exposure by inhalation alone that EPA potency is equivalent to a unit risk of 7×10^{-4} ppb^{-1} vinyl chloride for a 70kg human breathing 20 m^3/day with 40% absorption. Thus, the potency used to calculate the current intake rate for no significant risk corresponds to a unit risk that is above the range of unit risks for inhalation in the revised risk assessment document. See Figure 8.1 of the revised document for more information.

The quantitative relationship of the 0.3 μg/day intake rate to the 10 ppb air quality standard is obtained by converting the 10 ppb (26 $\mu g/m^3$) to its equivalent intake rate of 210 μg/day for a human breathing 20 m^3/day with 40% absorption. Thus, the air quality standard, which was set at the detection limit at the time of adoption (1978), is 690 times greater than the existing DHS determination of intake rate posing "no significant risk."

Response to Comments: The B.F. Goodrich Company

Comment: The "primary deficiency of the CARB document on identifying VCM as an air toxic from landfills is that it fails to note these important epidemiology studies:

1. Doll, Sir R., (1988) "Effects of Exposure to Vinyl Chloride: an Assessment of the Evidence", Scandinavian Journal of Work, Environment, and Health, 14(2):61-78.

2. Wu, W.; Steenland, K.; Brown, D.; Wells, V.; Jones, J.; Schulte, P. and Halperin, W. "Cohort and Case-Control Analyses of Workers Exposed to Vinyl Chloride - an Update". NIOSH Report Draft, October, 1988.

3. Wong, O.; Whorton, M.D.; Ragland, D.; Klassen, C.; Samuels, D. and Chaxton, K. "Final Report - An Update of an Epidemiology Study of Vinyl Chloride Workers, 1942-1982". Prepared for Chemical Manufacturer's Association, October 17, 1986."

Response: Reference to Doll's recent review of cancer mortality in occupational studies is a useful addition to the risk assessment, and it has been included in the revised document.

The Wu et al. study has recently been published in the Journal of Occupational Medicine 31(6) 518-523 (1989). That study provides useful additional information on following up the worker outcomes for one of the four plants of the Waxweiler (1976) study of vinyl chloride workers. DHS staff has included a discussion of this recent work in the revision.

The Wong et al study, an industry-wide compilation, remains unpublished. Nevertheless, the original version of the risk assessment did cite it by authors in Tables B-1 and B-2, and by corporate authorship, Environmental Health Associates, in the list of references. The revision uses a consistent method to site this work (Wong et al., 1986).

IV. LANDFILL GAS TESTING PROGRAM UPDATE

DRAFT

IV. LANDFILL GAS TESTING PROGRAM UPDATE

Landfill Gas Testing Program data on page A-31 of the preliminary draft report were amended on page A-29 of the second draft to include test results through December 1989.

V. AIR RESOURCES BOARD STAFF LETTER TO THE GOODYEAR TIRE AND RUBBER COMPANY REGARDING THE REQUEST FOR AN EXTENSION OF THE FIRST COMMENT PERIOD

...E OF CALIFORNIA
AIR RESOURCES BOARD
... O STREET
... BOX 2815
SACRAMENTO CA 95812

George Deukmejian, Governor

DRAFT

September 29, 1989

C.A. See
Corporate Environmental Engineering
Department 1100
Goodyear Tire & Rubber Company
1144 East Market Street
Akron, Ohio 44316-0001

Dear Ms. See:

Thank you for your response to the draft report Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant. Your comments will be considered and addressed in Part C of the second draft of the report.

The second draft of the report will be mailed to you and other members of the public for final review. It will include Parts A, B, and C of the report as well as an executive summary which summarizes Parts A and B. A 20-day comment period will be given for your review. During this comment period, only comments on the executive summary and any revisions made to the report will be accepted. All of the comments received and our responses will then be incorporated as an addendum to Part C. The final draft report, including Part C, will then be submitted to the Scientific Review Panel for its review.

The Scientific Review Panel has requested that all public comments be directed to the Air Resources Board within the time spans allotted for the two comment periods. In accordance with this process, we are unable to extend the first comment period as you requested.

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

Sincerely,

Robert Barham, Chief
Toxic Air Contaminant
Identification Branch

DRAFT

The Goodyear Tire & Rubber Company

Akron, Ohio 44316-0001

CORPORATE ENGINEERING

September 1, 1989

Air Resources Board
Toxic Air Contaminant Identification Branch
P.O. Box 2815
Sacramento, California 95812
ATTN: Vinyl Chloride
Mr. Robert Barham, Chief

Dear Mr Barham:

The following comments are offered in response to the "Report to the Air Resources Board on Vinyl Chloride - Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant".

Clarification is requested concerning the relationship between the California ambient air quality standard for vinyl chloride - 10 ppb, as it was discussed in the report, the level of concentration of vinyl chloride which poses "no significant risk" to the population - 0.3 micrograms/day and the interaction of these two values in the regulation of toxic air contaminants.

In the sampling and determination of the concentration of vinyl chloride, the use of analytical techniques comparable to and as reliable as the method outlined in the report should be permitted.

DRAFT

An adequate review of the medical studies of the effect of exposure to vinyl chloride can not be satisfactorily completed before the end of the first comment period. Therefore, a request is being made for an extension of the initial comment period.

If you have questions, please call the writer at 216-796-2698.

Sincerely,

C A See

C A See
Environmental Engineer
Corp Environmental Engineering

CAS:cas

I. PART C ADDENDUM
COMMENTS RECEIVED

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION IX
215 Fremont Street
San Francisco, CA 94105

June 8, 1990

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Air Resources Board
Attn: Vinyl Chloride
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma,

Thank you for the opportunity to comment on the Air Resources Board's technical support document entitled "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant" dated May 1990. Please incorporate the comments listed below into the the final report. Also, the Environmental Protection Agency's risk assessment group is conducting a detailed review of the report. Any additional comments resulting from this review will be delivered by June 22 of this month. Ms. Barbara Cook of your office assured me that these additional comments will be addressed by the Scientific Review Panel.

Please note that the Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. As part of the Remedial Investigation at the site, EPA is conducting a 12-month ambient air quality study at the OII landfill. Twenty-four hour air samples are being collected every eighth day at nine permanently located stations (including 2 background stations) near the landfill. The detection limit for vinyl chloride for this study is 0.30 parts per billion. Meteorological data is also being collected for this study. The results of this study will be used to support EPA's risk assessment for the OII landfill.

Please include the following paragraph in the Executive Summary:

> The Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. Subsequent to the Air Resources Board's vinyl chloride sampling during 1987, the Environmental Protection Agency (EPA) has implemented more stringent landfill gas control measures. EPA has also selected a remedy for landfill gas control that is expected to substantially reduce landfill gas emissions from the OII landfill. It is fully anticipated that these control measures will substantially lower the levels of vinyl chloride in the ambient air in the vicinity of the OII landfill.

Thank you for the opportunity to comment.

Sincerely,

for Sheila Susman
Roy Herzig,
Environmental Engineer

Waste Management of North America, Inc.
Government Affairs
925 L Street, Suite 970
Sacramento, California 95814
(916)448-6675
Fax: (916)448-2471

June 11, 1990

Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
AIR RESOURCES BOARD
P.O. Box 2815
Sacramento, CA 95812

ATTENTION: Vinyl Chloride

SUBJECT: PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT BY THE CALIFORNIA AIR RESOURCES BOARD (ARB)

Thank you for the opportunity to provide comment on the ARB's proposal to identify vinyl chloride as a toxic air contaminant. Waste management of North America (WMNA) is a comprehensive waste management services company owning and operating, among other things, landfills and waste hauling companies in the State of California. In addition, Chemical Waste Management, Inc. (CWM) provides comprehensive hazardous waste management services including hazardous waste collection, transportation, treatment, and disposal in California.

Both WMNA and CWM are supportive of your efforts to identify vinyl chloride as a toxic air contaminant. Indeed, identification of this compound as a toxic air contaminant is mandated by state law by virtue of the fact that it is identified as a hazardous air pollutant pursuant to federal law. However, we are concerned about the bases for identification that are contained in your staff report in two primary areas:

1. Presence of vinyl chloride in the atmosphere and the inference that landfills in California are the principle source of this proposed toxic air contaminant, and

2. The degree of public health risk that is posed by vinyl chloride.

LANDFILLS AS A SOURCE OF VINYL CHLORIDE

On page A-23, the second paragraph states, "Based on the emission estimates for two landfills in California (BKK and OII), landfills are the largest identified source category of vinyl chloride emissions in the state. The information necessary to estimate vinyl chloride emissions for the hundreds of other landfills in California is not available." Other references to landfills being the largest source of vinyl chloride emissions are made elsewhere throughout the report. It is erroneous to assume that these two landfills are representative of all landfills. Both BKK and OII are landfills that are currently included on the state superfund list of hazardous substance release sites. Both of these sites are reported to have accepted significant quantities of waste vinyl chloride during their operating life.

In fact, contrary to the statement made above, significant information DOES exist that landfills are NOT a significant source. The Air SWAT programs mandated by Health and Safety Code Section 41805.5 show that waste management units operated by WMNA are not a significant source of vinyl chloride emissions. Unfortunately the ARB's report makes only passing reference to the Air SWAT data. Even this passing reference indicates that, while the presence of vinyl chloride has been detected in some landfills, the concentrations and amounts are vastly lower that those represented by BKK and OII. Rather than attribute vinyl chloride emissions to landfills, the report would be more accurate in attributing such emissions to superfund sites that once received vinyl chloride waste for disposal.

Attached to this letter I have included summary tables of the Air SWAT results for six of the landfills owned and operated by WMNA. This data shows that, while vinyl chloride is detectable at low to very low levels within the landfills themselves it is, with only minor exception, virtually undetectable in surface samples and in downwind ambient air samples. Finalization of the rulemaking for vinyl chloride as a toxic air contaminant should be delayed until this recent and very critical information can be properly incorporated into the report. In fact, section 39660(f) of the Health and Safety Code mandates that DHS and the ARB give priority to the evaluation and regulation of substances as air toxic contaminants based on a variety of factors including amount or potential amount of emissions and ambient concentrations in the community. To proceed with identification of vinyl chloride as a toxic air contaminant while identifying landfills as the largest source of emissions based on two unrepresentative sites would be

a disservice to the waste management industry and contrary to state law. This is made even more true by not using readily available Air SWAT data which provides a much more accurate indication of the true contribution of waste management units to emissions of vinyl chloride.

PUBLIC HEALTH RISK OF VINYL CHLORIDE

While we do believe that it is ultimately appropriate to regulate vinyl chloride as an air toxic contaminant, we are concerned that the unit risk factor that you have attributed to this compound is overly conservative. I have also attached to this letter a copy of a brief paper on Carcinogenic Risks from Landfill Emissions dated June 6, 1988. This paper was submitted in comment on a preliminary draft document circulated by EPA in March, 1988, "Air Emissions from Municipal Solid Waste Landfills--Background Information for Proposed Standards and Guidelines". This information provides a much more realistic assessment of the health risks posed by municipal landfills not only from the standpoint of vinyl chloride but a number of other compounds as well. In summary this brief paper, based on an assessment of the cumulative impact of all landfill emissions, concludes, "Using a dispersion model for area emissions, we find that for persons spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for persons staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}."

In addition, I have attached some specific comments prepared by Dave Dolan, Waste Management Inc. toxicologist, listing specific concerns we have pertaining to the risk assessment information contained in the ARB's Technical Support Document for Vinyl Chloride. The report Mr. Dolan cites in his second item (U.S. EPA, 1985) is entitled, "Techniques for the Assessment of the Carcinogenic Risk to the U.S. Population due to Exposure from Selected Volatile Organic Compounds from Drinking Water via the Ingestion, Inhalation, and Dermal Routes".

RECOMMENDATION

Due to the fact that the ARB knows that the Air SWAT data is now available to assess the impact of vinyl chloride, identification of vinyl chloride as an air toxic contaminant should more properly be delayed until this information can be included in the report to provide a realistic assessment of landfills as a very limited source of risk to adjacent communities.

Thank you for the opportunity to comment on your draft Technical Support Document. If you have any questions or concerns pertaining to these comments, please do not hesitate to contact me.

Sincerely,

Charles A. White, Manager
Regulatory Affairs

CAW:fal
Attachments
cc: Dave Dolan
Sara Broadbent
Sue Briggum

TABLE 2-1
SUMMARY OF ALTAMONT ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared with Upwind Concentration) 24-Hour Continuous
	Landfill Gas	Integrated Surface Sample	
Primary Target Monitoring Compound			
Vinyl Chloride	3,000	3.0	0.0
Supplemental Target Monitoring Compounds			
Benzene	<500	<2.0	--
Ethylene Dibromide	<50	<0.5	--
Ethylene Dichloride	32	<0.2	--
Methylene Chloride	21,000(a)	<1.0	--
Perchloroethylene	5,400	0.8(b)	--
Carbon Tetrachloride	<5	<0.2	--
Methyl Chloroform	210	0.5(c)	--
Trichloroethylene	8,600	0.9(d)	--
Chloroform	430	<0.8	--
Methane	480,000,000	3,000	--

Note: ppbv = parts per billion by volume.

(a) This result is potentially due to limitations of the analytical methods specified by the ARB in the Testing Guidelines (i.e., a non-Calderon constituent may coelute with methylene chloride).
(b) Altamont integrated surface sample value of 0.8 ppbv for perchloroethylene is similar to the ARB background value of 0.6 ppbv for the Bay Area Region (1985 data) in which Altamont is located.
(c) Altamont integrated surface sample value of 0.5 ppbv for methyl chloroform is nearly identical to the laboratory detection limit (<0.5 ppb), and is well below the ARB background value of approximately 2.1 ppbv for the Bay Area Region (1985 data) in which Altamont is located.
(d) Altamont integrated surface sample value of 0.9 ppbv for trichloroethylene is similar to the ARB background value of approximately 0.5 ppbv for the Bay Area Region (1985 data) in which Altamont is located.

TABLE 2-1
SUMMARY OF LANCASTER ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared with Upwind Concentrations)	
	Landfill Gas(c)	Integrated Surface Sample	24-Hour Continuous(c)	Directionally Controlled(c)
Primary Target Monitoring Compound				
Vinyl Chloride	4,629	<2.0	0.2(b)	0.0
Supplemental Target Monitoring Compounds				
Benzene	571	<2.0	0.0	0.0
Ethylene Dibromide	<1	<0.5	0.0	0.0
Ethylene Dichloride	<20	<0.2	0.0	0.0
Methylene Chloride	2,094	<1.0	4.0(b)	2.3(b)
Perchloroethylene	578	0.4(a)	0.2 (b)	0.0
Carbon Tetrachloride	<5	0.8	4.8 (b)	0.7(b)
Methyl Chloroform	824	<0.5	0.9(b)	3.7(b)
Trichloroethylene	442	<0.6	0.0	0.0
Chloroform	40	<0.8	0.0	0.0
Methane	62,000,000	10,000	-	-

Note: ppbv = parts per billion by volume.

(a) Lancaster integrated surface sample value of 0.4 ppbv for perchloroethylene is similar to the ARB background value of 0.2 ppbv for the Southwest Desert Region in which Lancaster is located (see Table 2-2).
(b) These downwind ambient increments are greater than expected considering the low concentrations for the integrated surface samples and landfill gas samples. However, these downwind increments are less than 5 ppbv, which corresponds to inherent data uncertainties with ASWAT ambient air data associated with limitations of the analytical methods specified by the ARB in the Testing Guidelines.
(c) Based on composite data which includes all samples.

TABLE 2-1
SUMMARY OF DAVIS STREET ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient
	Landfill Gas	Integrated Surface Sample	24-Hour Ambient Air (Net Downwind Increase Compared with Upwind Concentration)[a]
Vinyl Chloride	<500	<2.0	0.0
Benzene	<500	<2.0	0.0
Ethylene Dibromide	<1	<0.5	0.0
Ethylene Dichloride	<20	<0.2	0.0
Methylene Chloride	<60	8[b]	0.0
Perchloroethylene	<10	<0.2	0.0
Carbon Tetrachloride	<5	<0.2	0.0
Methyl Chloroform	<10	1.1[c]	0.4[d]
Trichloroethylene	<10	<0.6	0.0
Chloroform	<2	<0.8	0.0
Methane	530,000,000	<2000	

Note: ppbv = parts per billion by volume.

(a) Based on composite data for all sampling days.
(b) Davis Street integrated surface sample value is higher than expected considering the nondetection of this constituent in the landfill gas sample. The reported value may have been affected by ambient background levels, which may exceed 10 ppbv in the Bay Area (see Table 2-2), and/or limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines, which may result in data uncertainties of approximately 5 ppbv.
(c) Davis Street integrated surface sample value of 1.1 ppbv is higher than expected considering the nondetection of this constituent in the landfill gas sample. The reported value is similar to the background value of 1.4 ppbv based on BAAQMD data for San Leandro. (See Table 2-2.)
(d) This downwind concentration increment may be due to limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines, which may result in data uncertainties of approximately 5 ppbv. The results presented above do not include the primary sampler results, which have a contamination bias of approximately 4 ppbv.

TABLE 5-1
SUMMARY OF DURHAM ROAD ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air (Net Downwind Increase Compared to Upwind Concentration)
	Landfill Gas	Integrated Surface Sample	24-Hour Continuous
Primary Target Monitoring Compound			
Vinyl Chloride	3,000	<2.0	0.0
Supplemental Target Monitoring Compounds			
Benzene	1,000	<2.0	--
Ethylene Dibromide	<1	<0.5	--
Ethylene Dichloride	<20	0.2	--
Methylene Chloride	7,500	<1.0	--
Perchloroethylene	5,200	0.3[a]	--
Carbon Tetrachloride	<5	<0.2	--
Methyl Chloroform	300	1.3[b]	--
Trichloroethylene	2,000	<0.6	--
Chloroform	260	<0.8	--
Methane	520,000,000	<2,000	--

Note: ppbv = parts per billion by volume.

(a) Durham Road integrated surface sample value of 0.3 ppbv for perchloroethylene is similar to the ARB background value of 0.6 ppbv for the Bay Area Region (1985 data), in which Durham Road is located.

(b) Durham Road integrated surface sample value of 1.3 ppbv for methyl chloroform is similar to the ARB background value of approximately 2.1 ppbv for the Bay Area Region (1985 data), in which Durham Road is located.

TABLE 2-1
SUMMARY OF BRADLEY ASWAT RESULTS (ppbv)

	Gas Characterization[c]		Ambient Air (Net Downwind Increase Compared with Upwind Concentrations)[c]	
	Landfill Gas	Integrated Surface Sample	24-Hour Continuous	Directionally Controlled
Primary Target Monitoring Compound				
Vinyl Chloride	33,625[a]	2.5	0.2	0.0
Supplemental Target Monitoring Compounds				
Benzene	900	1.5	0.1	0.3
Ethylene Dibromide	<3	<0.5	0.0	0.0
Ethylene Dichloride	<30	<0.2	0.0	0.0
Methylene Chloride	2570	<1.0	0.0	1.3
Perchloroethylene	375	0.4	<0.1	0.1
Carbon Tetrachloride	<5	0.2	<0.1	0.0
Methyl Chloroform	<10	7.5[b]	0.8	0.0
Trichloroethylene	1435	<0.6	0.0	0.0
Chloroform	<4	<0.8	0.3	0.6
Methane	500,000,000	<5,000	—	—

Notes: 1. ppbv = parts per billion by volume.
2. The landfill gas samples were collected in December 1987/August 1988, integrated surface samples in May 1988/August 1988, and ambient samples in May 1988.

(a) Based on composite data, which include all downwind samples.
(b) This result may have been affected by sample matrix interferences, coelution of constituents with similar GC retention times, and other inherent limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines. Ambient air concentration results confirm that Bradley Landfill gas emissions for this constituent do not affect offsite air quality.
(c) Value is similar to the ARB range of background values (1.11 - 7.07) for the South Coast Region.

TABLE 2-1
SUMMARY OF KIRBY CANYON ASWAT RESULTS (ppbv)

	Gas Characterization		Ambient Air
	Landfill Gas	Emission Screening	24-Hour Continuous Downwind(a)
Vinyl Chloride	41,000(b)	—	<2.0
Benzene	2,500	—	<2.0
Ethylene Dibromide	<1	—	<0.5
Ethylene Dichloride	<20	—	<0.2
Methylene Chloride	59,000(b)	—	<1.0
Perchloroethylene	2,100	—	0.7(c)
Carbon Tetrachloride	<5	—	<0.2
Methyl Chloroform	190	—	1.0(d)
Trichloroethylene	2,200	—	<0.6
Chloroform	2,000	—	<0.8
Methane	2,600,000	<50,000	—

Note: ppbv = parts per billion by volume.

(a) One sample day with two collocated samplers.
(b) These results may have been affected by sample matrix interferences, co-elution of constituents with similar GC retention times, and other inherent limitations of the ASWAT analytical methods specified by the ARB in the Testing Guidelines. Ambient air concentration results confirm that Kirby Canyon Landfill gas emissions for these constituents do not affect offsite air quality (in fact, they were not detected in the ambient samples).
(c) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, this concentration of 0.7 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.5-0.8 ppbv mean with 1.6 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.
(d) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, the concentration of 1.0 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.6-4.1 ppbv mean with 47.3 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.

TABLE 2-2
COMPARISON OF KIRBY CANYON AMBIENT AIR RESULTS (ppbv) (BASED ON THE 24-HOUR CONTINUOUS DOWNWIND STATION) AND AVAILABLE REGIONAL DATA

	Mean			Maximum		Number of Observations	
	Kirby Canyon	S.F. Bay Area[a]	San Jose[b]	Kirby Canyon[c]	S.F. Bay Area[a]	Kirby Canyon[d]	S.F. Bay Area[a]
Vinyl Chloride	<2.0	(c)	(c)	<2.0	(c)	2	(c)
Benzene	<2.0	1.8-3.2	4.4	<2.0	15.6	2	91
Ethylene Dibromide	<0.5	0-0.01	(c)	<0.5	0.1	2	82
Ethylene Dichloride	<0.2	0.05-0.07	(c)	<0.2	0.3	2	84
Methylene Chloride	<1.0	0.7-4.3	2.6	<1.0	11.9	2	82
Perchloroethylene	0.7[e]	0.5-0.8	0.5	1.3	1.6	2	84
Carbon Tetrachloride	<0.2	0.2	0.1	0.2	0.5	2	83
Methyl Chloroform	1.0[f]	0.6-4.1	1.8	1.2	47.3	2	83
Trichloroethylene	<0.6	0.3-0.7	0.3	<0.6	1.0	2	43
Chloroform	<0.8	0.03-0.05	0.05	<0.8	0.1	2	84

Note: ppbv = parts per billion by volume.

(a) Based on available ARB data for the San Francisco Bay Area (California Toxic Air Quality Data - Summary of 1985 Toxic Air Quality Data, Preliminary).
(b) Based on available 1986 BAAQMD data for San Jose (Toxic Air Monitoring Summary, 1986-1987, Board of Directors Meeting, September 2, 1987).
(c) Information not available for this report.
(d) One sample day with two collocated samplers.
(e) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, this concentration of 0.7 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.5-0.8 ppbv mean with 1.6 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.
(f) This concentration is higher than expected considering the low concentration detected in the landfill gas sample. However, the concentration of 1.0 ppbv is similar to BAAQMD/ARB results for the San Jose/Bay Area (0.6-4.1 ppbv mean with 47.3 ppbv maximum). Therefore, the Kirby Canyon results are attributable to background conditions.

ATTACHMENT 3[2]

DATE: June 11, 1990

FROM: Chuck White

TO: David Dolan DD

RE: Comments on the Air Resources Board's "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant"

I have reviewed Part B of the Air Resources Board's "Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant". The ARB is to complimented for the thoroughness of this report. There are, however, several issues that deserve some attention. Given the short amount of time available for this memo, please excuse its terseness.

First, why bother using the linearized multistage model under the pretense that it is a true mechanistic model (which it is not), when a simple linear regression usually yields nearly identical estimates of q_1^* ($r^2 = 0.98$)(Personnel conversation with Curtis Travis, Oak Ridge National Laboratory)?

Second, the discussion of uncertainty in the quantitative risk estimates is given short shrift. Although the uncertainties or absence of exposure data in the occupational cohort studies is mentioned, there is no discussion of the conservatism built into the risk estimates by the selection of data for extrapolation, and the extrapolation assumptions, and the effects their underlying assumptions may have on the risk estimates. For instance, the use of the most sensitive sex/strain/species instead of the average may alter risk estimates by "several orders of magnitude." (U.S. EPA, 1985) Similarly, the issues the extrapolation of rodent potency estimates to humans, particularly on the basis of surface area, and the use of upper 95th percentile estimates of carcinogenic potency instead of the MLE, may alter potency estimates by an order of magnitude, or more. (U.S. EPA, 1985)

Third, it is perplexing that the Krewski et al. (1987) chapter is referenced, yet the 36-fold lower carcinogenic potency factor they derive is omitted from the brief discussion. Some discussion on the merits and limitations of the Krewski et al. analysis is necessary.

Fourth, the ARB cites the concordance of the potency estimate derived from the Drew et al. (1983) study and the Maltoni et al. (1984) experiments. It is unclear whether the Maltoni experiments were conducted in his medieval castle/laboratory where the mycobacterium infection is endemic, or in some other facility. (Personnel conversation with E.E. McConnell, National Toxicology Program) In the U.S., mycobacterium infections in test animals would likely violate GLPs, and serve as grounds for invalidating a study.

Fifth, the recommended use of a potency factor derived from animal instead of the human occupational study of Waxweiler et al. (1976) is not robust, given that the human data already represents an upper-bound estimate in the target species of concern (i.e., humans). The additional rationale that the selection of the highest animal estimate is justified by the limited evidence of an effect by age at first exposure (Drew et al., 1983) suggests that perhaps the ARB should consider using a true mechanistic model, perhaps one based upon the MVK model paradigm, as the basis of its potency determinations.

cc: Jim McHenry

5/32.

ATTACHMENT 2

Carcinogenic Risks from Landfill Emissions.

Addendum to

Comments on a Preliminary Draft Document circulated by the EPA in March, 1988:

Air Emissions from Municipal Solid Waste Landfills--
Background Information for Proposed Standards and Guidelines

by

Edmund A.C. Crouch, Ph. D. and Laura C. Green, Ph. D.
Environmental Health and Toxicology Group
Meta Systems Inc.
Cambridge, MA 02141

Produced at the request of

The National Air Pollution Control Techniques Advisory Committee to the EPA

and

Waste Management Inc.

June 6, 1988

CONTENTS

An estimate of carcinogenic risks from landfill emissions.

Introduction

On May 18, 1988, we presented testimony to the National Air Pollution Control Techniques Advisory Committee to the EPA on the risk assessment aspects of a Preliminary Draft Document, "Air Emissions from Municipal Solid Waste Landfills -- Background Information for Proposed Standards and Guidelines." The gist of that testimony was that the carcinogenic risks predicted by the Draft Document were incorrect. The analysis that follows is our attempt to derive such risks more correctly. In particular, we derive estimates of "average" and "worst-case" risks of cancer that could be attributed to volatile organic compounds that may be emitted from municipal solid waste landfills. The estimates are all "standard" in the sense that they are deliberate overestimates, predicated upon "no-threshold" models for all chemical carcinogens of interest. It is our toxicologic opinion that many of the chemicals of interest here are in fact likely to contain thresholds in their dose-response curves for carcinogenesis, such that the very low-level exposures involved carry with them no excess risk of cancer to humans. Nonetheless, we have not "taken credit" for this probability, but instead modeled all compounds as if they carry excess risks of cancer at all non-zero levels of exposure.

1. Data summary

Table 1.1 summarizes measurements of landfill gases collected at 8 municipal landfills, labelled A to H. All these measurements are given in ppm by volume, and include entrained air (the amount of which can be estimated from the nitrogen and oxygen content of the gas). The landfills labelled B, C, G and H were used in the past for co-disposal of municipal waste and hazardous waste, although this practice has now ceased. This former practice of co-disposal is likely to have led to emissions of larger quantities of chemicals of interest than would have occured from the disposal of municipal solid waste alone.

Table 1.2 shows the average concentrations of components of the emitted gases from each landfill. These averages may be compared with the values given in the EPA Draft Document, Table 3.9. Despite the differing data sources, the average concentrations are very similar. In this data, carbon tetrachloride was never detected, whereas the EPA data has an average concentration of 0.0115 ppmV. Also, the average concentration of 1,1-dichloroethene (vinylidene chloride) is a factor 10 lower here than in the EPA data. In both cases, the concentrations were very low even in the EPA data.

Also shown in Table 1.2 are the molecular weights of all the measured components, together with upper bound estimates of "unit risk" for the known carcinogens. These estimates were taken directly from the Carcinogen Assessment Group (CAG) assessments where they have made such estimates. Otherwise they come from CAG estimates for "potency" of a compound, and assume that a human breathes 20 m^3/day of air, and that 100% of a compound is absorbed. At this breathing rate, if a material is present at 1 ug/m^3 in air, a person will inhale 20 ug/day or 3.33×10^{-4} mg/kg-day for a 60 kg person. For a compound with potency P mg/kg-day, this results in a unit risk (risk from 1 ug/m^3 of air) of 3.33×10^{-4} P. The estimates in Table 1.2 generally agree

with those in the EPA Draft Document, except for carbon tetrachloride, where we take the upper end of a suggested range (EPA uses an average of the range); vinyl chloride, where a more recent estimate by the CAG (which we use) has raised the carcinogenic potency estimate by a large factor; and vinylidene chloride, where our estimate is again substantially higher than that of the EPA Draft Document.

Using the molecular weights of the components, together with the unit risks, we can define an average unit risk for the "as measured" average landfill gas. This is obtained by finding the weighted average unit risk for all components, where the weighting factor is the product of molecular weight and volumetric concentration for each component. The result obtained is 1.6×10^{-9} per ug/m^3 for the landfill gas including entrained air, and approximately 1.9×10^{-9} per ug/m^3 after correction for entrained air. We do not use this average, since it is preferable to compute risk estimates on a landfill by landfill case, taking into account the differing concentrations and emission rates at each landfill.

The unit cancer risks estimated by the EPA in Table 2-4 of the Draft Document suffer from major deficiencies. The first two "scenarios" cannot be justified at all. Averaging together the unit risks of the various carcinogens found in landfill gas could only be justified if there were equal emission rates (by mass) of those carcinogens, but it is clear that this is incorrect. Furthermore, the Draft Document includes one carcinogen (Table 2-3, ethylene dichloride) which was apparently never found in their samples of landfill gas (Table 3-9, although it is listed twice in Table 3-8). The "scenario 1" estimate appears to ignore measurements of non-methane VOCs which indicate that the major components (certainly more than 75%) are simple alkanes (especially ethane and propane). Furthermore, it is unclear what is meant in this document by non-methane VOCs. Since these are

TABLE 1.1 (contd.)
Average Concentrations (ppmV)

SITE	E	F	G	H
Carbon tetrachloride	nd	nd	nd	nd
Chlorobenzene	4.3E-01	nd	nd	2.1E+01
Chloroethane	9.1E-02	7.0E-01	3.8E-01	nd
Chloroform	nd	2.5E+00	nd	nd
Chloromethane	1.2E+00	1.1E+01	3.6E+00	6.2E-01
Dibromochloromethane	nd	nd	nd	nd
1,1-Dichloroethane	7.6E-01	2.0E-01	1.6E+00	2.8E-01
1,2-Dichloroethane	nd	nd	nd	nd
1,1-Dichloroethene	nd	nd	nd	nd
t-1,2-Dichloroethene	1.1E-01	nd	nd	nd
1,2-Dichloropropane	2.2E-01	nd	nd	nd
c-1,2-Dichloropropene	nd	nd	nd	nd
t-1,3-Dichloropropene	nd	nd	nd	nd
Methylene chloride	3.2E+00	9.2E+00	1.4E+01	3.4E-01
1,1,2,2-Tetrachloroethane	1.1E-01	nd	nd	nd
Tetrachloroethene	6.9E+00	3.8E+00	1.2E+01	1.4E+00
1,1,1-Trichloroethane	2.0E-01	nd	1.7E-01	nd
1,1,2-Trichloroethane	nd	nd	nd	nd
Trichloroethene	4.1E+00	6.0E-01	2.9E+00	nd
Trichlorofluoromethane	4.4E-01	2.0E-01	7.6E+00	1.3E-01
Vinyl Chloride	5.3E+00	3.1E+00	2.6E+00	4.2E+00
1,2-Dichlorobenzene	nd	nd	nd	nd
1,3-Dichlorobenzene	nd	nd	nd	nd
1,4-Dichlorobenzene	nd	nd	nd	2.0E+00
Chlorodifluoromethane	6.9E-01	6.0E-01	4.0E-01	4.7E-01
Dichlorodifluoromethane	nd	nd	nd	nd
Dichlorofluoromethane	4.6E-01	8.0E-01	2.0E+00	nd
Methane	4.7E+05	5.1E+05	3.7E+05	5.1E+05
Ethane	9.5E+02	7.6E+02	5.0E+02	1.6E+03
Propane	1.1E+01	5.6E+01	1.5E+01	2.5E+01
n-Butane	nd	1.7E+01	2.8E+00	nd
n-Pentane	4.1E+00	5.5E+00	2.9E+00	1.5E+00
n-Hexane	6.1E+00	6.4E+00	6.9E+00	4.0E+00
Acrylonitrile	nd	nd	nd	nd
Benzene	2.7E+00	2.0E+00	2.0E+00	7.2E+00
Toluene	1.2E+02	5.8E+01	1.4E+02	5.2E+01
Ethylbenzene	2.4E+01	1.4E+01	2.3E+01	2.7E+01
Total Xylenes	7.2E+01	3.4E+01	8.4E+01	7.1E+01
TNMHC (as C6)	9.7E+02	9.9E+02	1.0E+03	1.3E+03
Carbon dioxide	3.8E+05	3.7E+05	3.0E+05	3.1E+05
Oxygen	1.7E+04	1.1E+04	6.5E+04	1.8E+04
Nitrogen	1.4E+05	1.1E+05	2.6E+05	1.6E+05

TABLE 1.2
Average concentration over sites, and unit risks

	Average conc. ppmV	Mol. weight	unit risk	potency	weighted unit risk
Carbon tetrachloride	nd	1.5E+02	4.3E-05	1.3E-01	
Chlorobenzene	2.7E+00	1.1E+02			
Chloroethane	3.3E-01	6.5E+01			
Chloroform	3.1E-01	1.5E+02	2.3E-05		3.9E-11
Chloromethane	4.3E+00	5.0E+01			
Dibromochloromethane	nd	2.1E+02			
1,1-Dichloroethane	2.5E+00	9.9E+01			
1,2-Dichloroethane	2.8E-02	9.9E+01	3.0E-05	9.1E-02	3.0E-12
1,1-Dichloroethene	9.8E-02	9.7E+01	3.9E-04	1.2E+00	1.3E-10
t-1,2-Dichloroethene	2.4E-01	9.7E+01			
1,2-Dichloropropane	5.1E-02	1.1E+02			
c-1,2-Dichloropropene	nd	1.1E+02			
t-1,3-Dichloropropene	nd	1.1E+02			
Methylene chloride	2.7E+01	8.5E+01	4.7E-07		3.8E-11
1,1,2,2-Tetrachloroethane	1.4E-02	1.7E+02	6.7E-05	2.0E-01	5.5E-12
Tetrachloroethene	1.4E+01	1.7E+02	9.5E-07		8.1E-11
1,1,1-Trichloroethane	1.7E-01	1.3E+02	1.9E-05	5.7E-02	1.5E-11
1,1,2-Trichloroethane	nd	1.3E+02			
Trichloroethene	5.0E+00	1.3E+02	1.7E-06		4.0E-11
Trichlorofluoromethane	1.4E+00	1.4E+02			
Vinyl Chloride	5.7E+00	6.2E+01	9.8E-05	2.9E-01	1.2E-09
1,2-Dichlorobenzene	nd	1.5E+02			
1,3-Dichlorobenzene	nd	1.5E+02			
1,4-Dichlorobenzene	2.5E-01	1.5E+02			
Chlorodifluoromethane	1.3E+00	8.6E+01			
Dichlorodifluoromethane	9.4E-02	1.2E+02			
Dichlorofluoromethane	4.4E+00	1.0E+02			
Methane	4.7E+05	1.6E+01			
Ethane	7.7E+02	3.0E+01			
Propane	2.4E+01	4.4E+01			
n-Butane	3.8E+00	5.8E+01			
n-Pentane	3.1E+00	7.2E+01			
n-Hexane	7.3E+00	8.6E+01			
Acrylonitrile	nd	5.3E+01	8.0E-05	2.4E-01	
Benzene	2.9E+00	7.8E+01	8.0E-06		6.4E-11
Toluene	7.6E+01	9.2E+01			
Ethylbenzene	1.5E+01	1.1E+02			
Total Xylenes	4.4E+01	1.1E+02			
TNMHC (as C6)	8.3E+02				
Carbon dioxide	3.6E+05	4.4E+01			
Oxygen	2.8E+04	3.2E+01			
Nitrogen	1.5E+05	2.8E+01			

2. Methodology

2.1 Emission rates

Table 1.1 gives the concentrations of various gases measured in collected gases at various landfills. Also available for each landfill is the rate at which those gases are released. Taking the product of total emission rate for landfill gas with these concentrations gives the volumetric emission rate for each gas. This volumetric emission rate may be converted to a mass emission rate by using the gas density, which we approximate by assuming all the gases behave perfectly. For the 8 landfills considered here, the average volumetric emission rate is 2.7×10^6 cfd per landfill, from an average amount of refuse in place of 5.4×10^6 tons per landfill. This is about 50% higher than assumed in the EPA Draft Document for wet landfills.

From the mass emission rate, we may use air dispersion modelling to estimate the expected long term average concentrations of each component of the landfill gas at various positions off-site. The product of those concentrations (in ug/m^3) and the upper bound unit risk estimate (measured in units of m^3/ug) gives an upper bound estimate to lifetime risk. The net effect of all the landfill gas can thus be obtained from the sum over all components of the product of mass emission rate and unit risk for each components. Table 2.1.1 shows this product (in units of m^3/s) for all detected components of the landfill gases which have unit risks defined. Also shown are the sums of products for each landfill.

TABLE 2.1.1
Mass emission rate x unit risk (m^3/s)

SITE	A	B	C	D
Chloroform	0	0	0	0
1,2-Dichloroethane	0	3.5E-03	0	3.8E-03
1,1-Dichloroethene	4.3E-02	5.2E-02	0	2.6E-01
Methylene chloride	3.8E-04	4.5E-02	1.2E-02	2.9E-02
1,1,2,2-Tetrachloroethane	0	0	0	0
Tetrachloroethene	5.4E-03	1.8E-02	5.8E-02	1.4E-01
1,1,1-Trichloroethane	2.0E-03	1.6E-03	4.7E-03	2.8E-02
Trichloroethene	2.4E-03	2.3E-02	3.3E-02	4.9E-02
Vinyl Chloride	1.5E-01	6.4E-01	2.7E+00	3.3E-01
Benzene	8.8E-03	5.2E-03	5.0E-02	4.0E-02
Total	2.2E-01	7.9E-01	2.8E+00	8.8E-01

SITE	E	F	G	H
Chloroform	0	1.7E-01	0	0
1,2-Dichloroethane	0	0	0	0
1,1-Dichloroethene	0	0	0	0
Methylene chloride	4.6E-03	7.0E-03	3.7E-02	1.3E-03
1,1,2,2-Tetrachloroethane	4.5E-02	0	0	0
Tetrachloroethene	4.0E-02	1.1E-02	1.2E-01	2.2E-02
1,1,1-Trichloroethane	1.9E-02	0	2.8E-02	0
Trichloroethene	3.3E-02	2.6E-03	4.3E-02	0
Vinyl Chloride	1.2E+00	3.6E-01	1.1E+00	2.6E+00
Benzene	6.1E-02	2.4E-02	8.2E-02	4.5E-01
Total	1.4E+00	5.8E-01	1.4E+00	3.1E+00

Average total 1.4E+00

The average total for all the landfills is 1.4 m^3/s, and the maximum is 3.1 m^3/s for landfill H (which was used in the past for co-disposal). In every case, the vinyl chloride present contributes the majority of the risk.

2.2 Nationwide average risk

To make an estimate of the nationwide average risk from landfill gas now requires a scale-up, together with some dispersion modelling. The landfills discussed in the previous sections have an average amount of refuse in place of 5.4 million tons, which is 1/900 of the total estimated refuse in place in municipal landfills in the U.S. (EPA Draft Document, page 3-1). The land area of the contiguous U.S. is about 7.84×10^6 km^2, so that the U.S. land area per average landfill is about 8.7×10^9 m^2, corresponding to a radius of about 52 km.

As a first approximation, the effects of landfills on the U.S can thus be obtained by finding the average effects of a single landfill on a radius of about 50 km around it. This approximation would be correct if (1) landfills were uniformly distributed over the U.S.; (2) the population were evenly distributed; and (3) no landfill had any effect beyond 50 km. It is plausible that the third of these is correct, since the chlorinated VOCs which contribute to carcinogenic risk are relatively short-lived (vinyl chloride, for example, has a half-life in air estimated at 1.5 - 1.8 days). The first two are clearly incorrect, but will be compensated by the overestimation of risks to those close to landfills (see below).

For an average landfill, we have an emission rate x carcinogenic unit risk of 1.4 m^3/s. Using the standard gaussian plume model, the average concentration obtained from this over the radial range 0.1 to 50 km corresponds to a lifetime risk of 1.6×10^{-8}. This assumes a uniform wind rose, a wind speed of 3 m/s, and a simple averaging over 7 wind stability classes (A, B, C, Dday,

Dnight, E, F), and emission height of 1 m, and a receptor height of 1.5 m. This averaging procedure has been found to give estimates within 20% of those obtained using the ISC model in particular cases with observed wind rose and stability class data, provided the average wind speed is used. The assumed average wind speed of 3 m/s (6.7 mph) is a reasonable estimate, probably a little low (resulting in an overestimate of risk) for most of the U.S. For 67 cities in the 50 contiguous states, just 3 report average windspeeds less than 6.7 mph.

The minimum distance used for this averaging, 100 m, corresponds to an estimate of the minimum distance from the center of a landfill at which people can be expected to be living. If landfill gas is collected at some landfill, it may be collected together at any point over the landfill. However, if it is collected it will be flared, so that there is negligible exposure of anybody to it. If it is not collected, then the emissions will take place over the whole landfill, and so the nearest person to the landfill may be closer than 100 m. In that case, however, the dispersion modelling performed above is a substantial overestimate for estimating exposures close to the landfill (within distances similar to the dimensions of the landfill). This is dealt with below for the worst case estimate.

The estimate of average effect, a lifetime risk of 1.6×10^{-8}, corresponds to an annual cancer incidence of 0.05 in the United States. Considering the differing methodologies, this agrees well with the EPA Draft Document estimate of 0.11 (Scenario 3, the only one which can be given any credence). However, the differences noted above, especially the dominant effect of vinyl chloride in these estimates, suggests that the EPA Draft Document is considerably in error. Insufficient data is given in the Draft Document to locate where such error may have arisen, but one likely place is in the Effects Model. The technique described of locating population centers relative to landfills is prone to lead to substantial

overestimates of exposure if a small error is made in the location of a population close to a landfill. The average exposure may then be dominated by those estimated for nearby populations.

2.3 Worst case risk estimates

The worst case risk estimate will be for those persons living near to a landfill. As mentioned above, however, the dispersion modelling used for the nationwide average (both here and in the EPA Draft Document) will give very misleading results close in. If landfill gas is collected together into a single vent, that gas will be flared. The worst case exposure estimate will correspond to a landfill with no collection system, in which case the emissions will take place from over the whole surface area of the landfill. The concentrations from such area emissions are considerably lower than those from a vent pipe emitting the same total quantity of gas, at equal distances from the edge of the area or the vent pipe.

To make an estimate of the worst case emissions, consider the landfill labelled H above (Table 1.1). This was previously used for co-disposal of hazardous waste as well as municipal waste. The total emission rate x unit risk for this landfill is 3.1 m^3/s, and it contains 12.6 million tons of refuse. The worst case will occur with maximum emissions per unit area of landfill, so we will assume waste piled to a height of 100 feet and with an average density of 1 ton/cu. yd. (double that assumed in the EPA Draft Document). The emission rate x unit risk per unit area for this landfill is then 8.2×10^{-6} m/s, and the landfill covers an area of about 3.2×10^6 m^2, corresponding to a diameter of about 640 m.

Using a dispersion model for area emissions, we find that for a person spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for a person staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}.

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48674

1803 BUILDING
July 3, 1990

Ms. Barbara Cook
Project Manager
California Air Resources Board
1102 Q Street
Sacramento, CA 95814

Dear Ms. Cook:

Attached are our comments on the unit risk derivation presented in the May, 1990 Draft Technical Support Document, Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant.

We appreciate your accepting our comments, which have been submitted to promote the best possible science in the performance of health risk assessments.

Pleased call on us should you require additional information.

Sincerely,

Neil C. Hawkins, Sc.D.
Senior Research Risk Analyst
Health and Environmental Sciences
1803 Building
(517) 636-8237

kal

Attachments

COMMENT: DRAFT TECHNICAL SUPPORT DOCUMENT, MAY, 1990, "PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT"

Derivation of a unit risk for Vinyl Chloride (CAS 75-01-4)

VCM is clearly a rat and human carcinogen, causing liver angiosarcoma in both species and zymbal gland tumors in rats. Thus, for regulatory purposes, there is interest in deriving a quantitative estimate of a level of no significant risk. There are two general approaches to this problem. One approach has been the use of safety factors or uncertainty factors applied to no-observed-effect-levels (NOEL's) in animals to derive a safe level in humans. The other general approach, which has been used more recently by regulatory agencies, has been the use of quantitative risk assessment to estimate levels of risk for any given exposure. The risk assessment process involves a number of decision points for which there is no scientific consensus as to the correct approach. These areas of uncertainty, including the presence or absence of thresholds, the shape of the dose response model, and animal to man conversion factors, have been resolved within the agencies through the use of policy decisions as to a default methodology. The default methodology is conservative in nature, so as to protect public health. However, the State of California Cancer Risk Assessment Guidelines as well as EPA and OSTP guidelines on the use of risk assessment clearly state that the default methodology should not be used when other data are available. In particular, epidemiology data and pharmacokinetic information should be incorporated into risk assessment when the appropriate data are available. The DHS unit risk for vinyl chloride of 20 x 10(-5) per ppb, as cited in the CARB Draft Technical Document (CARB, 1990), does not utilize the available pharmacokinetic or epidemiological information.

Pharmacokinetic Information

Pharmacokinetic (PK) information can be used in two ways to augment risk assessments for vinyl chloride. PK data have been used to demonstrate and explain nonlinear behavior at both the high dose and low dose portions of the dose-response curve. The bioassay data of Maltoni (1979) clearly indicated a plateau in the dose-response curve at high doses. This phenomenon can be explained by the use of a Michaelis-Menton function to calculate metabolite concentrations, as suggested by Watanabe *et al.* (1976), and implemented by Gehring *et al.* (1978), Crump (1982) and USEPA (1987). However, this methodology only explains the high-dose results in the animal bioassay rather than addressing the problem of low-dose extrapolation. Low-dose risk assessments utilizing PK data have been discussed by Gehring *et al.* (1979) and Anderson *et al.* (1980).

Purchase *et al.* (1980) reviewed risk assessments for VCM and showed that, among the linear models used, risk estimates varied from the current DHS value, (equivalent to a unit risk of 20 x 10(-5) per ppb), upwards (less risk) at least a factor of 100-fold. The different values derived from animal models vary primarily on the basis of whether or not pharmacokinetic information has been utilized in the assessment. In evaluating the use of pharmacokinetic data, Anderson *et al.* (1980) conclude that: "Based on the present understanding of the mechanism of carcinogenesis, we believe this to be a more rational approach to the low-dose extrapolation problem."

Gehring *et al.* (1979) fit a number of extrapolation models to the metabolized dose of VCM, and showed that risk estimates derived without consideration of low-dose metabolite formation potentially overestimate risk by at least an order of magnitude. For example, the one-hit model applied to metabolized dose predicts a risk of 189 per million at 1 ppm for an occupational exposure (Gehring, 1979). By comparison, use of nominal dose (air concentration), predicts upper bound "risks" of 37,000 per million using the unit risk of 20 x 10(-5) per ppb. Other viable dose response models predict much lower risk.

Not withstanding the fact that the health criteria represent one aspect of many inputs considered in the standard setting process, we submit it is essential to base any proposed regulation on the most complete information possible. For this reason we believe that risk assessments for vinyl chloride should include PK data, or preferably, the use of actual human data.

Risk assessments derived from epidemiology data

In the early 1970's, vinyl chloride was reported to cause a rare form of cancer, angiosarcoma of the liver, among workers who had been exposed at extremely high levels for many years in polyvinyl chloride (PVC) polymerization plants. Since this discovery, there have been approximately 50 angiosarcoma of the liver deaths reported throughout the United States and Canada which have been associated with previous vinyl chloride exposure. Eighty percent of these deaths occurred in four PVC plants where exposures to vinyl chloride were known to have been over 500 ppm in the 1950's and 1960's. Today, there are strict emission limitations under the NESHAP regulation, and the OSHA regulated 8-hour time weighted average for vinyl chloride is 1 ppm. It is particularly noteworthy that there has never been a reported death from angiosarcoma of the liver among Louisiana chemical workers who have worked with vinyl chloride.

Vinyl chloride has not been shown to cause cancer at any other anatomical site in humans. Epidemiologic studies conducted in the 1970's suggested that there may be an association with brain and lung cancer, however, recent updates of these studies have reported either no association, or associations only at a much lower statistical level of significance.

A world-recognized expert in epidemiology, Sir Richard Doll, recently reviewed the existing vinyl chloride literature as it pertains to cancer in humans. He concluded that vinyl chloride is a known occupational carcinogen (only for angiosarcoma of the liver) which is due to high occupational exposure levels which have not existed since this association was reported in the early 1970's. According to Doll, the risk for cancer in communities surrounding vinyl chloride production plants from environmental emissions in today's tightly controlled and well-regulated environment "must be negligible." (Doll, 1988)

Generally, risk assessments utilize animal data as the basis for quantification of risk. Human epidemiology data often do not have sufficiently precise exposure estimates or sufficiently well-defined populations to be of quantitative value. Human results are clearly preferred, when available, however, and should be included in any risk assessment review. In the case of VCM there are at least three assessments of sufficient precision which utilize the human database to estimate risk. In one analysis (Barr, 1982), negative epidemiological studies of people living near VCM production facilities have been used to estimate human potency. Barr estimates that 100 ppb is the approximate lifetime dose corresponding to a human risk of 10(-6). Purchase *et al.* (1987) note that Barr's estimate is similar to the highest estimates of 10(-6) dose levels derived from animal data and are orders of magnitude higher than the conservative dose estimates which do not take into account low dose PK. This result is consistent with other observations that humans may be less sensitive than animals to the carcinogenic effects of VCM.

Gehring *et al.* (1979) compared the results of an epidemiological study of approximately 10,000 occupationally exposed workers to the values predicted by four different mathematical models derived from animal data. They conclude that the observed human results are inconsistent with the two linear non-threshold models used, and are consistent with both the probit model and a linear threshold model. The latter two models predict 10^{-6} risk levels at occupational exposure levels in excess of 1 ppm.

These analyses by no means prove the validity of the two models and undoubtedly numerous other models would fit and give quite different results for predicting the ambient level corresponding to a 10^{-6} risk level. However, these analyses do show that human epidemiology data can be used to derive risk estimates for VCM exposures and that the models indicate that the linear non-threshold models are conservative by a substantial margin. This is to be expected in light of the well known conservativeness of the models. U.S. EPA, for instance, when presenting risks estimates describes them as upper bounds and notes that: **"the true value of the risk is unknown and may be as low as zero"** (Federal Register, 1986).

In an analysis of alternative modeling assumptions for animal to human extrapolation, Elizabeth Anderson, (1984) as head of the U.S. EPA Cancer

Assessment Group found that alternative plausible modeling assumptions would lead to risk estimates that were 15-fold to 10,000-fold lower than the standard LMS procedure. Thus it is essential to use the available human data to place some perspective on the results predicted solely from animal data.

In an independent review of VCM, the National Health Council of the Netherlands (1987) derived ambient exposure levels corresponding to risk levels of 10(-6) in humans. Their estimates were derived from both animal data and from epidemiological human data. While noting that the estimates did not differ greatly, they expressed a preference for the human data and reported a value of 1 μg/cubic meter as corresponding to a risk of 10(-6). This value is approximately 80 times higher than the exposure level derived using the DHS unit risk of 20 x 10(-5) per ppb.

The over prediction of the models can be further demonstrated for VCM by comparing predictions of risk utilizing the DHS unit risk with human exposure scenarios. To make this comparison, Table 1 shows the "risk" predicted from the DHS model for a number of occupational exposure situations. The relevance of the specific exposure scenarios are also discussed below.

The specific exposure scenarios used in Table 1 were based upon a retrospective study (Barnes, 1976), in which past typical VCM exposures in PVC plants were estimated as: 1000 ppm in 1945-1955, 400-500 ppm in 1955-1960, 300-400 ppm in 1960-1970, 150 ppm in mid-1973 and considerably lower afterwards. Considering the latency of carcinogenesis in general, and for VCM in particular, tumor incidence rates noted in the 1980's reflect exposures from the 1960's.

It can be seen from Table 1 that incidence rates predicted from the linear animal model are completely incompatible with that observed in actual human studies. For example, in the study examined by Gehring (1970) there were only 5 observed cases in 9677 workers. This is approximately three orders of magnitude less than that which would be predicted by the DHS model.

Thus, there are a number of assessments based upon human epidemiological data which would indicate that linear models utilizing animal data overpredict risk by at least one to two orders of magnitude. In the interests of assuring that any proposed regulation is supported by as comprehensive a review of the available health data as possible, we submit these assessments should be incorporated into any risk assessments which will be used for regulatory control. This is particularly important in view of the fact that they are based upon human data rather than on laboratory animal results.

It can be seen from the above analysis that standard risk assessment methodology and the use of reported literature results lead to orders of magnitude over-estimates of the predicted risk from emissions of VCM from

existing facilities. We recommend that these inconsistencies in the risk estimates be resolved if they are to be used as the basis for any proposed regulation.

TABLE 1. "RISK" PREDICTED FROM LMS MODEL
(using unit risk of 20×10^{-5} per ppb)

Occupational Exposure Scenario	Upper Bound on "Risk" (Cases Per 10,000)
400 ppm 30 years	9999
400 ppm 20 years	9995
300 ppm 30 years	9998
300 ppm 20 years	9964
200 ppm 30 years	9960
200 ppm 20 years	9770
100 ppm 30 years	9400
100 ppm 10 years	6090
100 ppm 5 years	3750

REFERENCES

1. California Air Resources Board (CARB), Draft Technical Support Document, Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant. May, 1990.

2. Watanabe, P.G., McGowan, G.R., and Gehring, P.J. Fate of [^{14}C] Vinyl Chloride After Single Oral Administration in Rats. *Toxicology and Applied Pharmacology 36, 339-352 (1976).*

3. Gehring, P.J., Watanabe, P.G. and Park, C.N. Resolution of Dose-Response Toxicity Data for Chemicals Requiring Metabolic Activation: Example - Vinyl Chloride. *Toxicology and Applied Pharmacology 44, 581-591 (1978).*

4. Crump, K.S. Quantitative Assessment of Human Risk From Exposure to Carcinogens with Special Reference to Vinyl Chloride. Contract for Occupational Health and Safety Division, Ontario Ministry of Labour (1982).

5. EPA. Incorporation of Biological Information in Cancer Risk Assessment: Example Vinyl Chloride. Office of Environmental Health and Assessment, U.S. Environmental Protection Agency. EPA/600/d-87/188 (1987).

6. Gehring, P.J., Watanabe, P.G., and Park, C.N. Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats *Toxicology and Applied Pharmacology. Vol. 49, No. 1 (June 15, 1979).*

7. Anderson, M.W., Hoel, D.G., and Kaplan, N.L. A General Scheme for the Incorporation of Pharmacokinetics in Low-Dose Risk Estimation for Chemical Carcinogenesis: Example-Vinyl Chloride. *Toxicology and Applied Pharmacology 55, 154-161 (1980).*

8. Federal Register, Volume 51, Number 185, Wednesday, September 24, 1986.

9. Purchase, I.F.H., Stafford, J., and Paddle, G.M. Vinyl Chloride: An Assessment of the Risk of Occupational Exposure. *Fd. Chem. Toxic. Vol. 25, No. 2, pp. 187-202, 1987.*

10. Barr, J.T. Risk Assessment for Vinyl Chloride in Perspective. Presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, USA, *(June 1982).*

11. National Health Council of The Netherlands. A Scientific Basis for the Risk Assessment of Vinyl Chloride. *Regulatory Toxicology and Pharmacology 7, 120-127 (1987).*

12. Anderson, E.L., Ph.D. Risk Analysis in Environmental Health with Emphasis on Carcinogenesis". Harvard School of Public Health, September 18-20, 1984.

13. Doll, R. Effects of Exposure to Vinyl Chloride: An Assessment of the Evidence, *Scand J Work Environment Health 14 (1988) 61-78.*

14. Maltoni, C. and G. Lefemine. *Annals of N.Y. Academy of Sciences.* 246: 195-218 (1979).

15. Barnes, A.W. Vinyl Chloride and the Production of PVC. *Proc. R. Soc. Med.* 69: 277 (1976).

II. PART C ADDENDUM
AIR RESOURCES BOARD STAFF RESPONSES TO COMMENTS ON PART A

A. COMMENT FROM THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

1. Comment: Please include the following paragraph in the Executive Summary:
"The Operating Industries, Incorporated (OII) landfill is currently a federally listed Superfund site. Subsequent to the Air Resources Board's sampling during 1987, the Environmental Protection Agency (EPA) has implemented more stringent landfill gas control measures. EPA has also selected a remedy for landfill gas control that is expected to substantially reduce landfill gas emissions from the OII landfill. It is fully anticipated that these control measures will substantially lower the levels of vinyl chloride in the ambient air in the vicinity of the OII landfill."

Response: The paragraph (corrected to indicate that OII sampling was performed by the South Coast Air Quality Management District during 1986) appears in the revised Executive Summary.

B. COMMENTS FROM WASTE MANAGEMENT OF NORTH AMERICA, INC.

1. Comment: It is erroneous to assume that BKK and OII landfills are representative of all landfills since both of these sites accepted significant quantities of vinyl chloride waste during operation.

Response: Landfill records of whether or not vinyl chloride waste was accepted may not be a reliable means of predicting the potential for vinyl chloride emissions. For decades, vinyl chloride waste (as well as other halogenated industrial waste which can form vinyl chloride) was disposed in some Class II as well as Class I landfills. In addition, Class III landfills accept disposed consumer products containing chlorinated compounds which can form vinyl chloride. Also, incomplete recording of vinyl chloride waste disposal and illegal vinyl chloride waste dumping have occurred to an unknown extent. However, a statement has been added to the report indicating that the vinyl chloride emissions measured at BKK and OII may not be typical of all landfills.

2. Comment: Significant information exists that landfills are not significant sources of vinyl chloride emissions. For example, data from the Air Solid Waste Assessment Testing Program (Landfill Gas Testing Program) mandated by Section 41805.5 of the California Health and Safety Code show that six waste management units operated by Waste Management of North America (WMNA), Inc. are not significant sources of vinyl chloride emissions.

Response: After considering the data available on potential sources of vinyl chloride emissions, the staff of the Air

Resources Board (ARB) concluded that landfills are a potential major source. Modeled estimates of vinyl chloride emissions for just BKK and OII landfills were far greater than emissions estimates for publicly-owned treatment works (POTWs) and polyvinyl chloride (PVC) fabrication and production facilities:

Source	Emissions (tons/year)	Inventory Year
BKK Landfill	44-197	1987
OII Landfill	4-51	1986
POTWs	1.7	1985
PVC fabrication	0.75	1982
PVC production	<0.5	1988

Although BKK and OII landfills may not be typical, one cannot rule out the possibility of elevated vinyl chloride emissions from other California landfills using preliminary Landfill Gas Testing Program data. The preliminary data show that vinyl chloride was detected at or above the detection limit in the internal landfill gas at 160 out of 340 landfills tested. Also, vinyl chloride was detected at or above the detection limit in the ambient air near 24 out of 251 landfills tested. However, because landfills vary in the amount and composition of wastes accepted as well as disposal methods used, estimating total statewide vinyl chloride emissions from landfills is not possible at this time. Therefore, the staff report has been revised to indicate that landfills are a potential major source-category.

3. Comment: Section 39660 (f) of the California Health and Safety Code mandates that the Department of Health Services (DHS) and the ARB give priority to the evaluation of a substance's amount or potential amount of emissions and ambient concentrations in the community. To proceed with identification of vinyl chloride as a toxic air contaminant (TAC) while identifying landfills as the largest source of emissions based on two unrepresentative sites (BKK and OII landfills) would be a disservice to the waste management industry and contrary to the law.

Response: In the revised vinyl chloride report, based on available data, the staff of the ARB conclude that landfills are a potential major identified source-category of vinyl chloride emissions. The staff further conclude that sufficient overall data are available to proceed with the identification of vinyl chloride as a TAC as provided in the statutes. Furthermore, vinyl chloride, as a federally designated hazardous air pollutant, must be identified as a TAC pursuant to Health and Safety Code Section 39655. Also, please see the responses to comments 1 and 2.

4. Comment: Waste Management of North America, Inc. recommends that identification of vinyl chloride be delayed until Landfill Gas Testing Program data are included in the report.

Response: Preliminary Landfill Gas Testing Program data have been included at appropriate places in the revised vinyl chloride report. In addition, a table of Landfill Gas Testing Program data has been provided in Appendix VI.

III. PART C ADDENDUM
DEPARTMENT OF HEALTH SERVICES RESPONSES TO COMMENTS ON PART B

RESPONSE TO COMMENTS:

WASTE MANAGEMENT OF NORTH AMERICA, INC.

June 11, 1990

PUBLIC HEALTH RISK OF VINYL CHLORIDE

COMMENT: "While we do believe that it is ultimately appropriate to regulate vinyl chloride as a toxic air contaminant, we are concerned that the unit risk factor that you have attributed to this compound is overly conservative."

RESPONSE: The DHS document of May, 1990, provides estimates of unit risk that use data, assumptions and methods that are highly defensible, based on standard procedures utilized by DHS and EPA. The analysis uses animal and human data. Dose rates to tissue have been obtained from a pharmacokinetic model. The range of unit risks does not include some of mouse data which is up to 2.5 times above the top of the range in the risk assessment, as indicated in the text at page 8-8. The best estimate of unit risk for regulatory purposes is the top of the tightly clustered -- less than 10-fold -- range, containing numerous results, including human results. The two top points include liver angiosarcoma in the female rat, this tumor being one of the most distinctively linked to vinyl chloride exposure in both rats and humans. DHS staff conclude that this choice is not overly conservative.

COMMENT: "I have also attached to this letter a copy of a brief paper on Carcinogenic Risks from Landfill Emissions dated June 6, 1988. . . . This information provides a much more realistic assessment of the health risks posed by municipal landfills not only from the standpoint of vinyl chloride but a number of

other compounds as well. In summary this brief paper, based on an assessment of the cumulative impact of all landfill emissions, concludes, 'Using a dispersion model for area emissions, we find that for persons spending their whole lives 100 m from the edge of such a landfill the lifetime risk is about 20×10^{-6}, while even for persons staying permanently at the edge of the landfill the lifetime risk is only 50×10^{-6}.'"

RESPONSE: The cited paper, which was an addendum to comments to EPA and not a journal article, was produced at the request of Waste Management Inc. and of The National Air Pollution Control Techniques Advisory Committee to the EPA. This response will focus on the unit risk estimate utilized in the document and not on site-specific factors such as emission rates, source areas and meteorology. The cited paper uses for vinyl chloride a unit risk of 22×10^{-5} ppb^{-1}, expressed as 9.8×10^{-5} $(\mu g/m^3)^{-1}$ in their Table 1.2. This risk estimate is essentially equivalent to the DHS best estimate of 20×10^{-5} ppb^{-1} for unit risk. Therefore, DHS is recommending essentially the same unit risk as is the basis for the calculation of risk for landfills that is advocated by the commenter.

The cited paper refers to EPA (1985b) as the source for that unit risk, but DHS staff, after obtaining and reviewing that document, calculate that the unit risk corresponding to the EPA's (1985a) potency of 2.95×10^{-1} $(mg/kg\text{-}day)^{-1}$ is 11×10^{-5} ppb^{-1}, using EPA's own assumption of 50% absorption, which the cited paper's authors evidently did not use. The reason for that EPA unit risk being 55% of the DHS best estimate stems from the EPA analysis combining male and female rats, giving a lower risk than the DHS use of females, the sex with the higher risk in this case. For comparative purposes the EPA 1985b unit risk has now been included in the document at page 8-13 and in Figure 8-1.

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SPECIFIC DOLAN COMMENTS

COMMENT: "First, why bother using the linearized multistage model under the pretense that it is a true mechanistic model (which it is not), when a simple linear regression usually yields nearly identical estimates of q_1^* ($r^2 = 0.98$) (Personnel conversation with Curtis Travis, Oak Ridge National Laboratory)?"

RESPONSE: The linearized multistage model affords an efficient unified approach to determining carcinogenic potencies of most substances for which there are enough data to determine the potency. Once the appropriate computer software and a knowledge of its use have been acquired, the model is quite convenient to use. This model accommodates pharmacokinetic conversion of dose rate and can account for a wide range of test results in a way that allows extrapolation that is frequently in accord with available knowledge of mechanisms. In contrast, the simple linear regression becomes inappropriate at high doses in many animal experiments. Even in the case of vinyl chloride, the multistage model indicates an improved fit to the data by including a quadratic term. Thus, a simple linear model would introduce some bias into the low dose extrapolation.

COMMENT: "Second, the discussion of uncertainty in the quantitative risk estimates is given short shrift. Although the uncertainties or absence of exposure data in the occupational cohort studies is mentioned, there is no discussion of the conservatism built into the risk estimates by the selection of data for extrapolation, and the extrapolation assumptions, and the effects their underlying assumptions may have on the risk estimates. For instance, the use of the most sensitive sex/strain/species instead of the average may alter risk estimates by 'several orders of magnitude.' (U.S. EPA, 1985). Similarly, the

issues of the extrapolation of rodent potency estimates to humans, particularly on the basis of surface area, and the use of upper 95th percentile estimates of carcinogenic potency instead of the MLE, may alter potency estimates by an order of magnitude, or more. (U.S. EPA, 1985)."

RESPONSE: DHS staff do not agree that there is unjustified conservatism built into the risk estimates. DHS used procedures that are standard for EPA and DHS, taking account of the pharmacokinetics of vinyl chloride. The DHS risk assessment did not use the most sensitive species and strain. Some of the mouse data resulted in unit risks up to 2.5 times higher than actually used in the risk assessment. The assessment does use data for the more sensitive sex in order to protect women as well as men because female rats had a 3-fold higher risk than male rats. The assessment does use the 95th percentile estimates, clearly identifying them by UCL throughout the document. The analysis uses these estimates in the risk assessment only when the ratio of UCL to MLE is less than 3, specifically avoiding the possibility of that ratio being "an order of magnitude, or more", as found in other circumstances by EPA (1984a).

In order to expand the discussion of uncertainties, DHS staff have added a brief paragraph to the document at page 8-13 as follows:

"All these estimates are subject to substantial uncertainties as have been discussed in the scientific literature (DHS, 1986, and EPA, 1984a). The available information does not suggest that there is a threshold for vinyl chloride's carcinogenic effect, though this remains uncertain. The multistage model is the best choice based on the plausible mechanism of vinyl chloride carcinogenicity. Nevertheless, our incomplete understanding of cancer makes this choice subject to uncertainty. Furthermore, the present approach uses other assumptions that are

designed to be somewhat health protective in the absence of precise knowledge. One of the most important of these is the extrapolation from humans to animals on the basis of surface area in accordance with DHS guidelines (1985). This approach may overpredict or underpredict human risk.

COMMENT: "Third, it is perplexing that the Krewski et al. (1987) chapter is referenced, yet the 36-fold lower carcinogenic potency factor they derive is omitted from the brief discussion. Some discussion on the merits and limitations of the Krewski et al. analysis is necessary."

RESPONSE: The Krewski et al. (1987) result of 0.0058 ppm^{-1} is based on virtually all the relevant female liver angiosarcoma data of Maltoni et al. (1984) and is unadjusted for lifetime exposure. When adjusted for lifetime exposure the unit risk is 9.7×10^{-5} ppb^{-1}. On this basis, the unit risk of Krewski et al, rather than being 36-fold lower, is actually 45% higher than the result from the analysis (BT-9, 15) which corresponds most closely in the document, 6.7 x 10-5 ppb^{-1}. This is among the highest rodent risks in the assessment. Because of the rather good agreement despite the differing analyses, adding a discussion of the merits and limitations is inappropriate for this document.

COMMENT: "Fourth, the ARB cites the concordance of the potency estimate derived from the Drew et al. (1983) study and the Maltoni et al. (1984) experiments. It is unclear whether the Maltoni experiments were conducted in his medieval castle/laboratory where the mycobacterium infection is endemic, or in some other facility. (Personnel conversation with E.E. McConnell, National Toxicology Program). In the U.S., mycobacterium infections in test animals would likely violate GLPs, and serve as grounds for invalidating a study."

RESPONSE: Both EPA and IARC have relied on the Maltoni et al. data for their assessments. DHS knows of no documentation that casts serious doubt on the validity of these data. The concordance of the Maltoni data is not only with Drew et al. but also with Bi et al.

COMMENT: "Fifth, the recommended use of a potency factor derived from animal instead of the human occupational study of Waxweiler et al. (1976) is not robust, given that the human data already represents an upper-bound estimate in the target species of concern (i.e., humans). The additional rationale that the selection of the highest animal estimate is justified by the limited evidence of an effect by age at first exposure (Drew et al., 1983) suggests that perhaps the ARB should consider using a true mechanistic model, perhaps one based upon the MVK model paradigm, as the basis of its potency determinations."

RESPONSE: The human data in itself does not represent an upper bound in humans because (1) that data does not include a lifetime exposure, and there is evidence of greater sensitivity of the young and (2) the human data that is sufficient for the risk assessment includes almost no females. As to the remainder of the comment, the DHS staff note that the MVK model does have the potential to be more closely linked to the biological observations of cell proliferation than the multistage model. When the necessary data are available and the mathematical analysis is adequately established, then an analysis related to the MVK model is worth consideration.

RESPONSE TO COMMENTS:
THE DOW CHEMICAL COMPANY
July 3, 1990

Derivation of a Unit Risk for Vinyl Chloride

COMMENT: "VCM is clearly a rat and human carcinogen ...". In order to address cancer concerns, regulatory agencies have recently used "quantitative risk assessment to estimate levels of risk for any given exposure." In order to resolve uncertainties in this process, agencies have developed default assumptions which are "conservative in nature so as to protect public health." California and federal guidelines "clearly state that the default methodology should not be used when other data are available. ... The DHS unit risk for vinyl chloride of 20 x 10^{-5} per ppb ... does not utilize the available pharmacokinetic or epidemiological information."

RESPONSE: The DHS staff disagree with the assertion that the current DHS risk coefficient does not utilize the available pharmacokinetic or epidemiological information. DHS staff, in response to comments on the first draft document, did specifically incorporate the available pharmacokinetic and epidemiological information into the analysis that produced the estimates of unit risk. All the DHS calculations of unit risk in the document under review directly use the available pharmacokinetic information. In addition, the risk assessment specifically shows how the best estimate of upper confidence limit (UCL) for unit risk, 20 x 10^{-5} per ppb, cited in the comment above, is consistent with human occupational data when adjusted from males in that workforce to females who would be exposed in the general population.

Pharmacokinetic Information

COMMENT: "Pharmacokinetic (PK) information can be used in two ways to augment risk assessments for vinyl chloride. PK data have been used to demonstrate and explain nonlinear behavior at both the high dose and low dose portions of the dose-responses curve." The Michaelis-Menton "methodology explains only the high-dose results. Low-dose risk assessments utilizing PK data have been discussed by Gehring et al. (1979) and Anderson et al. (1980)."

RESPONSE: Contrary to the implication of the comment, Gehring et al. (1979) and Anderson et al (1980) used the Michaelis-Menton methodology to incorporate PK data at all doses, high and low, in essentially the same way as the DHS document. The low dose extrapolations in those two studies differed from the DHS document in that they explored extrapolation not only by the single stage model, as did the DHS document, but also by the log-probit model. DHS staff consider the log-probit model to be inappropriate based on the data that became available after these articles were published and the apparent mechanism of carcinogenesis.

COMMENT: "Purchase et al. (1980) reviewed risk assessment for VCM and showed that, among the linear models used, risk estimates varied from the current DHS value, (equivalent to a unit risk of 20 x 10^{-5} per ppb), upwards (less risk) at least a factor of 100-fold. The different values derived from animal models vary primarily on the basis of whether or not pharmacokinetic information has been utilized in the assessment. In evaluating the use of

pharmacokinetic data, Anderson et al. (1980) conclude that: "Based on the present understanding of the mechanism of carcinogenesis, we believe this to be a more rational approach to the low-dose extrapolation problem."

RESPONSE: Contrary to the comment, Purchase et al. (1987) do not make clear comparisons among linear models, nor do they make clear comparisons between those models that use pharmacokinetic adjustment and those that do not. The work of Anderson et al. (1980), does clearly account for the role of the pharmacokinetic adjustment and the role of the carcinogenesis model. Anderson et al. (1980) found that for the multistage model, which extrapolates linearly to zero exposure, "incorporating the pharmacokinetics has only a moderate effect on the low-dose estimates." Table 1 in that work shows that the effect of incorporating Gehring's simple pharmacokinetics into the multistage model is to increase - - by either or 4- or 26-fold, depending on the specific choice of rat data - - the extrapolations of risk estimates to low dose. The more appropriate choice of rat data, eliminating the two highest and therefore most saturated exposures, corresponds to the 4-fold increase.

DHS staff agree with the Anderson et al. statement about the rationality of the pharmacokinetic approach, provided appropriate data are available.

COMMENT: "Gehring et al. (1979) fit a number of extrapolation models to the metabolized dose of VCM, and showed that risk estimates derived without consideration of low-dose metabolite formation potentially overestimate risk by at least an order of magnitude. For example, the one-hit model applied to metabolized dose predicts a risk of 189 per million at 1 ppm for an occupational exposure (Gehring, 1979). By comparison, use of nominal dose (air concentration), predicts upper bound "risks" of 37,000 per million using the unit risk of 20×10^{-5} per ppb. Other viable dose response models predict much lower risk."

RESPONSE: Gehring et al. in their 1979 article did not derive any estimates of risk without using their model for low-dose metabolite formation. The four models in that article use the metabolized dose at all dose levels. In that article the authors did characterize the results of their models C (linear forced through the origin) and D (one-hit) as overpredicting the number of liver angiosarcomas reported in the Equitable Environmental Health (1978) study. However, a follow up study (Wong et al., 1986) of those worker populations showed a marked increase in incidence of deaths attributable to liver and biliary cancer. Neither of these papers on workers has appeared in the peer-reviewed literature, making acceptance of either of their epidemiological results problematic.

All the DHS estimates of risk use a metabolized exposure that is essentially equivalent to the metabolized dose of Gehring et al. (1978, 1979) at low exposures. For the 1 ppm occupational example in Gehring et al (1979), their assumptions of 40 hr/wk for 35 years does not give a risk of 37,000 per million for the DHS unit risk of 20×10^{-5} per ppb but gives 22,000 per million. This risk is 126-fold greater than the Gehring et al. result of 189 per million, not because of differences in analysis of the data but because of three different choices in applying the results of the rat analysis to the human. In the one-hit analysis for the rat the result of Gehring et al. (1979) is a unit risk of 1.1×10^{-5} per ppb, when adjusted to lifetime exposure. This result is actually somewhat greater than that of the nearest analysis in the DHS document, for BT-1,2, giving an MLE of $q1 = 0.8 \times 10^{-5}$ per

ppb. The sources of the higher risk estimate for DHS are (1) the use of later Maltoni et al.(1984) data, BT-9,15 for the best estimate rather than the earlier Maltoni and Lefemine (1975) data used by Gehring et al.(1978), resulting in a 3.2-fold increase, (2) the use of the 95% upper confidence level on risk rather than the mean regression estimate (similar to maximum likelihood estimate), resulting in a 2.3-fold increase , and (3) the use of DHS standard scaling of humans to animals by body weight to the two-thirds power rather than the Gehring et al. ad hoc scaling that has never been accepted, resulting in a 17.7-fold increase. The result of multiplying all these increases together is an overall 130-fold increase.

COMMENT: "Not withstanding the fact that the health criteria represent one aspect of many inputs considered in the standard setting process, we submit it is essential to base any proposed regulation on the most complete information possible. For this reason we believe that risk assessments for vinyl chloride should include PK data, or preferably, the use of actual human data."

RESPONSE: DHS staff agree and have used both in the risk assessment.

Risk Assessments Derived from Epidemiology Data

COMMENT: After introductory remarks concerning vinyl chloride in the workplace, the commenter asserts, "It is particularly noteworthy that there has never been reported death from angiosarcoma of the liver among Louisiana chemical workers who have worked with vinyl chloride."

RESPONSE: It is difficult to respond to the comment about Louisiana chemical workers without specific reference to surveillance programs and exposure estimates.

COMMENT: "Vinyl chloride has not been shown to cause cancer at any other anatomical site in humans. Epidemiologic studies conducted in the 1970's suggested that there may be an association with brain and lung cancer, however, recent updates of these studies have reported either no association, or associations only at a much lower statistical level of significance."

A world-recognized expert in epidemiology, Sir Richard Doll, recently reviewed the existing vinyl chloride literature as it pertains to cancer in humans. He concluded that vinyl chloride is a known occupational carcinogen (only for angiosarcoma of the liver) which is due to high occupational exposure levels which have not existed since this association was reported in the early 1970's.

RESPONSE: In his review article Doll (1988), cited in the next comment, discusses this issue at length. He concludes in a manner contrary to that of the comment. "It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deathes as angiosarcoma of the liver."

COMMENT: "According to Doll, the risk for cancer in communities surrounding vinyl chloride production plants from environmental emissions in today's tightly controlled and well-regulated environment "must be negligible." (Doll, 1988)."

RESPONSE: Doll (1988) did not estimate unit risks or any other numerical measure of the relationship between exposure and response. He did not specify numerically what he or his reference considers to be a negligible risk outside a vinyl chloride plant. Also, he does not consider other environmental exposures such as landfill sites. So his remark is difficult to apply to the present assessment.

COMMENT: "Generally, risk assessments utilize animal data as the basis for qualification of risk. Human epidemiology data often do not have sufficiently precise exposure estimates or sufficiently well-defined populations to be of quantitative value. Human results are clearly preferred, when available, however, and should be included in any risk assessment review. In the case of VCM there are at least three assessments of sufficient precision which utilize the human database to estimate risk. In one analysis (Barr, 1982), negative epidemiological studies of people living near VCM production facilities have been used to estimate human potency."

RESPONSE: The previous response to comments from the Vinyl Institute pointed out that the Barr (1982) analysis is too unsubstantial epidemiologically to be considered in this risk assessment.

COMMENT: "Barr estimates that 100 ppb is the approximate lifetime dose corresponding to a human risk of 10^{-6}. Purchase et al. (1987) note that Barr's estimate is similar to the highest estimates of 10^{-6} dose levels derived from animal data and are orders of magnitude higher than the conservative dose estimates which do not take into account low dose PK. This result is consistent with other observations that humans may be less sensitive than animals to the carcinogenic effects of VCM."

RESPONSE: Contrary to the comment, Barr, in his Table 1 and consistent with his text, found that the lifetime exposure for 10^{-6} risk was greater than 1 ppm, not 100 ppb, which was a mischaracterization appearing in the Table 4 of Purchase et al. (1987). The present DHS document gives 0.5 ppb as the lower confidence limit on lifetime exposure for 10^{-6} risk. Barr offers no rationale for using the weak data he selected from a 1975 EPA report in order to calculate his epidemiological estimate. These data do not appear to be appropriate for that purpose, and such inappropriate use of data would account for disagreement with the DHS value by orders of magnitude.

Also contrary to the comment, Purchase et al. (1987) do not specifically comment on Barr's estimate in their text. As stated in the response above, Purchase et al. do not present clear comparisons of effects of pharmacokinetics or of the results of using different basic forms of models for carcinogenesis. Finally, the commenter has offered no supported observations to show "that humans may be less sensitive than animals to the carcinogenic effects of VCM."

COMMENT: "Gehring et al. (1979) compared the results of an epidemiological study of approximately 10,000 occupationally exposed workers to the values predicted by four different mathematical models derived from animal data. They conclude that the observed human results are <u>inconsistent</u> with the two linear non-threshold models used, and are <u>consistent</u> with both the probit model and a linear threshold model. The latter two models predict 10^{-6} risk levels at <u>occupational</u> exposure levels in excess of 1 ppm."

RESPONSE: As pointed out in the response above and in the previous response to comments of the Vinyl Institute, the comparisons that Gehring et al. (1979) made are now out of date because of a follow up study of Wong et al. (1986), which found much higher rates of liver cancer incidence in vinyl chloride workers than in the data used by Gehring et al.

COMMENT: "These analyses by no means prove the validity of the two models and undoubtedly numerous other models would fit and give quite different results for predicting the ambient level corresponding to a 10^{-6} risk level. However, these analyses do show that human epidemiology data can be used to derive risk estimates for VCM exposures and that the models indicate that the linear non-threshold models are conservative by a substantial margin. This is to be expected in light of the well known conservativeness of the models. U.S. EPA, for instance, when presenting risks estimates describes them as upper bounds and notes that: "the true value of the risk is unknown and may be as low as zero" (Federal Register, 1986)."

RESPONSE: The DHS document does use human epidemiology data in the risk assessment. The DHS staff does not agree that the linear nonthreshold models extrapolate conservatively by a substantial margin, relative to actual incidence of cancer. Certainly, such models extrapolate conservatively compared to the log-probit model (Gehring et al. 1979: Model A), but that model is not in accord with present understanding of mechanisms of carcinogenesis applicable to vinyl chloride, whereas the linearized multistage model is in accord with such understanding and therefore most likely to extrapolate to low exposures accurately rather than being overly conservative. The feature of the unit risks that is health protective and might be characterized as in the conservative direction is the use of the 95% upper confidence limit (UCL) in order to provide adequate protection in the great bulk of cases. Any model with sufficient data can incorporate this feature. EPA does call such estimates "upper bounds," a term that is now commonly used for UCL although that usage is not in accord with the strict mathematical definition. The true risk is very unlikely to be exactly zero; so the quote from EPA, though possible as a point of logic, does not appear to enhance the readers perspective, particularly in cases of the maximally exposed individual.

COMMENT: "In an analysis of alternative modeling assumptions for animal to human extrapolation, Elizabeth Anderson, (1984) as head of the U.S. EPA Cancer Assessment Group found that alternative plausible modeling assumptions would lead to risk estimates that were 15-fold to 10,000-fold lower than the standard LMS procedure. Thus it is essential to use the available human data to place some perspective on the results predicted solely from animal data."

RESPONSE: The main issue in this comment is the question of what is considered plausible. If an extreme curve-fitting model such as the log-probit is compared against the more mechanism oriented linearized multistage model, then many-fold lower risks will be obtained for the log-probit.

COMMENT: "In an independent review of VCM, the National Health Council of the Netherlands (1987) derived ambient exposure levels corresponding to risk levels of 10^{-6} in humans. Their estimates were derived from both animal data and from epidemiological human data. While noting that the estimates did not

differ greatly, they expressed a preference for the human data and reported a value of 1 μg/cubic meter as corresponding to a risk of 10^{-6}. This value is approximately 80 times higher than the exposure level derived using the DHS unit risk of 20×10^{-5} per ppb."

RESPONSE: As pointed out in the DHS document at page 8-5, the Netherlands council obtained 1.2×10^{-6} per ppb for the unit risk of mortality due to liver cancer and 2.5×10^{-6} per ppb for all cancer. "Both these results were based on estimated atmospheric exposure. When those results are modified to take account the pharmacokinetics and to provide 95% upper confidence limits, the results are close to the present results." The DHS adjustment of the council's worker exposure of 500 ppm is 115 ppm, requiring a 4.3-fold adjustment upwards of their unit risks to account for pharmacokinetics. The council's average unit risk needs to be multiplied by about 2.3 to estimate the corresponding UCL value. The unit risks resulting from both multiplications are 10-fold greater, or 1.2×10^{-5} and 2.5×10^{-5} per ppb. These values are about half the corresponding epidemiology estimates in the document, based on the data of Waxweiler et al. (1976), which was one of the studies used by the Netherlands council for data on mortality due to cancer in vinyl chloride workers.

COMMENT: The over prediction of the models can be further demonstrated for VCM by comparing predictions of risk utilizing the DHS unit risk with human exposure scenarios. To make this comparison, Table 1 shows the "risk" predicted from the DHS model for a number of occupational exposure situations.

"It can be seen from Table 1 that incidence rates predicted from the linear animal model are completely incompatible with that observed in actual human studies. For example, in the study examined by Gehring (1970) there were only 5 observed cases in 9677 workers. This is approximately three orders of magnitude less than that which would be predicted by the DHS model.

Thus, there are a number of assessments based upon human epidemiological data which would indicate that linear models utilizing animal data overpredict risk by at least one to two orders of magnitude. In the interests of assuring that any proposed regulation is supported by as comprehensive a review of the available health data as possible, we submit these assessments should be incorporated into any risk assessments which will be used for regulatory control. This is particularly important in view of the fact that they are based upon human data rather than on laboratory animal results.

It can be seen from the above analysis that standard risk assessment methodology and the use of reported literature results lead to orders of magnitude over-estimates of the predicted risk from emissions of VCM from existing facilities. We recommend that these inconsistencies in the risk estiamtes be resolved if they are to be used as the basis for any proposed regulation."

RESPONSE: The incompatibility of predicted and observed incidence rates, as derived in the comments, arises because of the commenter's errors in making the predictions and the citation of incidence data that are not current and that do not permit adequate estimates of exposure. Thus, the commenter has made no sustainable case for overprediction or inconsistency of risk estimates in the document.