State of California
AIR RESOURCES BOARD

Staff Report: Initial Statement of Reasons for Proposed Rulemaking

Public Hearing to Consider the Adoption
of a Regulatory Amendment Identifying
Carbon Tetrachloride as a Toxic Air Contaminant

Agenda Item No.: 87-
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(This report has been reviewed by the staffs of the California Air Resources Board and the California 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 or commercial products constitute endorsement or recommendation for use.)

EXECUTIVE SUMMARY

INTRODUCTION AND RECOMMENDATION

Health and Safety Code section 39655 defines a toxic air contaminant as an air pollutant which the Air Resources Board or the Department of Food and Agriculture finds "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 staffs of the Air Resources Board (ARB) and the Department of Health Services (DHS) have reviewed the available scientific evidence on the presence of carbon tetrachloride in the atmosphere of California and its potential adverse effect on public health. Based on the finding of carcinogenicity and the results of the risk assessment, the DHS staff finds that carbon tetrachloride meets the definition of a toxic air contaminant. Therefore, the staff of the Air Resources Board recommends that carbon tetrachloride be identified by the Board as a toxic air contaminant. In making this recommendation, the ARB and DHS staffs found that there is not sufficient available scientific evidence at this time to support the identification of an exposure level below which carcinogenic effects would not have some probability of occurring and recommend that carbon tetrachloride be treated as having no threshold.

The Scientific Review Panel (SRP), established by Health and Safety Code section 39670, reviewed the report in accordance with Health and Safety Code section 39661. The findings of the SRP are attached at the end of the Executive Summary.

Carbon tetrachloride was chosen for evaluation because: it has been identified by the International Agency for Research on Cancer (IARC) as an animal carcinogen and a potential human carcinogen; its presence in the atmosphere has been documented; and it is emitted from several sources in the state.

SOURCES OF CARBON TETRACHLORIDE

An emissions inventory compiled by the ARB staff indicates that in 1984, a minimum of 60 tons of carbon tetrachloride was emitted in California. The major identified emission sources of carbon tetrachloride in California are: 1) carbon tetrachloride production; 2) pesticide/grain fumigant usage; 3) chlorinated paraffin wax production; and 4) fluorocarbon production. Of these four sources, carbon tetrachloride production and pesticidal/grain fumigant usage accounted for over 80 percent of the estimated emissions. Other emission sources of carbon tetrachloride include oil companies, scientific laboratories, organic chemical manufacturing companies, and publicly owned treatment works. An effort was made by the ARB staff to estimate the emissions from these sources; however, the staff was unable to obtain the necessary information to do so. The ARB staff believes that emissions from these sources are not significant when compared to the emissions from the identified sources.

The Environmental Protection Agency (EPA) has canceled the registrations of pesticide products containing carbon tetrachloride as an active ingredient. Grain fumigants containing carbon tetrachloride will no longer be allowed for agricultural uses in the United States and thus, future emissions are expected to be reduced. Grain fumigant usages accounted for 30 percent of the 1984 estimated emissions in California. The ARB staff believes that this reduced usage would offset any increases in emissions that could result from possible increases in carbon tetrachloride use.

EXPOSURE TO CARBON TETRACHLORIDE

Once carbon tetrachloride is in the troposphere, it is a stable gaseous compound. Due to the lack of rapid tropospheric removal mechanisms, carbon tetrachloride accumulates in the lower atmosphere and has an estimated atmospheric lifetime* of 50 years.

* Atmospheric lifetime is defined as the time required for a given amount of compound to decrease 1/e (0.368) of its original value at time zero.

In 1985, the ARB established a twenty station monitoring network throughout California to measure levels of potentially toxic compounds, including carbon tetrachloride. From the toxic monitoring network, a statewide annual average carbon tetrachloride concentration of 0.13 parts per billion (ppb) (0.82 microgram per cubic meter ($\mu g/m^3$)) was estimated. This annual average concentration is comparable to the documented global background levels of 0.11 and 0.15 ppb (0.69 and 0.94 $\mu g/m^3$). Therefore, the ARB staff believes the statewide annual average carbon tetrachloride concentration reflects the global background concentration. This means that the most common source of exposure to ambient carbon tetrachloride is from the global background concentration which is not related to emission sources in California.

While everyone is exposed to at least the background concentration, people living or working near emission sources of carbon tetrachloride are likely to be exposed to concentrations several times greater than this. Based on dispersion modeling analysis, the ARB staff estimated that 550 people in the San Francisco Bay Area can be exposed to a maximum annual average concentration of 0.62 ppb (3.9 $\mu g/m^3$), with peak hourly levels as high as 170 ppb (1070 $\mu g/m^3$). In the South Coast Air Basin, 1,500 people can be exposed to a maximum annual average concentration of 0.32 ppb (2.0 $\mu g/m^3$). These maximum annual average concentrations are the sum of estimated annual average concentrations above background from modeled emission sources and the statewide annual average concentration of 0.13 ppb (0.82 $\mu g/m^3$) as estimated from the ARB monitoring network.

The ARB staff also estimated the annual average population-weighted concentrations for the modeled emission sources. This concentration is defined as the annual concentration that the "average" person in the modeling area is exposed to. Applying these concentrations and the population in the modeled areas to the DHS upper-bound risk estimates, the range of excess cancer cases that could possibly result from the release of carbon tetrachloride emissions in each area can be estimated. For the Bay Area sources, the annual average population-weighted concentration for 210,000 people within the modeling area is estimated to be 0.014 ppb

(0.09 $\mu g/m^3$) above the background concentration. The annual average population-weighted concentration for the South Coast Air Basin source is estimated to be 0.0016 ppb (0.01 $\mu g/m^3$) above background for the 2,270,000 people in this modeling area.

With respect to indoor levels of carbon tetrachloride, the ARB staff reviewed available draft reports and conference papers which assessed the carbon tetrachloride concentrations in the indoor (mostly homes) and the outdoor ambient environments. Because of uncertainties in the studies that were reviewed, the ARB staff could not establish the relationship between indoor and outdoor concentrations. Some of the monitoring data suggested that indoor and outdoor carbon tetrachloride concentrations within an area are similar, while other results showed differences between the two. Elevated indoor concentrations could be caused by indoor sources such as commercial cleaning products, consumer products, and water which may contain carbon tetrachloride. Elevated outdoor concentrations could be influenced by local emission sources in the area. At this time, there is not sufficient information to establish how emission sources contribute to elevated indoor or outdoor carbon tetrachloride concentrations.

In addition to inhalation of ambient air, another route of exposure for carbon tetrachloride is through the ingestion of water and grain products that contain carbon tetrachloride. Based on limited information, it appears that for a small percentage of the population in the South Coast Air Basin, ingestion of water containing carbon tetrachloride can be a significant exposure route. Intake of carbon tetrachloride at the maximum levels in drinking water can cause an estimated intake similar to that from the inhalation of ambient air at the maximum annual average concentrations from modeled emission sources. The ARB is currently sponsoring a study of publicly owned treatment works (POTWs) in California to determine the concentrations of selected compounds, including carbon tetrachloride. Preliminary results suggest that the carbon tetrachloride concentrations are lower than the concentrations found in an earlier POTWs study. The ARB staff believes that the lower concentrations reflect the reduced usage of carbon tetrachloride by industrial sources in California.

The usage of carbon tetrachloride as a grain fumigant is the likely cause of how this compound gets into food products. Ingestion of food products containing carbon tetrachloride at elevated levels may be an important exposure route. Available data was adequate only to determine an upper limit of potential intake and the ARB staff could not determine the percent of the population exposed to different levels of carbon tetrachloride. Therefore, the relative importance of ingestion of food products containing carbon tetrachloride cannot be determined at this time. The ARB staff believes that because of EPA's restrictions on the use of grain fumigants containing carbon tetrachloride, levels found in food products will likely be reduced significantly in the future.

HEALTH EFFECTS OF CARBON TETRACHLORIDE

Accidental acute exposure incidents and animal experiments indicate that carbon tetrachloride can produce liver and kidney damage and have numerous effects on the nervous system. Chronic exposure to carbon tetrachloride to humans in occupational settings has produced neurological effects and elevation of serum liver enzymes indicating liver damage. Long-term animal exposure to similar levels of carbon tetrachloride found in occupational settings has produced liver and kidney damage. The potential for reproductive effects due to carbon tetrachloride exposure cannot be ascertained since it has not been adequately studied at this time.

Adverse health effects other than cancer are not expected to occur due to inhalation of carbon tetrachloride at current or future atmospheric concentrations. Both peak exposure concentrations and measured ambient concentrations are at least two orders of magnitude lower than those concentrations which are associated with chronic adverse health effects in occupational settings or which have produced acute effects in animal experiments.

RISK DUE TO ATMOSPHERIC CARBON TETRACHLORIDE

The cancer risk assessment for carbon tetrachloride used by DHS was developed by EPA based on animal studies in which carbon tetrachloride was administered orally. For exposure to 0.16 ppb (1 $\mu g/m^3$) of carbon tetrachloride, the DHS staff estimated the upper limit risk to be between 10 and 42 excess lifetime cancers per million people continuously exposed over their lifetime. The DHS staff believes that this range represents the best estimate of the excess risk associated with inhalation exposure to carbon tetrachloride based on the available data.

The hazard posed by exposure to atmospheric carbon tetrachloride to California's population of 26,600,000 was estimated by applying the DHS unit risk estimate to the statewide annual mean concentration of 0.13 ppb (0.82 $\mu g/m^3$). The DHS estimated upper-bound excess lifetime cancer risk from exposure to the statewide annual mean concentration is between 8 and 34 cancer cases per million people exposed continuously over 70 years. Thus, the number of excess lifetime cancer incidences for Californians who are exposed to 0.13 ppb (0.82 $\mu g/m^3$) is estimated to be between 210 and 910.

However, people living near emission sources of carbon tetrachloride can be exposed to concentrations above the background level. Based on modeling analysis of emission sources in the San Francisco Bay Area and the South Coast Air Basin, the ARB staff estimated the population-weighted concentrations above background to be 0.014 ppb (0.09 $\mu g/m^3$) for 210,000 people in San Francisco Bay Area and 0.0016 ppb (0.01 $\mu g/m^3$) for 2,270,000 people in the South Coast Air Basin. The combined number of excess lifetime cancer incidences from exposure to these sources is estimated to range from less than one to two.

The DHS staff emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent best estimates based on current scientific knowledge and methods. The upper-bound excess lifetime risks that were estimated above are health-conservative estimates; the actual risks are likely to be below these values.

ALTERNATIVES

Government Code Section 11246.14 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 carbon tetrachloride as a toxic air contaminant is to not identify it. The ARB staff is not recommending this alternative because the staff believes that carbon tetrachloride meets the statutory definition of a toxic air contaminant. There are no alternatives considered by the ARB staff which would be more effective in carrying out the purpose for which the regulation is proposed or would be as effective and less burdensome to affected private person than the proposed regulation.

SUMMARY OF ENVIRONMENTAL IMPACTS OF THE IDENTIFICATION OF CARBON TETRACHLORIDE AS A TOXIC AIR CONTAMINANT

The identification of carbon tetrachloride as a toxic air contaminant is not in itself expected to result in any environmental effects. The identification of carbon tetrachloride as a toxic air contaminant by the Board may result in the Board and air pollution control districts adopting toxic control measures in accordance with Health and Safety Code sections 39665 and 39666. Any such toxic control measures would result in reduced emissions of carbon tetrachloride to the atmosphere, resulting in reduced ambient concentrations, concurrently reducing the health risk due to carbon tetrachloride exposure. Therefore, the identification of carbon tetrachloride as a toxic air contaminant may ultimately result in environmental benefits. Environmental impacts identified with respect to specific control measures will be included in the consideration of such control measures pursuant to Health and Safety Code sections 39665 and 39666.

TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CARBON TETRACHLORIDE

PART A - PUBLIC EXPOSURE TO, ENVIRONMENTAL FATE OF, AND SOURCES OF, ATMOSPHERIC CARBON TETRACHLORIDE IN CALIFORNIA

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May 1987

(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. Literature reviewed for this report is based on information obtained from searches of computer databases available through May 1987.)

FINAL DRAFT
REPORT TO THE AIR RESOURCES BOARD
ON CARBON TETRACHLORIDE

Part A - Public Exposure to, Environmental Fate of, and Sources of, Atmospheric Carbon Tetrachloride

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I. EXPOSURE TO CARBON TETRACHLORIDE

A. EXPOSURE ABOVE GLOBAL BACKGROUND CONCENTRATIONS

Many Californians are exposed to carbon tetrachloride concentrations greater than the global background concentration; particularly people who reside or work near carbon tetrachloride emission sources. Major emission sources exist in several areas around the state. The San Francisco Bay Area has two large sources of carbon tetrachloride located near each other: the Dow Chemical Plant in Pittsburg (a carbon tetrachloride producer) and the E. I. du Pont Plant in Antioch (a fluorocarbon producer). Together, these two facilities emitted an estimated 31 tons of carbon tetrachloride in 1984. The South Coast Air Basin (SoCAB) also has two sources that emit carbon tetrachloride. They are Allied Chemical in El Segundo (a fluorocarbon producer) and Neville Chemicals in Santa Fe Springs (a chlorinated wax producer). Together, these sources emitted approximately 3 tons of carbon tetrachloride in 1984.

Carbon tetrachloride is used in pesticidal applications mainly as a grain fumigant. In 1984, approximately 20 tons of carbon tetrachloride were emitted into the atmosphere from grain fumigant usages. This was the second largest source of carbon tetrachloride emissions in California. Most of the grain fumigants were used in Yolo and San Joaquin counties.

Other potential sources of carbon tetrachloride emissions are oil companies, scientific laboratories, organic chemical manufacturing companies, pesticide manufacturing companies, publicly owned treatment works, and small sources that use carbon tetrachloride as a miscellaneous solvent or as a feedstock in a manufacturing process. The ARB staff attempted to estimate the emissions from these other sources, but the

staff was unable to obtain the information to do so. These sources are primarily located in the San Francisco Bay Area and the South Coast Air Basin. However, the ARB staff believes that these are not significant emission sources.

In order to determine the impact of emission sources on nearby population, the ARB staff modeled the emissions from the Dow and du Pont facilities in the San Francisco Bay Area and Neville Chemical facility in the South Coast Air Basin. The modeling and exposure assessments indicate that some people in the San Francisco Bay Area are exposed to annual average peak concentrations as high as 0.49 parts per billion (ppb)(3.1 microgram per cubic meter (ug/m^3)) of carbon tetrachloride above the background concentration of 0.13 ppb (0.82 ug/m^3), while some people in the South Coast Air Basin are exposed to an annual concentration as high as 0.19 ppb (1.2 ug/m^3) above the background concentration. The maximum annual average concentration that people in the Bay Area and South Coast modeling regions can be exposed to is the sum of the highest annual average concentration above background and the background concentration. Thus, the maximum annual average concentration for the modeled regions are 0.62 ppb (3.9 ug/m^3) and 0.32 ppb (2.0 ug/m^3) respectively. In general, peak hourly average concentrations can be 100 to 1,000 times the maximum annual average concentration. Under worst case meteorological conditions, the peak hourly average concentration from the Dow facility could be as high as 170 ppb (1070 ug/m^3). Cumulative and non-cumulative population exposures from the modeling assessments of the two sources in the Bay Area and the single source in the South Coast Air Basin are summarized in Tables I-1 and I-2 and Figure I-1 and I-2.

Table I-1

Estimated Annual Average Carbon Tetrachloride Exposure Levels Above Background Near Dow Chemical and E.I. du Pont

Carbon Tetrachloride Concentration* (ppb)	(ug/m^3)	Population	Cumulative* Population
<0.001	<0.006	25,000	210,000
0.001 - 0.05	0.006-0.31	174,000	185,000
0.051 - 0.10	0.31-0.63	4,800	11,000
0.101 - 0.15	0.63-0.94	3,000	6,400
0.151 - 0.20	0.94-1.26	1,000	3,400
0.201 - 0.25	1.26-1.57	0	2,400
0.251 - 0.30	1.57-1.88	1,500	2,400
0.301 - 0.35	1.88-2.20	390	930
0.351 - 0.40	2.20-2.51	0	550
0.401 - 0.45	2.51-2.83	0	550
0.451 - 0.50	2.83-3.15	550	550
>0.50	>3.14	0	0

* Estimates have been rounded. Concentrations do not include background contribution.

Figure I-1

Estimated Annual Average Carbon Tetrachloride Exposure Levels Above Background Near Dow Chemical and E.I. du Pont

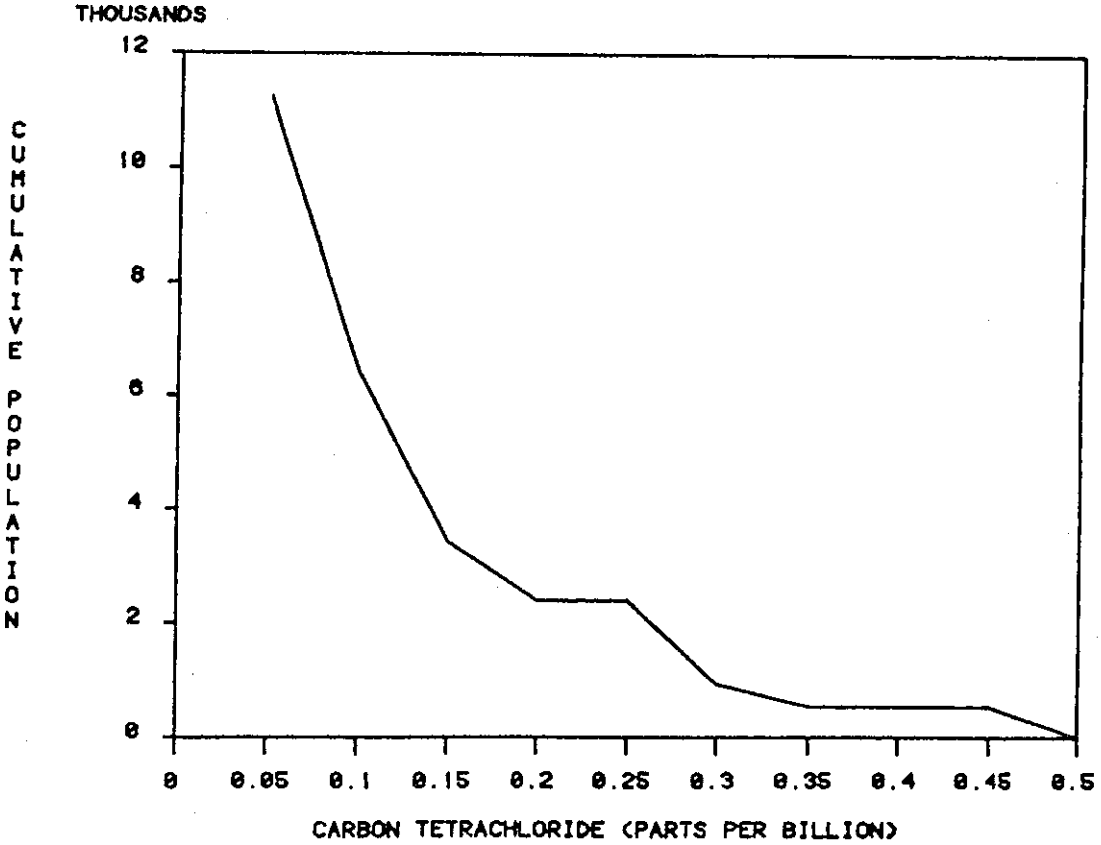


Table I-2

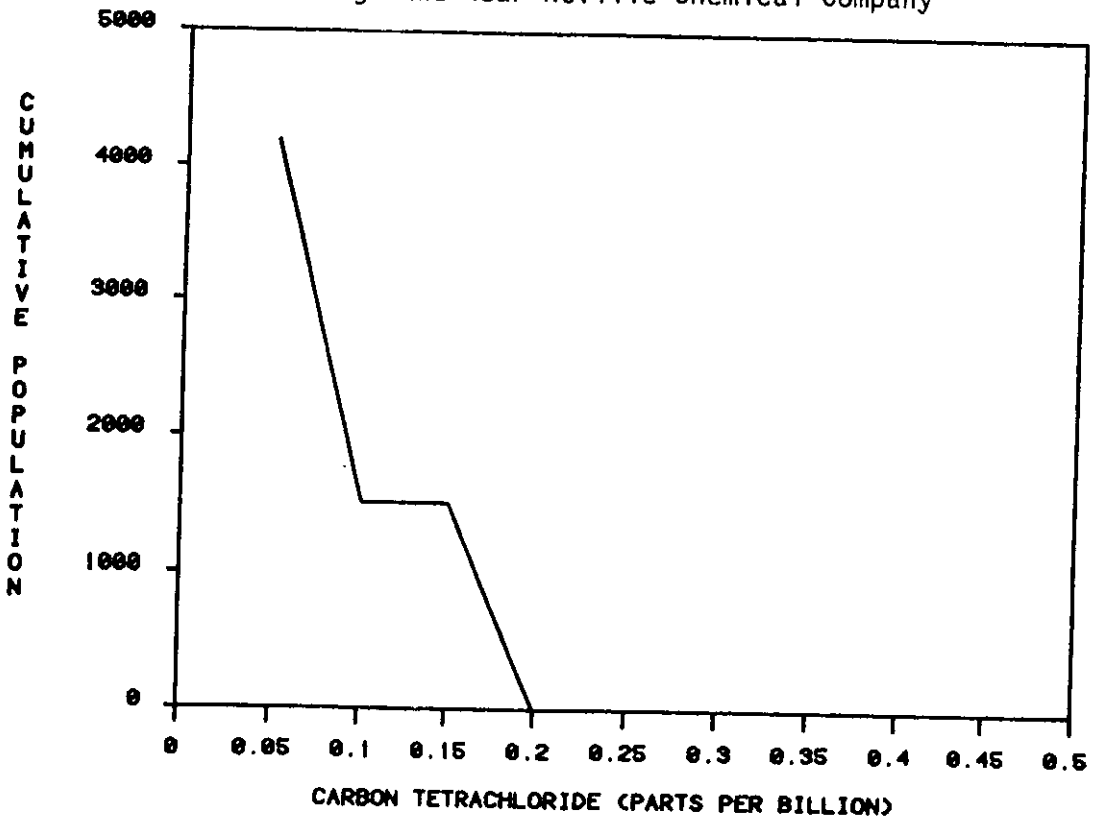
Estimated Annual Average Carbon Tetrachloride Exposure Levels Above Background Near Neville Chemical Company

Carbon Tetrachloride Concentration* (ppb)	(ug/m^3)	Population	Cumulative* Population
<0.001	<0.006	1,350,000	2,270,000
0.001 - 0.05	0.006-0.31	920,000	924,000
0.051 - 0.10	0.31-0.63	2,700	4,200
0.101 - 0.15	0.63-0.94	0	1,500
0.151 - 0.20	0.94-1.26	1,500	1,500
>0.200	>1.26	0	0

* Estimates have been rounded. Concentrations do not include background contribution.

Figure I-2

Estimated Annual Average Carbon Tetrachloride Exposure Levels Above Background Near Neville Chemical Company



The ARB staff used the Industrial Source Complex Short Term (ISCST) Gaussian dispersion model to estimate the concentration of carbon tetrachloride at gridded receptors around the source (Neville Chemical) or sources (Dow Chemical and du Pont). Meteorological data, as required by the ISCST model, were obtained from Travis Air Force Base for the Bay Area analysis and the Long Beach Airport for the South Coast Air Basin analysis. Population data were derived from the 1980 census, the emission estimates for the facilities were obtained from the Bay Area Air Quality Management District or the South Coast Air Quality Management District.

The concentration for each square kilometer receptor in the 31 X 31 kilometer receptor array was multiplied by the population in the grid cell surrounding the receptor. The exposure value for each receptor was summed to obtain the total exposure contributed by this facility. The concentration and population exposure represent levels that do not include ambient background contributions; possible additive or cumulative exposure is not addressed in this analysis.

Figure I-3 illustrates the annual carbon tetrachloride concentrations interpolated to a 31 X 31 kilometer gridded area surrounding Dow Chemical and du Pont. The two emission points from Dow Chemical are at the center of the grid and the small single peak at the right represents du Pont. Estimates of annual average above background carbon tetrachloride concentrations range from less than 0.001 ppb (0.0006 ug/m^3) at the edges of the gridded area to 0.49 ppb (3.1 ug/m^3) near the center of the source. Therefore, a person near the center of the source can be exposed to concentrations almost 4 times higher than background concentrations. The maximum annual average concentration of 0.62 ppb (3.9 ug/m^3) was estimated for this source by adding the highest concentration of 0.49 ppb

Figure I-3

Annual Average Carbon Tetrachloride Concentrations

Above Ambient (ppb) Near Dow Chemical and E.I. du Pont

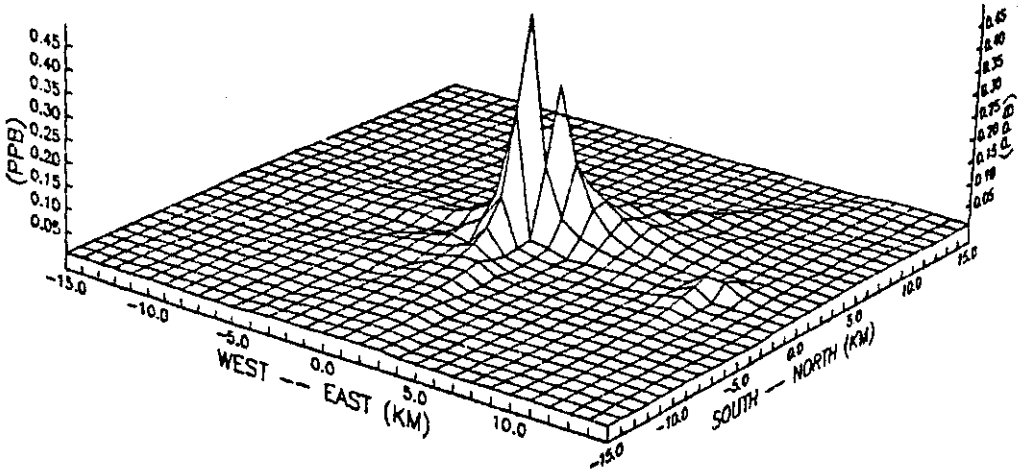
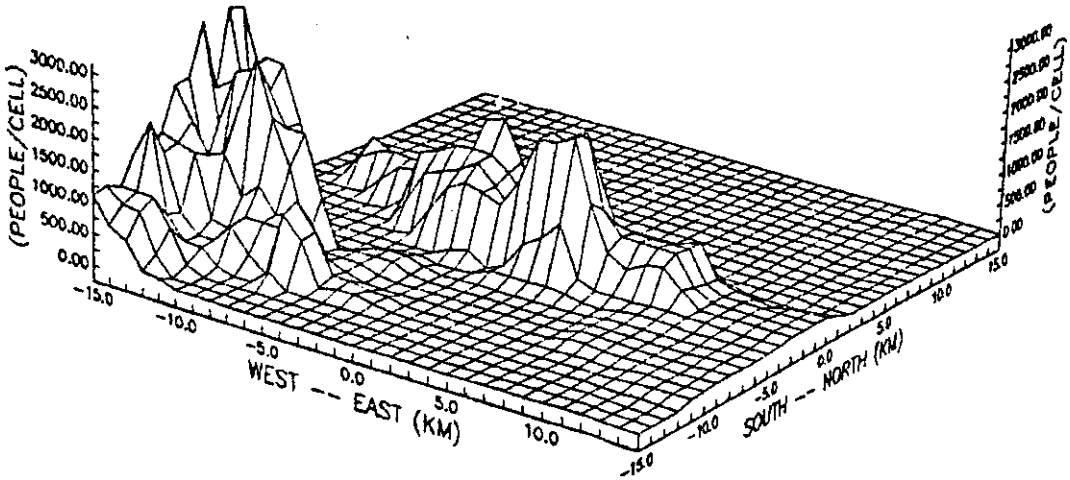


Figure I-4

Population Density Near Dow Chemical and E.I. du Pont



(3.1 ug/m^3) from the emission source and the background concentration of 0.13 ppb (0.82 ug/m^3). A plot of population density within the study area is shown in Figure I-4. The cities of Pittsburg and Antioch are in the center while Concord is at the lower left.

Figure I-5 illustrates the annual carbon tetrachloride concentrations interpolated to a 31 X 31 kilometer gridded area surrounding Neville Chemical Company. Annual average above background concentrations are estimated to range from less than 0.0001 ppb (0.0006 ug/m^3) at the edges of the gridded area to 0.19 ppb (1.2 ug/m^3) near the center of the source. People near the source can be exposed to concentrations 1 1/2 times that of the background concentrations. The maximum annual average concentration of 0.32 ppb (2.0 ug/m^3) for this source is estimated by adding the highest modeled concentration of 0.19 ppb (1.2 ug/m^3) and the background concentration of 0.13 ppb (0.82 ug/m^3). A plot of population density within the Neville Chemical gridded area is shown in Figure I-6.

In addition to estimating the range of annual average concentrations for each area that was modeled, the ARB staff also estimated the annual average population-weighted concentrations. This concentration is defined as the annual concentration that the "average" person in the modeled area is exposed to. For the Bay Area modeling analysis of Dow/duPont, it was estimated that 210,000 people are exposed to an annual average population-weighted concentration of 0.014 ppb (0.09 ug/m^3) above background. In the South Coast Air Basin, the Neville Chemical Company modeling analysis indicated that 2,270,000 people are exposed to an estimated annual average population-weighted concentration of 0.0016 ppb (0.01 ug/m^3) above background.

Figure I-5

Annual Average Carbon Tetrachloride Concentrations

Above Ambient Levels Near Neville Chemical Company

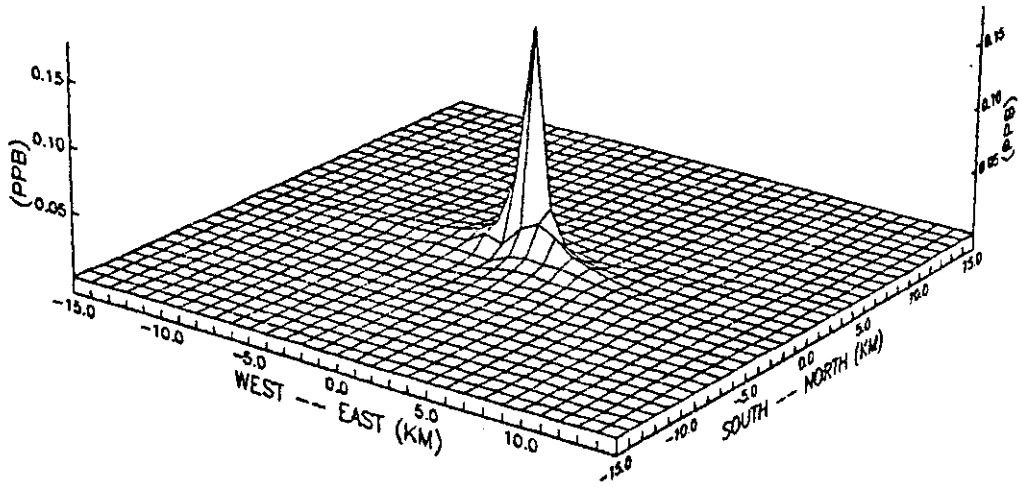
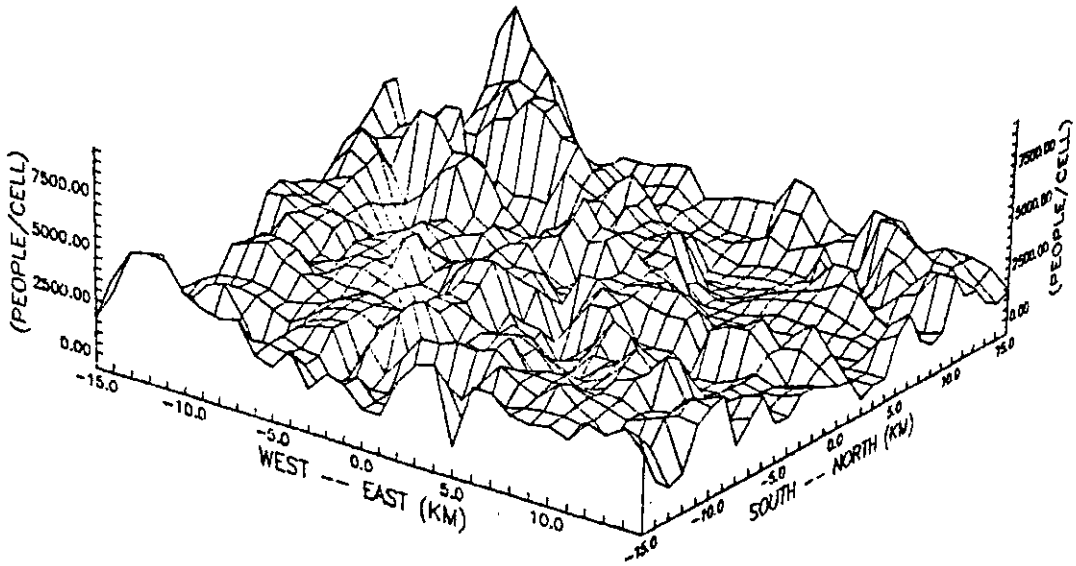


Figure I-6

Population Density Near Neville Chemical Company



To determine the annual average population-weighted concentration, the carbon tetrachloride concentrations in each gridded receptor area within the modeling region are estimated from dispersion modeling analysis. The concentration in each grid is multiplied by the population within the grid and divided by the total population in the modeling region. These values are then summed to give an estimate of the annual average population-weighted concentration for the modeling area. Since the risk is linear to the exposure, the population-weighted annual average concentration along with the DHS upper-limit risk estimate can be used to calculate the excess cancer cases from the release of emissions from the modeled emission sources.

B. EXPOSURE TO GLOBAL BACKGROUND CONCENTRATIONS

Carbon tetrachloride in the atmosphere is emitted mainly by anthropogenic sources. It has been suggested that carbon tetrachloride may be formed in the troposphere from the photolysis of perchloroethylene (Singh, et al., 1976). However, under normal atmospheric conditions, this formation process appears to have an insignificant impact on carbon tetrachloride concentrations in California.

Once in the atmosphere, carbon tetrachloride is very persistent with an atmospheric lifetime estimated to be approximately 50 years. Researchers estimate that the tropospheric carbon tetrachloride concentration is increasing at a rate of approximately 2 percent per year and that presently, a global background concentration between 0.11 and 0.15 ppb (0.69 and 0.94 ug/m^3) exists in the troposphere (Environmental Studies Board, 1978, Prinn, et al., 1983). Based on the ARB's monitoring network, the geographic annual average concentration in California is estimated to be 0.13 ppb (0.82 ug/m^3). Thus, Californians are exposed to at least this concentration of

carbon tetrachloride.

Diffusion of carbon tetrachloride from the troposphere to the stratosphere where ultraviolet photolysis can occur is the major identified removal mechanism of carbon tetrachloride. Other possible removal mechanisms for carbon tetrachloride include reactions with hydroxyl radicals and ground state oxygen atoms, absorption into the ocean, adsorption onto particulate matter, and wet deposition. However, all of these mechanisms do not occur rapidly enough to significantly remove carbon tetrachloride from the atmosphere. Therefore, the emission rate is greater than the removal rate for carbon tetrachloride which causes it to accumulate to form the global background level. Chapter III discusses these tropospheric removal mechanisms for carbon tetrachloride in greater detail.

In order to validate the theory that there are no rapid removal mechanisms for carbon tetrachloride, several researchers have estimated global background concentrations based on global emissions and known atmospheric removal mechanisms for carbon tetrachloride and compared the calculated values with measured concentrations. Table I-3 presents the range of carbon tetrachloride concentrations calculated and/or measured by these researchers.

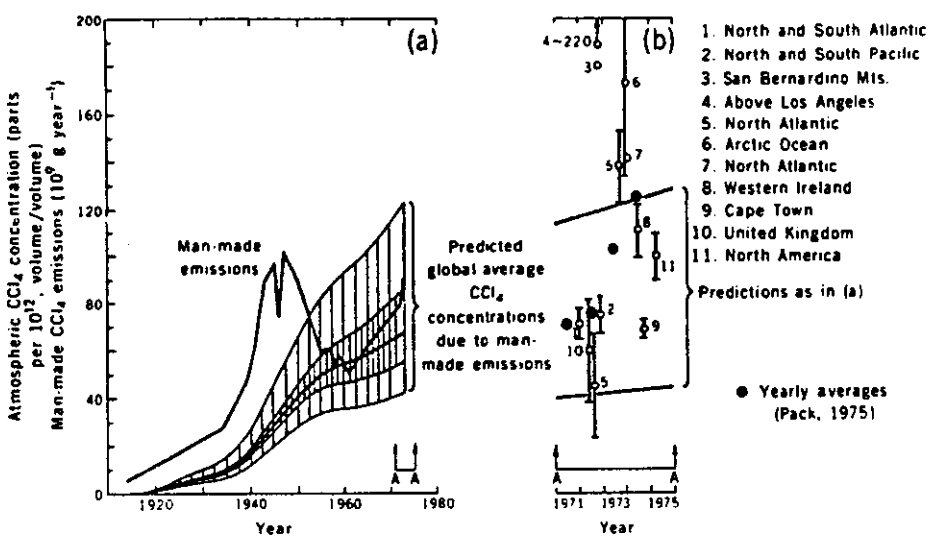
Comparison of the calculated and measured carbon tetrachloride concentrations indicate that the calculated concentrations based on global emissions and known removal mechanisms are in good agreement with the measured concentrations. This implies that all major removal mechanisms were accounted for in the calculated values. The values in Table I-3 are 1976 estimates and should be increased by about 20 percent to account for releases into the atmosphere since 1976 (see Section II). This would give an estimated

Table I-3
Tropospheric Carbon Tetrachloride Concentrations (ppb)*

	Concentration	References
Calculated Tropospheric Concentrations	0.070-0.095	Singh et al., 1976
	0.050-0.130	Galbally, 1976
	0.060-0.088	Altshuller, 1976
	0.120-0.162	NRC, 1976a
Measured Tropospheric Concentrations	0.130	Rasmussen, et al., 1986
	0.103-0.144	Kirschmer, et al., 1983
	0.110-0.150	Borchers, et al., 1983
	0.112-0.132	Prinn, et al., 1983
	0.120-0.140	Rasmussen, 1976
	0.110-0.130	Su & Goldberg, 1977
	0.130-0.170	Lovelock, 1976
	0.061-0.069	Penkett, 1976
	0.130-0.170	Pearman, 1976
	0.060	Goldman, 1976
	0.059-0.065	Sandalls, 1976

*Based on information from a search of computer databases available through May 1987.

Figure I-7
Global Emissions and Resultant Global Concentrations



(a) Predicted global average concentration of carbon tetrachloride due to man-made emissions. The inner hatched area indicates the uncertainty due to loss mechanisms. The shaded area indicates the uncertainty due to loss mechanisms and a ± 30 percent variation in the emission rates. (b) Observed carbon tetrachloride concentrations and predicted global average concentrations from (a).

range of approximately 0.06 to 0.20 ppb (0.38 to 1.26 ug/m^3) for 1986. Figure I-7 shows a direct comparison estimate of global emissions and the resultant estimates of global concentration from the time carbon tetrachloride was first produced (Galbally, 1976).

The most complete and comprehensive study reviewed by ARB staff was the Atmospheric Lifetime Experiment or ALE (Prinn, et al., 1983). Although the purpose of the ALE study was to estimate the atmospheric lifetime of carbon tetrachloride and other halogenated compounds, a number of other useful conclusions came out of the study. It demonstrated that there is a fairly uniform background concentration for carbon tetrachloride which varies only by a few parts per billion around the world and that this concentration is increasing steadily at a rate of approximately 2 percent per year. The ALE study also provided a well documented estimate of the atmospheric lifetime for carbon tetrachloride, 52 $\pm$ 15 years. Because the conclusions of the ALE study are fundamental to the conclusions given here, the study has been summarized in Appendix A.

C. AMBIENT CARBON TETRACHLORIDE CONCENTRATIONS IN CALIFORNIA

In 1985, the ARB established a 20 station monitoring network throughout California to measure potentially toxic compounds, including carbon tetrachloride. These monitoring sites were selected so that measured concentrations would be representative of the concentrations that the local population is exposed to. The preliminary 1985 monitoring data indicates that Californians are exposed to an estimated statewide annual average concentration of 0.13 ppb (0.82 ug/m^3). This concentration is consistent with the global background concentrations which have been measured or estimated by various researchers (see Chapter 1, Section B). The ARB staff

Table I-4
1985 ARB Carbon Tetrachloride Monitoring Data
Range of Estimated Mean Concentrations

Air Basin Site Location	Lower Bound (ppb)	Lower Bound (ug/m^3)	Mean Concentration (ppb)	Mean Concentration (ug/m^3)	Upper Bound (ppb)	Upper Bound (ug/m^3)
Sacramento Valley						
Citrus Heights	0.12	0.75	0.13	0.82	0.14	0.88
San Diego						
Chula Vista	0.10	0.63	0.11	0.69	0.12	0.75
El Cajon	0.11	0.69	0.12	0.75	0.13	0.82
San Francisco Bay Area						
Concord	0.12	0.75	0.14	0.88	0.17	1.06
Fremont	0.13	0.82	0.16	1.0	0.19	1.19
Richmond	0.12	0.75	0.14	0.88	0.15	0.94
San Francisco	0.12	0.75	0.13	0.82	0.15	0.94
San Jose	0.13	0.82	0.15	0.94	0.18	1.13
San Joaquin Valley						
Bakersfield	0.14	0.88	0.16	1.0	0.17	1.06
Fresno	0.13	0.82	0.15	0.94	0.16	1.0
Merced	0.12	0.75	0.14	0.88	0.15	0.94
Modesto	0.12	0.75	0.14	0.88	0.15	0.94
Stockton	0.14	0.88	0.16	1.0	0.19	1.19
South Central Coast						
Santa Barbara	0.11	0.69	0.12	0.75	0.13	0.82
Simi Valley	0.11	0.69	0.12	0.75	0.13	0.82
South Coast						
El Monte	0.11	0.69	0.12	0.75	0.13	0.82
Los Angeles	0.12	0.75	0.13	0.82	0.14	0.88
North Long Beach	0.12	0.75	0.13	0.82	0.14	0.88
Riverside	0.11	0.69	0.12	0.75	0.13	0.82
Upland	0.12	0.75	0.14	0.88	0.16	1.0
Statewide			0.13	0.82		

believes that almost all of the ARB monitoring stations are measuring carbon tetrachloride concentrations that represent global background levels. Table I-4 summarizes the annual mean carbon tetrachloride concentrations along with the upper and lower bounds for each of the monitoring stations. The upper and lower bounds give a range of the annual average concentration for each station by taking into account the variability of the sampling data and the small number of samples taken at each station.

Out of 20 monitoring stations, three stations are believed to have slightly elevated annual mean concentrations. These stations are Bakersfield, Fremont, and Stockton. Several factors could cause elevated or high annual mean carbon tetrachloride concentrations in an area. These factors are: (1) the contribution from major point sources of carbon tetrachloride emission sources; (2) minor sources in conjunction with certain meteorological conditions such as temperature inversions; and (3) the photodissociation process of chloroethylenes (perchloroethylene) to form carbon tetrachloride in the troposphere. These factors were reviewed by the ARB staff to determine if any or all of these factors could have caused elevated mean carbon tetrachloride concentrations at any of the monitoring sites.

The ARB staff believes that the most important factor which can influence the elevated mean carbon tetrachloride concentrations are effects caused by local emission sources in the area. Based on known or identified carbon tetrachloride emission sources in California, the Stockton site may be expected to have an elevated mean concentration. This is because of the use of carbon tetrachloride containing pesticides in the area. The Fremont station, on the other hand, may be influenced by smaller sources which are unaccounted for in the inventory along with poor dispersion conditions. At

this time, there is not sufficient information to identify these minor sources. The ARB staff could not account for the elevated mean concentration at the Bakersfield station. However, the small number of samples taken and the uncertainties in the analytical and sampling procedures are believed to cause the elevated mean concentration at this station.

In order to determine if small unidentified sources were impacting the measured annual mean concentrations, the ARB staff compared measured carbon tetrachloride concentrations to periods of stagnant atmospheric conditions. Because carbon monoxide (CO) is emitted uniformly throughout the year, high CO concentrations are an indication of poor meteorological dispersion. Therefore, if stagnant conditions were contributing to high carbon tetrachloride concentrations, there should be a correlation between high CO concentrations and high carbon tetrachloride concentrations. The results of the CO and carbon tetrachloride correlation comparison showed no relationship between high carbon tetrachloride levels and conditions of poor dispersion (high CO levels) with the exception of the Fremont station with a correlation coefficient of 0.52. This implies that poor dispersion may be a factor which contributed to elevated carbon tetrachloride at the Fremont station. There was no close correlation for any of the other sites. Table I-5 summarizes the CO versus carbon tetrachloride correlation analysis. The plots of CO versus carbon tetrachloride are shown in Appendix B.

The absence of a strong CO versus carbon tetrachloride correlation at most of the stations indicates that if small emission sources are

Table I-5

Results of the Carbon Monoxide to
Carbon Tetrachloride Correlation Analysis

Air Basin Site Location	Number of Observations	Correlation Coefficient
Sacramento Valley		
Citrus Heights	29	0.02
San Diego Air Basin		
Chula Vista	20	0.06
El Cajon	18	0.04
San Francisco Bay Area Air Basin		
Concord	18	0.17
Fremont	17	0.52
Richmond	16	0.03
San Francisco	15	0.04
San Jose	17	0.00
San Joaquin Valley Air Basin		
Bakersfield	25	0.14
Fresno	23	0.02
Merced	-	-
Modesto	23	0.03
Stockton	19	0.20
South Central Coast Air Basin		
Santa Barbara	19	0.05
Simi Valley	11	0.00
South Coast Air Basin		
El Monte	-	-
Los Angeles	20	0.25
North Long Beach	22	0.13
Riverside	20	0.04
Upland	20	0.00

causing elevated concentrations, they are probably intermittent releases of carbon tetrachloride. Currently, two samples a month are taken at each site. The ARB staff feels that two samples a month is not sufficient to reliably estimate the effects of intermittent sources on annual average concentrations. If carbon tetrachloride is identified as a toxic air contaminant, the ARB staff will identify any small sources which may be causing elevated exposures.

Based on a laboratory study under controlled experimental conditions, it has been suggested that carbon tetrachloride can be formed from the photodissociation of perchloroethylene (perc). If the formation process is important in the atmosphere, one would expect a correlation between perc concentrations and carbon tetrachloride concentrations. Since intensity of sunlight is important in this formation process, the ARB staff analyzed the perc and carbon tetrachloride monitoring data for the months of May through September to determine if there is a correlation between the perc and carbon tetrachloride concentrations. Based on our analysis, little correlation was found. Although carbon tetrachloride may be formed by this process, it does not appear to be an important factor in the measured carbon tetrachloride levels in California. The ARB staff feels that there is insufficient information to determine the impact of this formation process under actual tropospheric conditions at this time. A more detailed discussion of the perc photolysis process is contained in Chapter III.

Based on the above analysis, the ARB staff believes that the statewide annual mean carbon tetrachloride concentrations estimated from the ARB monitoring data is essentially the global background concentration and thus, the annual average exposure level for Californians. Elevated concentrations above the global background are occurring in some areas from major point sources, pesticidal usages, and unidentified small users of carbon tetrachloride. However, the information currently available is not sufficient to establish the magnitude of any impacts from either unidentified small sources or atmospheric formation on carbon tetrachloride levels in California. Although annual mean concentrations measured at both the Fremont and Stockton monitoring sites could have been influenced by local sources, the measured mean concentrations are very close to the statewide average and may be an artifact of the small number of samples taken at each site. Therefore, because all of the annual mean concentrations are within $\pm$ 0.03 ppb ($\pm$ 0.19 ug/m^3) of the statewide average, the only exposure estimates above the global background concentration that have been made are for those with major identified point sources in California.

D. EXPOSURE TO CARBON TETRACHLORIDE THROUGH OTHER MEDIA

Although the primary focus of this report is exposure to carbon tetrachloride from the ambient air, exposure can also occur from elevated concentrations in the indoor air, as well as, ingestion of carbon tetrachloride found in drinking water and food products. Table I-6 summarizes the range of intake of carbon tetrachloride from different exposure routes for an adult during the year while Figure I-8

TABLE I-6

Yearly Intake of Carbon Tetrachloride

Through Different Exposure Routes

Exposure Route	Yearly Intake (ug/year)*	
Inhalation		
Ambient and Indoor Air		6,000 - 30,000
Ingestion		
Food	<3,000	
Drinking Water	<400 - 20,000	
Total from Ingestion**		<3,000 - 24,000
Total**		< 9,000 - 54,000

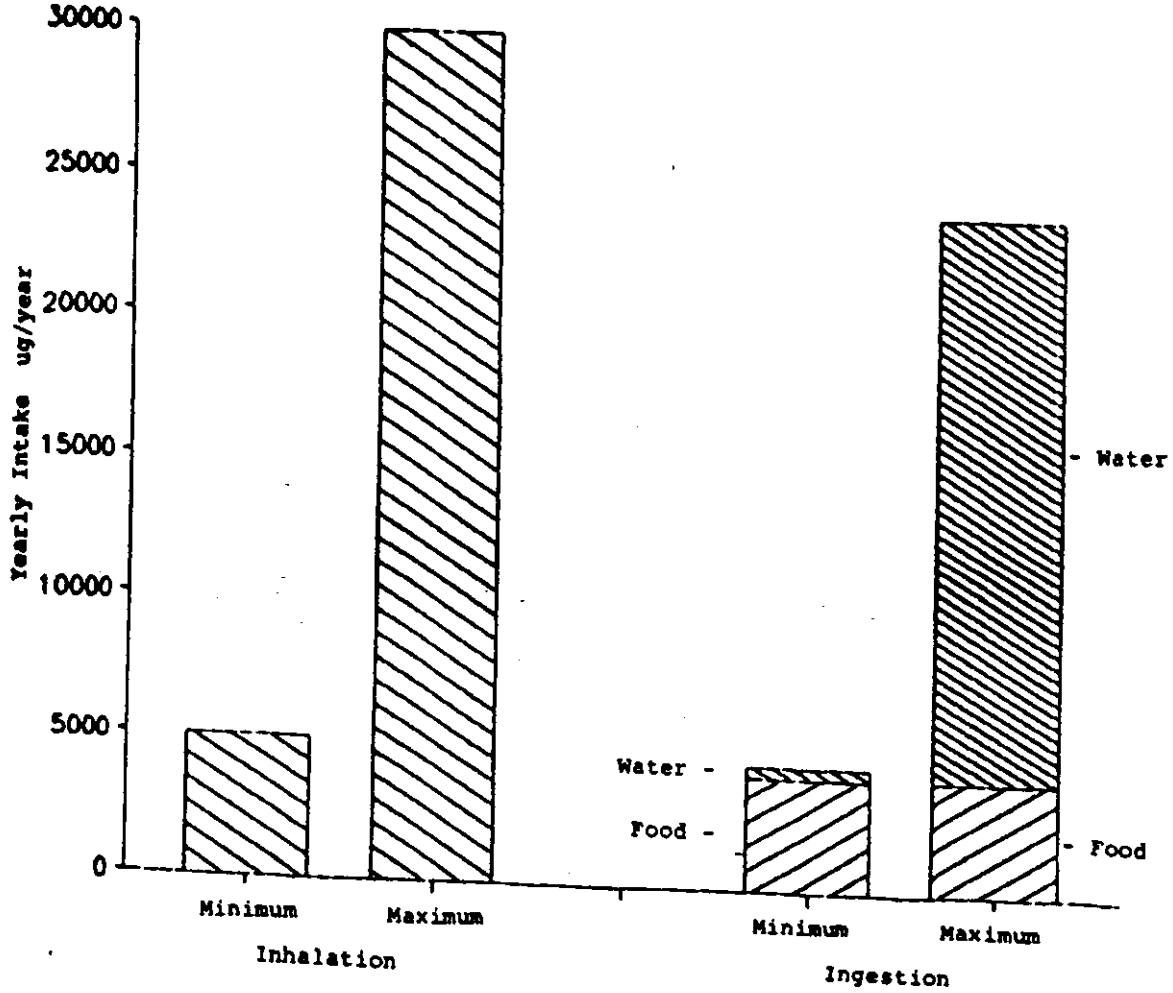
* The upper ranges of the yearly intakes are based on the maximum concentrations found in the different exposure media while the lower range values represent more typical concentrations found in these media. Therefore, the ARB staff believe that the lower ranges of the yearly intakes represent more realistic exposure estimates for most of California's population. Estimates for the yearly intake for each media have been rounded off to one significant figure.

** Total has been rounded.

NOTE: The estimates presented in Table I-6 are based on limited data and should not be considered absolute. This data was tabulated to illustrate the relative intake of carbon tetrachloride over an annual period. Refer to Appendix C for the assumptions used by the ARB staff in determining these estimates.

Figure I-8

Range of the Yearly Intake of Carbon Tetrachloride
Through Different Exposure Routes



presents this information in graphical form. These estimates are based on the maximum concentrations found in each exposure route (see Appendix C for assumptions and sample calculations).

1. Indoor Exposure to Carbon Tetrachloride

Based on the review of available draft reports and conference papers, the ARB staff could not establish with any degree of certainty the relationship between indoor and outdoor concentrations. This is because of uncertainties that were found in the studies that were reviewed. The uncertainties are discussed briefly in this section and in greater detail in Appendix D.

The ARB staff believes that for carbon tetrachloride the ambient outdoor concentration sets the baseline or lower limit for indoor concentrations. This is due to normal air exchanges between the indoor and outdoor air, the small contribution from indoor sources, and the absence of indoor removal processes for carbon tetrachloride. Air exchanges between the indoor and outdoor environments are caused by wind and temperature induced pressure differences which cause air movement from one environment to the other.

This exchange of air typically occurs in residences at a rate of 0.2 to 2.5 exchanges per hour (Diamond and Grimsrud, 1983). The exchange rate can be higher if it is influenced by the operation of air conditioners or the opening of windows. Thus, the air exchange is always rapid relative to the atmospheric persistence of carbon tetrachloride.

If present, indoor removal processes would be expected to lower the indoor concentration below the outdoor concentration, but for carbon

tetrachloride, there are no known (or suspected) removal processes unique to the indoor environment. Thus, indoor concentrations lower than outdoor concentrations are not expected.

If present, indoor sources would cause the indoor concentration to be higher than the outdoor baseline concentration. However, there are few indoor sources of carbon tetrachloride. Since 1972, carbon tetrachloride has been banned from consumer products by the Consumer Products Safety Commission (CPSC). However, some households may still have and use these consumer products. It is also possible that carbon tetrachloride is a component in present day consumer products as an "inert" ingredient. Carbon tetrachloride was found in a commercial cleaning product which may have contributed to elevated concentrations measured by Wallace (Wallace, 1986). However, conversation with the CPSC staff indicated that because of the CPSC ban, these types of products are not in widespread use. Other potential sources of indoor carbon tetrachloride include the use of water containing carbon tetrachloride. Some uses such as taking showers or washing dishes may contribute to the indoor carbon tetrachloride concentration. At this time, the contribution of these indoor sources to elevated indoor concentrations have not been correlated or determined.

Indoor and outdoor carbon tetrachloride concentrations have only recently been measured (US EPA, 1984; Wallace, et al., 1984, 1986; Hartwell, et al., 1984; DeBartoli, 1985; Pliel, 1985; Pellizzari, et. al., 1984). These studies include conference papers and draft reports which have not been peer reviewed. Based on a review of these

Table I-7

Summary of Indoor/Outdoor Carbon Tetrachloride Monitoring Studies

Study Location	# of Samples	Median Concentration[1] (ppb)	Median Concentration[1] (ug/m^3)	%of Samples Above LOQ[2]	Median Duplicate % RSD[3]
Hartwell, et al., 1985					
Greensboro					
Indoor	20	0.03	0.17	55	N.R.[4]
Outdoor	20	0.008[6]	0.04[5]	45	N.R.
Baton Rogue					
Indoor	27	0.01[5]	0.075[5]	48	N.R.
Outdoor	27	0.02	0.15	52	N.R.
Houston					
Indoor	10	0.20	1.3	100	N.R.
Outdoor	10	0.29	1.85	100	N.R.
Wallace, et al., 1984					
New Jersey Feb 81					
Indoor	346-348[6]	0.23[5]	1.5[5]	31	27[7]
Outdoor	81-86[6]	0.13	0.81	53	24[7]
Wallace, et al., 1986					
Los Angeles Feb 84					
Indoor	117	0.10	0.65	97	15
Outdoor	24-25	0.10	0.65	97	28
Los Angeles May 84					
Indoor	52	0.10	0.65	99	42
Outdoor	23	0.11	0.64	100	51
Antioch-Pittsburg Jun 84					
Indoor	71	0.14	0.71	94	12
Outdoor	10	0.05	0.33	95	43[8]
Pliel, 1985					
North Carolina					
Summer					
Indoor	15	0.14[1]	0.88[1]	100	<5
Winter					
Indoor	16	0.14[1]	0.88[1]	100	<5
Outdoor	12	0.15[1]	0.94[1]	100	<5
DeBartoli, 1985					
Northern Italy					
Indoor	16	0.9	6	94	N.R.
Outdoor	16	0.8	5	88	N.R.

1 Median concentrations, except for the Pliel study where mean concentrations are reported.
2 LOQ - limit of quantitation
3 % RSD - relative standard deviation of duplicate field samples.
$\frac{\text{standard deviation}}{\text{mean}} \times 100\%$
4 N.R. - not reported
5 Estimated median concentration as reported by the author. Less than 50% of samples were measurable. Quantitation limits vary between indoor and outdoor environments and with time.
6 Number of samples reported varied with compound of interest.
7 Mean percent RSD.
8 Value for one pair of field duplicate sample.

monitoring studies, the ARB staff could not establish with certainty if indoor and outdoor carbon tetrachloride concentrations were significantly different. This uncertainty is due to several factors. Some studies showed equal concentrations indoors and out, while others did not. In some studies, a large percentage of the samples were below the limit of detection. Other studies did not report quality assurance results and therefore, the uncertainty in the data could not be assessed. For some studies that reported quality assurance results, uncertainties were large relative to differences between reported indoor and outdoor concentrations. Therefore, the ARB staff was unable to determine if the measured differences were real. However, in the absence of better data, the ARB staff believes that most indoor concentrations are equal to outdoor concentrations. This conclusion is supported by the rapid air exchanges that occurs between the indoor and outdoor environments and the absence of either indoor removal mechanisms or sufficient indoor sources to cause major differences between indoor and outdoor concentrations. The ARB staff believes that conclusions regarding the difference between indoor and outdoor carbon tetrachloride concentrations would require additional research and better monitoring data from future studies. Table I-7 summarizes the findings of these studies. Appendix D discusses each of the indoor/outdoor carbon tetrachloride studies in greater detail.

2. Exposure to Carbon Tetrachloride from Food Products

The maximum intake of food products containing carbon tetrachloride is estimated to be less than 4,000 ug/year. In terms of intake, this

estimate may be as significant as the lower limit estimate of intake from the inhalation of ambient air containing carbon tetrachloride. The intake from food products containing carbon tetrachloride is based on very limited information and is an upper limit estimate. EPA is also proposing to ban the use of grain fumigants containing carbon tetrachloride in the United States (Zarow, 1986). This is expected to have a significant impact on reducing the concentration found in food products (Langley, 1986). Because of the above reasons, the ARB staff believes that the maximum intake estimate does not represent the intake level that would normally occur from the ingestion of food products containing carbon tetrachloride. Due to the limited data that is available, the ARB staff could not determine a more accurate intake estimate at this time.

Limited available data indicate that carbon tetrachloride residues in ready-to-eat food products have an average concentration of 2 ug/kg (Pesticide & Toxic Chemical News, 1985). Though the average carbon tetrachloride concentration in food products is low, significantly higher concentrations have been detected in grains treated with fumigants containing carbon tetrachloride. It appears that the amount of carbon tetrachloride remaining as a residue in food grains is dependent upon the fumigation dosage, storage conditions, length of aeration, and extent of processing (U.S. EPA, 1985b) Carbon tetrachloride has been detected in fumigated wheat at concentrations ranging from 76,000 ug/kg (one week after aeration) to 23,000 ug/kg (seven weeks after aeration). Bread prepared from treated wheat aerated

for three days contained carbon tetrachloride at concentrations up to 40 ug/kg (Berck, 1974). This is in agreement with Jagielski who reported that the carbon tetrachloride concentration in white bread prepared from treated grain is expected to be below 50 ug/kg provided that the concentration prior to processing is below 50 ug/kg (Jagielski, et al., 1978). The EPA staff also agrees that this concentration is a reasonable upper limit estimate of carbon tetrachloride concentration in processed grain products (McKinney, 1987). Because of EPA's ban on grain fumigants containing carbon tetrachloride and the limited available data, the ARB staff believes that the carbon tetrachloride concentration is likely to be below this upper limit estimate. Therefore, the yearly intake of carbon tetrachloride from this exposure route is also likely to be below the maximum intake level estimated by the ARB staff.

3. Exposure To Carbon Tetrachloride from Drinking Water

The lower range of intake of carbon tetrachloride from drinking water is estimated to be less than the intake from inhalation or ingestion of food products containing carbon tetrachloride. The estimated annual intake ranges from less than 400 ug to 20,000 ug per year (see Table I-6 and Figure I-8). The maximum intake was based on the highest carbon tetrachloride concentration measured by the California Department of Health Services (DHS) during a 1985 groundwater sampling study. Over ninety-eight percent of the samples that were analyzed were below the limit of detection of the analytical equipment which is 0.5 ug/liter (Rogers, 1986a). Rogers also stated that the

sources of drinking water in California are surface waters for 60 percent of the population and underground water systems for the remaining 40 percent of the population. Since carbon tetrachloride is relatively volatile, it is rarely detected in surface drinking water and is found more commonly in ground water systems (Rogers, 1986b). The ARB staff believes that most Californians are ingesting less than 400 ug/year of carbon tetrachloride from drinking water.

Of the 2947 wells DHS sampled, which represent 819 large public groundwater systems, less than 2 percent or 38 wells were above 0.5 ug/liter. The concentrations of the carbon tetrachloride that was detected range from 0.6 ug/liter to 29 ug/liter with a median of 2.2 ug/liter. Seventy-five percent of the samples with carbon tetrachloride concentrations above the limit of detection were located in the South Coast Air Basin (DHS, 1986). DHS has indicated that several wells with elevated carbon tetrachloride levels have since been closed. These preliminary results are consistent with EPA findings where EPA estimated that over 86 percent of the population in the United States is exposed to levels below 0.5 ug/liter and that 12.5 percent of the population are exposed to between 0.5 and 5 ug/liter. The remaining 1.5 percent of the population is exposed to levels between 5 and 30 ug/liter (U.S. EPA, 1984).

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II. SOURCES OF ATMOSPHERIC CARBON TETRACHLORIDE

A. PRODUCTION

Carbon tetrachloride (also known as methane tetrachloride, benziform, perchloromethane, and tetrachloromethane) was first produced on a large scale in the United States in 1907, primarily as a dry cleaning agent and for use in fire extinguishers (Grayson, 1980). This compound is currently produced in the United States by nine facilities. Only one company, Dow Chemical, has a carbon tetrachloride production facility in California, which is located in Pittsburg. The facility has a production capacity of about 40,000 tons per year (EPA, 1985a), which is about 11 percent of the carbon tetrachloride produced in the United States (U.S. International Trade Commission, 1984).

Figure II-1 shows United States production, imports, exports, and uses of carbon tetrachloride for the years 1978 to 1983. Production of carbon tetrachloride in the United States increased from approximately 286,000 tons in 1983 to about 356,000 tons in 1984, while production capacity stands at approximately 444,000 tons (Chemical and Engineering News, 1985). Producers expected a 5 percent increase in carbon tetrachloride production in 1985 in response to the increased demand for chlorofluorocarbons (Chemical Marketing Reporter, 1985). The increased demand for chlorofluorocarbons was attributed to the higher demand for refrigerants in the automobile industry and for foaming agents in the housing construction industry (Chemical Marketing Reporter, 1984).

B. USAGE

In 1983, the national use estimates for carbon tetrachloride were: 94 percent for fluorocarbon 11 (trichlorofluoromethane) and fluorocarbon

Figure II-1

U.S. Production, Imports, Exports, and Uses of

Carbon Tetrachloride

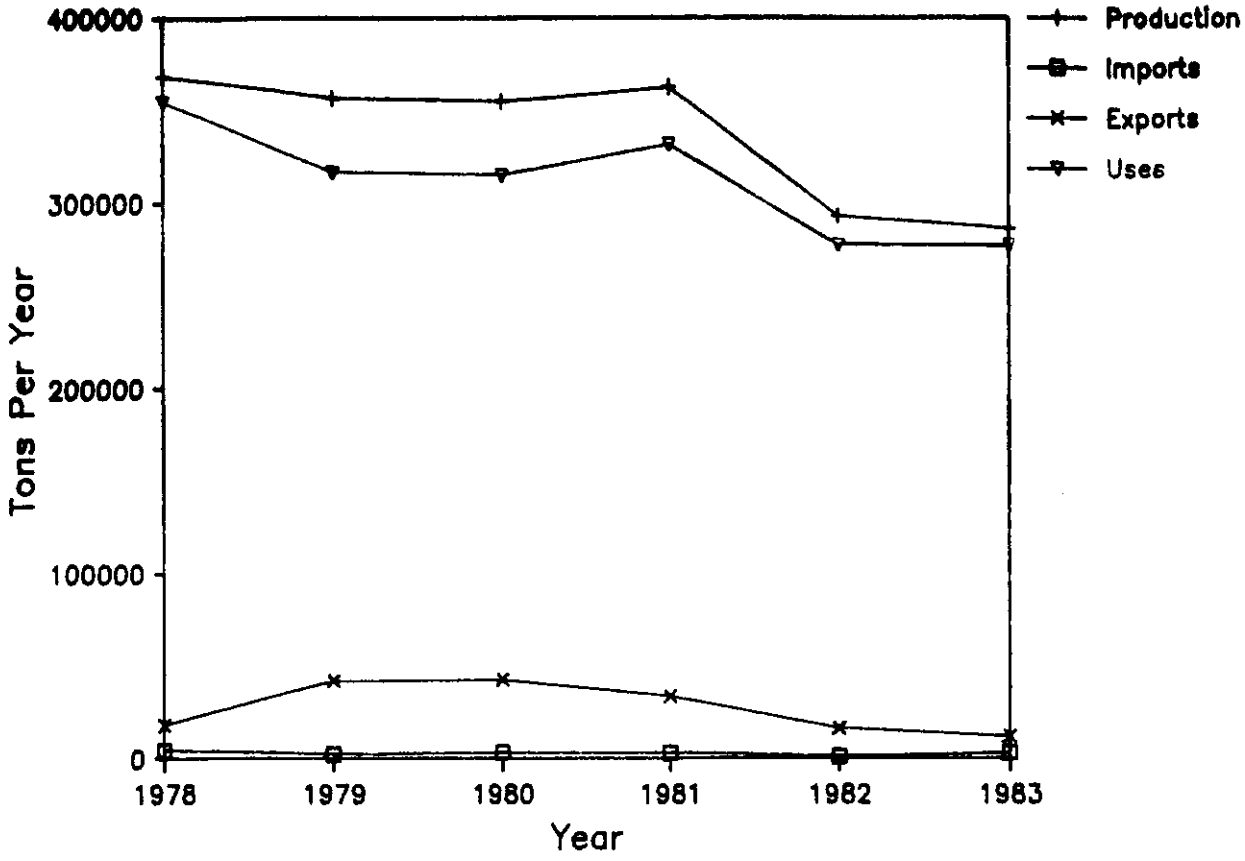
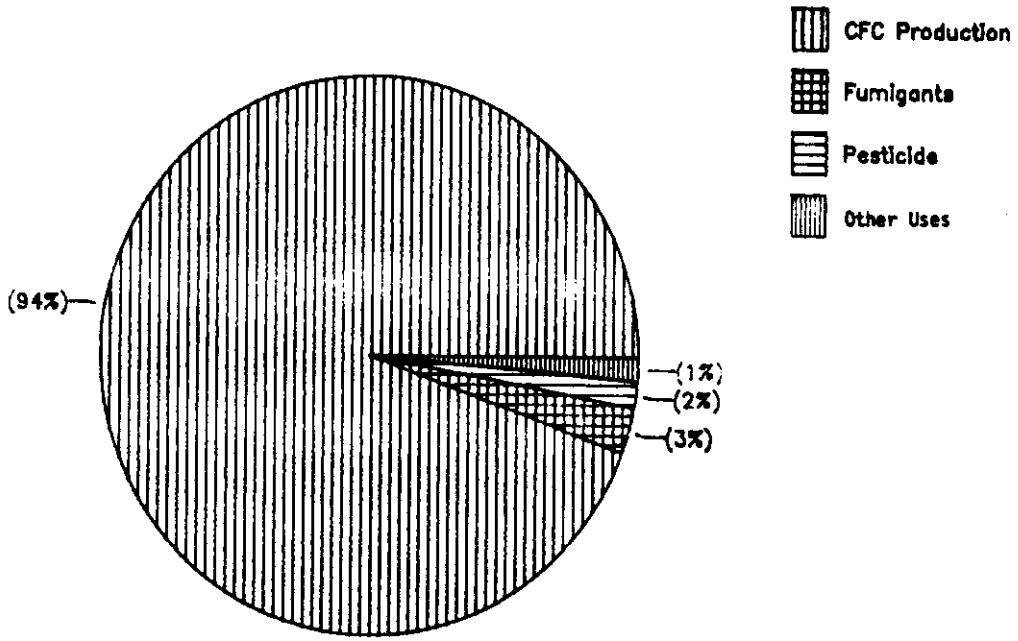


Figure II-2

National Use of Carbon Tetrachloride in 1983



12 (dichlorodifluoromethane) production, 3 percent as a grain fumigant, 2 percent for pesticide production, and 1 percent for other uses. Other uses of carbon tetrachloride include the production of chlorine and carbon tetrabromide (tetrabromomethane), use as a solvent in pharmaceutical manufacturing, and use in household and industrial products (EPA, 1983a). Figure II-2 summarizes the national carbon tetrachloride usages in 1983. In California the use of carbon tetrachloride in the production of fluorocarbon 11 and 12 represents about 89 percent of the carbon tetrachloride produced in the state. Other uses of carbon tetrachloride in California include grain fumigant usage, chlorinated paraffin wax production and miscellaneous solvent use.

Fluorocarbons 11 and 12 were used as aerosol propellants before their use as propellants was restricted by the United States Environmental Protection Agency (EPA) in 1978 (Chemical Purchasing, 1981). Currently, fluorocarbon 11 is used as a blowing agent in the manufacturing of plastic foams and fluorocarbon 12 is used as a refrigerant.

The use of carbon tetrachloride as an industrial solvent and as a dry cleaning agent has decreased in recent years due to concern about its toxicity and the availability of chemical alternatives (Environmental Studies Board, 1978). Its use as a pesticide is also expected to decrease due to EPA's federal regulation which restricts the use of carbon tetrachloride as a grain fumigant (51 FR 15372). Carbon tetrachloride has been banned as a fire extinguishing agent because of its tendency to decompose and form phosgene when sprayed into flames (McKetta, 1979).

C. CURRENT STATIONARY SOURCE EMISSIONS

Carbon tetrachloride is directly emitted from: 1) the production of carbon tetrachloride, chlorofluorocarbons, chlorine, and carbon tetrabromide; 2) the use of pesticides containing carbon tetrachloride; 3) the formulation of liquid pesticides containing carbon tetrachloride; 4) the use of carbon tetrachloride as a solvent in pharmaceutical manufacturing; and 5) the use of carbon tetrachloride as an industrial solvent. Carbon tetrachloride is also emitted when it is formed as a by-product during the production of ethylene dichloride (1,2-dichloroethane), perchloroethylene (tetrachloroethylene), and trichloroethylene (trichloroethene). Based on available information, there are no facilities in California that produce carbon tetrabromide, ethylene dichloride, or trichloroethylene. The Bay Area Air Quality Management District estimated carbon tetrachloride emissions from perchloroethylene production from Dow Chemical to be insignificant when compared to carbon tetrachloride storage tank emissions. Information from Dow Chemical and a solvent distributor, Van Waters and Rogers, indicated that carbon tetrachloride is shipped into and out of California by many distributors to small sources. At the present time, the ARB staff has insufficient information to determine the quantity and uses of carbon tetrachloride distributed to all small sources in California. Table II-1 summarizes carbon tetrachloride emissions and sources in California.

1. Emissions from the Production of Carbon Tetrachloride and Its Uses in Other Products

Dow Chemical's Pittsburg facility is currently the only company in California producing carbon tetrachloride. To produce carbon

TABLE II-1

Estimated Carbon Tetrachloride Emissions in California

Source	Location*	Source Type	Emissions (Tons/Year)	Inventory Year	Reference
Carbon Tetrachloride Production	BAAQMD	Point	30	1984	2
Pesticide/Fumigant Usage	SJV & Yolo-Solano	Area	20	1984	10
Chlorinated Paraffin Wax Production	SCAQMD	Point	3	1984	28
Fluorocarbon Mfg.	BAAQMD & SCAQMD	Point	2	1984	2,28
Misc. Use**	BAAQMD	Point	1	1984	2
Chemical Mfg.		Point	Not available		
Industrial Solvent		Point	Not available		
Oil Companies		Point	Not available		
Perchloroethylene Production		Point	Not available		
Pharmaceutical Mfg.		Point	Not available		
Publicly Owned Treatment Works		Point	Not available		
Scientific Laboratories		Point	Not available		
Total***			60 tons/year		

* BAAQMD: Bay Area Air Quality Management District
SCAQMD: South Coast Air Quality Management District
SJV: San Joaquin Valley
Yolo-Solano: Yolo-Solano Counties

** Emissions as reported by the BAAQMD. Information on carbon tetrachloride usage by the 3 sources are not available.

*** Total of available emission estimates as rounded.

tetrachloride, a hydrocarbon chlorinolysis process is used. A typical flow diagram of this process with possible emission sources is shown in Fig. II-3. Emission sources from this process are storage tanks, valves, flanges, pumps, and compressors. Fresh chlorine along with recycled chlorine and hydrogen are introduced into a vaporizer. The mixed gases are then fed to a refractory-lined reactor which typically operates at temperatures between 500°C and 700°C. Effluent from the reactor consists mainly of carbon tetrachloride, perchloroethylene, hydrogen chloride (HCl), and excess chlorine (Cl_2) with some unreacted hydrocarbons. The hot effluent gas is quenched, followed by the removal of HCl and Cl_2. The liquid stream which results from the process of quenching is separated into carbon tetrachloride and perchloroethylene by distillation (EPA, 1985a). Because the entire process occurs in a closed system, process loss emissions from carbon tetrachloride production are attributed primarily to equipment leaks. The design of the basic operations and the level of control may vary from plant to plant.

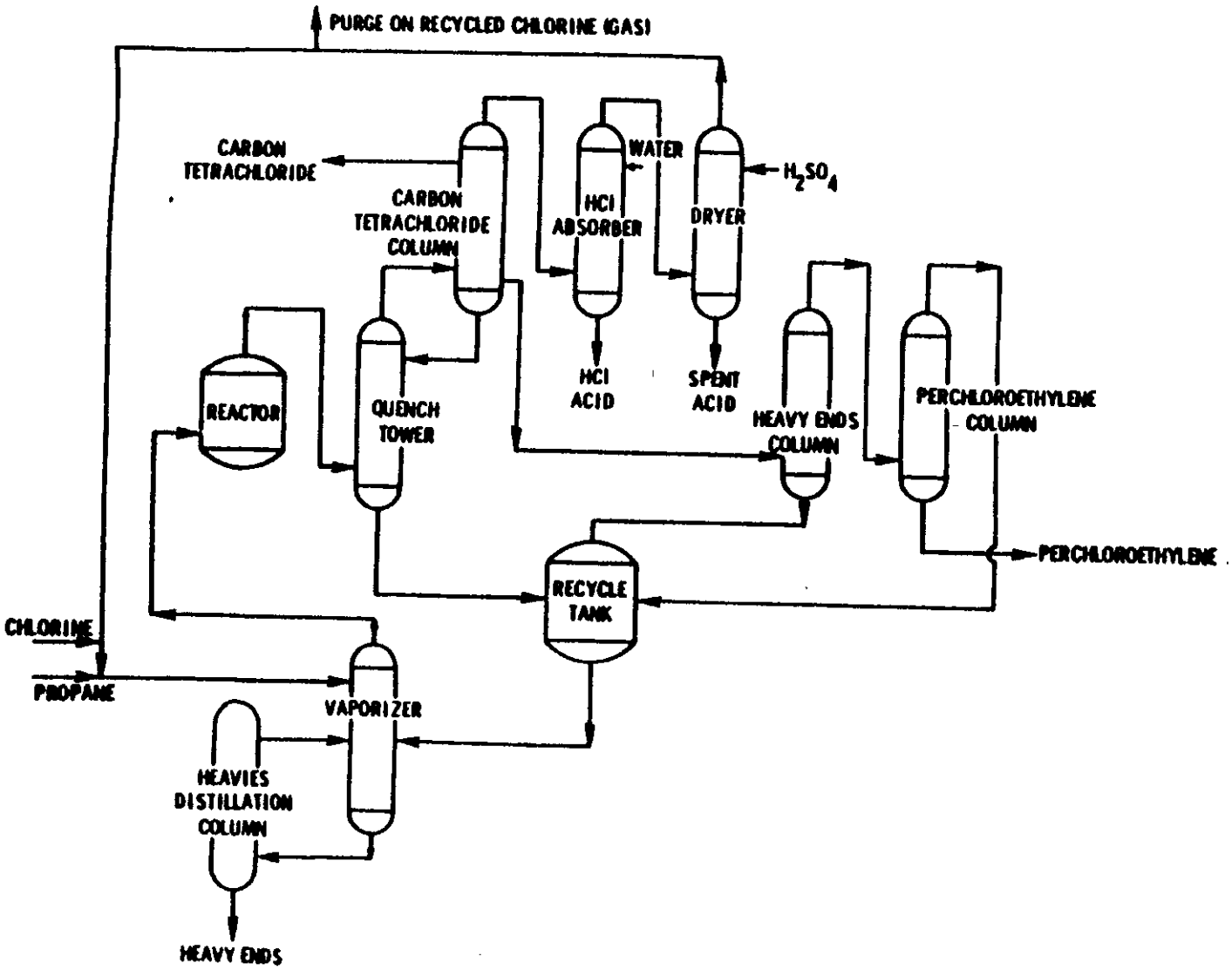
At Dow's Pittsburg facility, carbon tetrachloride is also emitted from the production of perchloroethylene. In addition, this facility uses carbon tetrachloride to formulate liquid pesticides. Based on information provided by Dow, emissions from the processes producing carbon tetrachloride, perchloroethylene, and liquid pesticide formulations are insignificant compared to the emissions from the carbon tetrachloride storage tank working and breathing losses (EPA, 1985a; BAAQMD, 1986).

In 1984, Dow reported carbon tetrachloride emissions to be approximately 30 tons. These emissions are from four fixed-roof storage

Figure II-3

Diagram for a Typical Hydrocarbon Chlorinolysis Process

Used in Producing Carbon Tetrachloride



tanks: two of the storage tanks have capacities of 17,000 gallons each and the other two have capacities of 700,000 gallons each (BAAQMD, 1986). Currently, these tanks are not controlled. Equipment leaks at Dow Chemical are regulated by the Bay Area Air Quality Management District (BAAQMD). The regulations require repair of volatile organic compound leaks greater than 10,000 ppm within 15 days for accessible, nonessential valves and flanges. For essential valves and flanges, leaks must be minimized within 15 days and repaired within six months. Loading and handling of carbon tetrachloride are minor emission sources at Dow and are currently not subject to controls or regulations.

The major use for carbon tetrachloride is as a feedstock in the production of fluorocarbon 11 and fluorocarbon 12. Only two facilities, Allied Chemical in El Segundo, and E. I. du Pont in Antioch, produce fluorocarbon 11 and fluorocarbon 12 in California. E. I. du Pont reported carbon tetrachloride emissions to be 1.5 tons in 1984 (BAAQMD, 1986). These emissions are from storage tanks which are currently uncontrolled. In 1983, Allied Chemical reported its carbon tetrachloride emissions to be 3 tons/year. During that year, Allied installed a vapor recovery system on its carbon tetrachloride storage tank which reduced the 1984 emissions to less than 0.03 tons. This facility is regulated by the South Coast Air Quality Management District (SCAQMD) which requires the plant to perform visual inspections for leaks in valves and flanges annually and visual inspection of pumps and compressors daily.

Fluorocarbons 11 and 12 are produced simultaneously from carbon tetrachloride by a process which substitutes fluorine atoms for chlorine atoms. The chlorofluorocarbons are then separated by distillation (du

Pont, 1986). It is estimated that approximately 3 percent of the carbon tetrachloride is lost in this process (Alexander Grant and Company, 1982), and up to 1 ppm may be separated with fluorocarbon 11 as a contaminant (du Pont, 1986).

Carbon tetrachloride is used as a solvent in the production of chlorinated wax (SCAQMD, 1983b). Currently, Neville Chemical Company in Santa Fe Springs, is the only producer of this wax in California. The 1984 emissions from this source were reported to be 3 tons (SCAQMD, 1984).

2. Emissions From The Use of Carbon Tetrachloride - Containing Products

Carbon tetrachloride is used in pesticides as a component of grain fumigant mixtures. These fumigants are applied to stored grain to control insect infestation (Holtorf and Ludvik, 1981; EPA, 1980). It is assumed most of the carbon tetrachloride used in grain fumigant mixtures evaporates due to its high vapor pressure (Leung et al., 1980; Woodrow, 1983). In 1984, carbon tetrachloride emissions from pesticide use were estimated to be 20 tons (California Department of Food and Agriculture, 1985). Future pesticidal uses will be reduced significantly due to recent restrictions by EPA which cancel the registration of pesticides containing carbon tetrachloride, thus, prohibiting the sale, distribution, and uses of these products in the United States (EPA, 1986). Other reported sources of carbon tetrachloride emissions are listed in Table II-1. Most of these sources are located in the San Francisco Bay Area and their emissions were estimated to be 1.2 tons per year.

3. Other Potential Emission Sources

Carbon tetrachloride is used as a solvent in the manufacturing of certain pharmaceutical products. Based on an EPA survey of authorized drug manufacturers in 1978, the estimated final distribution of carbon tetrachloride usage was: 11 percent air emissions, 7 percent sewer disposal and 82 percent incineration (EPA, 1978). Carbon tetrachloride is also used as a solvent in the manufacture of specialty and small volume chemicals such as chlorosulfonated polyethylene (Hypalon), tetrachloropyridene, and 4-amino-3,5,7-trichloropicolinic acid (EPA, 1984). The ARB staff has not identified any of these types of sources in California.

Information from a carbon tetrachloride producer (Dow Chemical) and a solvent distributor (Van Waters and Rogers) indicated that carbon tetrachloride is shipped into and out of California. In general, the sources are small and have purchased carbon tetrachloride in small quantities at one time. Carbon tetrachloride is used by these sources in manufacturing processes as a feedstock or as an industrial solvent. Localized emission releases to the atmosphere in an area may account for the elevated carbon tetrachloride concentrations measured at some of the ARB monitoring stations, such as the Fremont station. The ARB staff is continuing with its investigation of these minor sources and is contacting solvent distributors and sources to assess potential emissions that are emitted from these sources in California.

Independent studies by EPA and ARB have shown that carbon tetrachloride may also be emitted from publicly owned treatment works (CARB, 1985; EPA, 1982; Pellizzari, 1982). Source tests for volatile

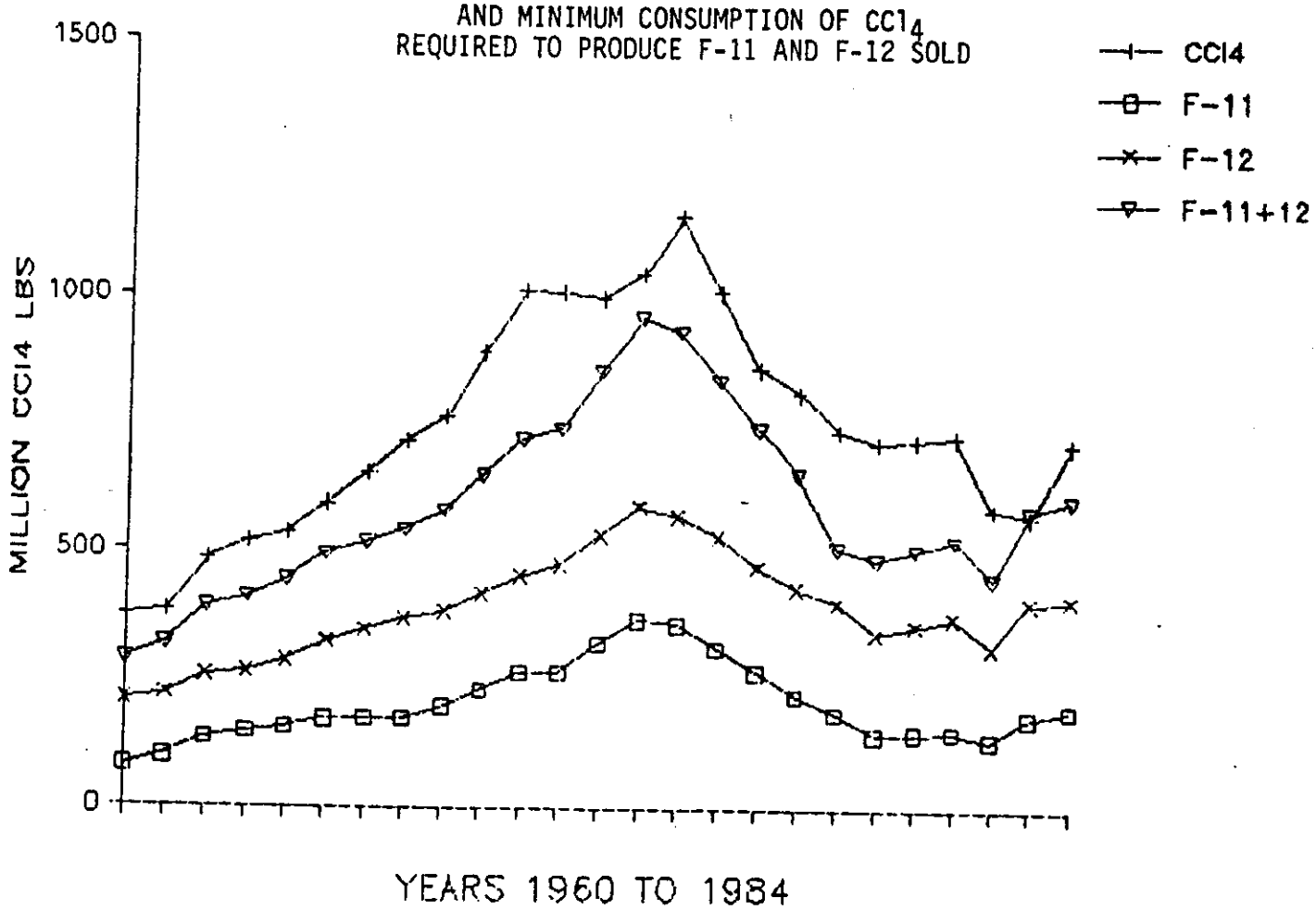
organic compounds by the ARB were conducted at two sewage treatment plants, one in Sacramento and one in Los Angeles. Concentrations up to 2 ppb were measured from the activated sludge process tanks (CARB, 1985). The source of carbon tetrachloride in the sewage is unknown. In addition to the source tests, the ARB is currently sponsoring a study to assess potential toxic compound emissions, including carbon tetrachloride, from publicly owned treatment works. The results are not available at this time, but this emission source will be evaluated if carbon tetrachloride is identified as a toxic air contaminant.

D. IMPACT OF TRENDS IN PRODUCTION, USAGE, AND EMISSIONS

Since 90 to 95 percent of the carbon tetrachloride produced is used in the production of fluorocarbons 11 and 12 (Chemical Marketing Reporter, 1986, 1983, 1981, 1978, 1975, 1972, 1969, 1966, 1964), production of carbon tetrachloride is tied closely to the sales of fluorocarbons 11 and 12 (see Figure II-4). It is estimated that a 1 to 2 percent growth in carbon tetrachloride demand is expected through 1990 (Chemical Marketing Reporter, 1986). However, if EPA does decide to regulate fluorocarbon production, as is expected, carbon tetrachloride demand after 1990 could be reduced significantly.

Emissions of carbon tetrachloride from California and the rest of the United States contribute to the global concentration of carbon tetrachloride. At the current rate of emissions, the global concentration will reach a steady state of approximately double its present value in about 100 years. If the emission rate continues to increase, the global concentration will increase more rapidly and will never reach a steady state.

FIG. II-4, U.S. PRODUCTION OF CCl4



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III. PERSISTENCE IN THE ATMOSPHERE

Once in the atmosphere, carbon tetrachloride is a very stable gaseous compound. Due to the lack of rapid atmospheric removal mechanisms, carbon tetrachloride accumulates in the lower atmosphere, the troposphere, and has a long tropospheric lifetime estimated to be approximately 50 years. Its persistence in the troposphere has led to a global background carbon tetrachloride concentration, which is representative of mean concentrations that are measured in California by the ARB monitoring stations.

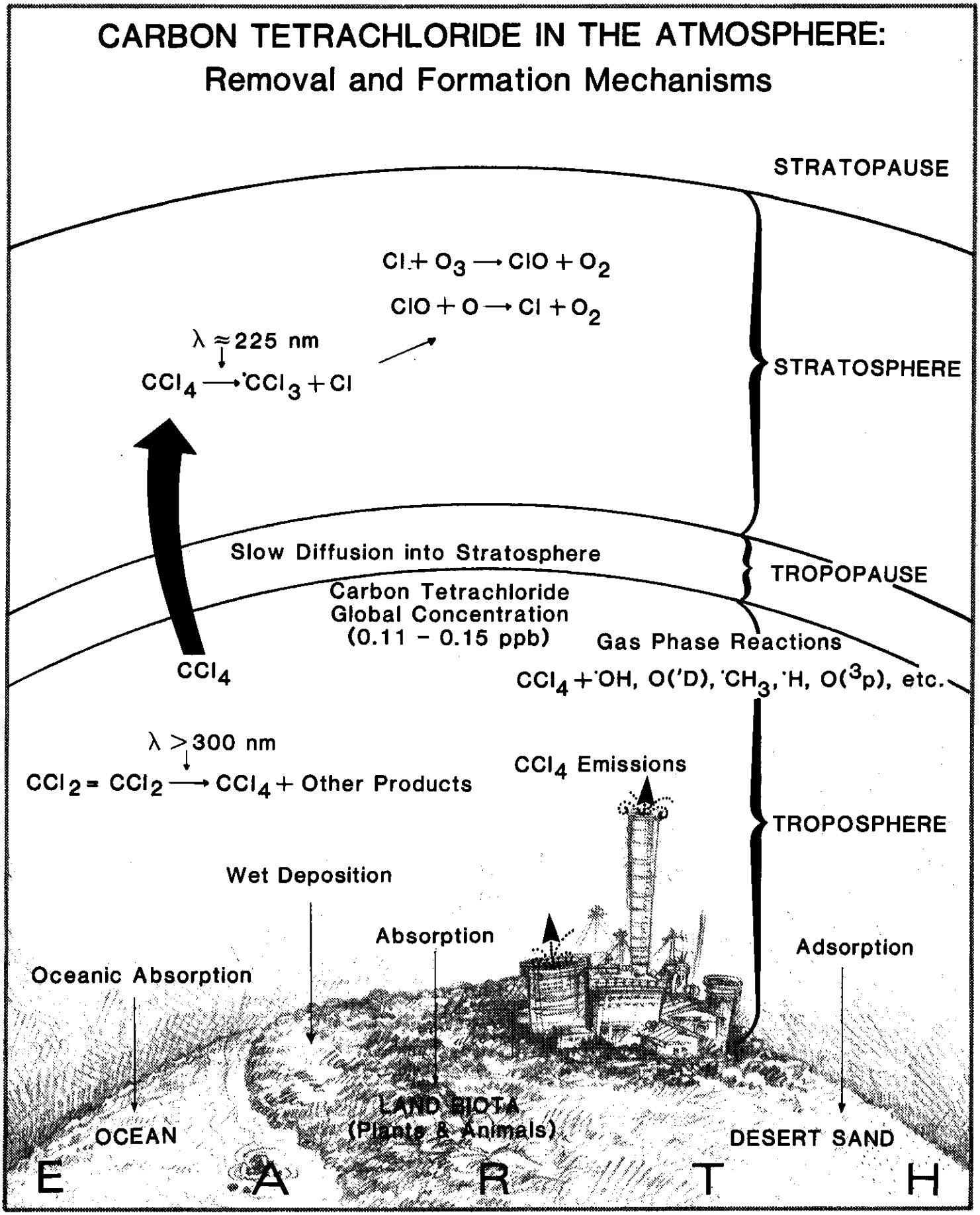
Carbon tetrachloride is emitted mainly from anthropogenic sources. It has also been suggested that carbon tetrachloride can be formed in the troposphere from the photolysis of perchloroethylene (perc). However, this formation process was based on perc photolysis experiments conducted under controlled laboratory conditions. Its impact under normal tropospheric conditions has yet to be determined or quantified.

Of the identified removal mechanisms, the diffusion of carbon tetrachloride from the troposphere to the stratosphere with ultraviolet photolysis then occurring is the major pathway for the removal of carbon tetrachloride. One of the photolysis products, chlorine atoms, is of concern because they can react with ozone to deplete the ozone layer in the stratosphere. This can result in increases in human skin cancer. Figure III-1 presents emission releases to the troposphere, potential tropospheric formation, and removal mechanisms for carbon tetrachloride.

A. PHYSICAL AND CHEMICAL PROPERTIES

The chemical formula of carbon tetrachloride (also known as methane tetrachloride, benziform, perchloromethane, and tetrachloromethane) is

FIGURE III-I


CARBON TETRACHLORIDE IN THE ATMOSPHERE:
Removal and Formation Mechanisms
STRATOPAUSE
$Cl + O_3 \rightarrow ClO + O_2$
$ClO + O \rightarrow Cl + O_2$
$\lambda \approx 225$ nm
$CCl_4 \rightarrow {}^{\cdot}CCl_3 + Cl$
STRATOSPHERE
Slow Diffusion into Stratosphere
TROPOPAUSE
Carbon Tetrachloride
Global Concentration
(0.11 - 0.15 ppb)
Gas Phase Reactions
CCl_4
$CCl_4 + {}^{\cdot}OH, O(^1D), {}^{\cdot}CH_3, {}^{\cdot}H, O(^3p)$, etc.
$\lambda > 300$ nm
$CCl_2 = CCl_2 \rightarrow CCl_4$ + Other Products
CCl_4 Emissions
TROPOSPHERE
Wet Deposition
Absorption
Adsorption
Oceanic Absorption
OCEAN
LAND BIOTA
(Plants & Animals)
DESERT SAND
E A R T H

CCl_4. Carbon tetrachloride is a colorless, non-flammable liquid with a density of 13.22 lbs/gal at 25°C (Zwiacher, et al., 1983) and a characteristic odor. It is miscible with most organic solvents such as benzene, chloroform, and ether, but is essentially insoluble in water. With a vapor pressure of 100 mm Hg at 23°C, carbon tetrachloride is relatively volatile. The density of carbon tetrachloride vapors is over five times that of air, thus, in cases where concentrated gaseous emissions occur, the plume will tend to settle to the ground before dispersing into the air (National Research Council, 1978). Carbon tetrachloride can decompose in direct flames to form phosgene. Reaction of carbon tetrachloride with steam results in the formation of chloromethanes, hexachloroethane, and perchloroethylene (U.S. EPA, 1984). Carbon tetrachloride's physical properties are shown in Table III-1.

B. ATMOSPHERIC FATE OF CARBON TETRACHLORIDE

1. Atmospheric Regions of Importance for Carbon Tetrachloride

The atmosphere can be divided into a number of different regions according to their temperature variations with altitude. These temperature regions are described in Table III-2 and in Figure III-2. For carbon tetrachloride, the important regions in terms of its persistence and removal from the atmosphere are the troposphere, the tropopause, and the stratosphere. The troposphere is the region where carbon tetrachloride is emitted. The tropopause acts as a barrier which inhibits the movement of air masses containing carbon tetrachloride from the troposphere to the stratosphere. Once carbon tetrachloride diffuses into the stratosphere, it undergoes photolysis which is the major removal mechanism for carbon tetrachloride.

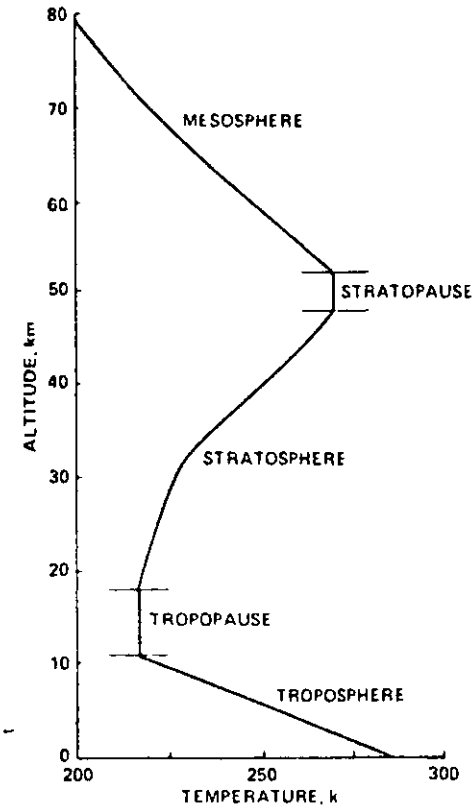
TABLE III-1

The Physical Properties of Carbon Tetrachloride

Properties	Value	Reference
Boiling Point, 760 mm Hg	76.72°C	Kirk-Othmer, 1979
Molecular Weight	153.82	Kirk-Othmer, 1979
Vapor Pressure, 23°C	100 mm Hg	Kirk-Othmer, 1979
Melting Point, 760 mm Hg	-22.92°C	Kirk-Othmer, 1979
Flash Point	None	Kirk-Othmer, 1979
Sol. in H_2O, 25°C, g/199g H_2O	0.08	Kirk-Othmer, 1979
Sol. H_2O in CCl_4, 25°C g/199g CCl_4	0.013	Kirk-Othmer, 1979
Octanol Coeff.	2.64	U.S. EPA, 1984
Vapor Density, Air=1	5.32	Kirk-Othmer, 1979
Density of Solid, g/cm, -80°C	1.81	Kirk-Othmer, 1979
Specific Gravity 0/4°C	1.63	Kirk-Othmer, 1979
Solidification	-23°C	Merck Index, 1983
Heat of Form. KCal/mole		
Liquid	-33.94	Kirk-Othmer, 1979
Vapor	-25.81	Kirk-Othmer, 1979
Latent Heat Fusion, KCal/Mole	0.61	Kirk-Othmer, 1979
Latent Heat Vaporization KCal/Ka	46.53	Kirk-Othmer, 1979

Figure III-2

Major Regions of the Atmosphere



The scale of temperature is in ^{o}K. To convert to ^{o}C, use the equation $^{o}C = {}^{o}K - 273$.

Table III-2

Major Regions of the Atmosphere and Their Characteristics

Region	Temperature Range (^{o}C)	Altitude Range (km)[1]
Troposphere	15 to -56	0 to (10-16)[2]
Stratosphere	-56 to -2	(10-16) to 50
Mesosphere	-2 to -92	50 to 85
Thermosphere	-92 to 1200	85 to 500

1. These figures give the boundary of each region.

2. The boundary between the troposphere and stratosphere varies from 10 - 16 km.

The troposphere contains approximately 80 percent of the total mass of the atmosphere. This is the region where almost all the "weather" such as rain, clouds, and snow occurs. The troposphere is characterized by a decrease in temperature (15° to $-56^{o}C$) with increasing altitude. Its composition is fairly homogeneous due to the mixing caused by the constantly circulating air masses. For persistent compounds like carbon tetrachloride, the ambient concentration can steadily increase because these compounds are effectively trapped in the troposphere by a thermal barrier, the tropopause.

The tropopause is the boundary region that separates the troposphere and the stratosphere. This region is characterized by a stable air mass of similar temperature which acts as a barrier to vertical lifting and mixing of cooler air masses from the troposphere to the stratosphere. Because this barrier prevents convective mixing, escape through the tropopause is limited to the relatively slow diffusion process. Diffusion of carbon tetrachloride from the troposphere into the stratosphere followed by photodissociation is the primary removal mechanism for carbon tetrachloride.

The stratosphere is characterized by increasing temperature with increasing altitude due to the presence of ozone which absorbs energy in the form of ultraviolet light. The ozone may reach a concentration as high as 10 parts per million (ppm) in the mid-region of the stratosphere. The ozone acts as a filter, stopping high energy, cancer-causing, ultraviolet radiation from reaching the earth's surface. Depletion of ozone in the stratosphere will allow ultraviolet radiation to penetrate to

the earth's surface which can cause increases in human skin cancer. Ultraviolet radiation below 290 nanometers is the same high energy radiation that causes carbon tetrachloride to photodissociate in the stratosphere.

2. Releases and Formation of Carbon Tetrachloride in the Atmosphere

In 1984, the ARB staff estimated that at least 60 tons of carbon tetrachloride was emitted in California from stationary sources and from pesticide/grain fumigant usage. No naturally occurring sources of carbon tetrachloride are known. It has been suggested that carbon tetrachloride can be formed in the troposphere by the photochemical reactions of tetrachloroethylene (perchloroethylene). The ARB staff believes that under normal tropospheric conditions, the amount that can be formed does not contribute significantly to ambient levels.

Under controlled laboratory conditions, Singh prepared synthetic mixtures of perchloroethylene in pure (ultrazero) air. These mixtures were irradiated for several days by simulated tropospheric sunlight in Tedlar bags or flasks. Singh estimated that 5.5 to 8.9 percent of the perchloroethylene was converted to carbon tetrachloride (Singh, et al., 1975). The authors stated that a chlorine sensitized photooxidation reaction is involved. However, in the atmosphere, the ARB and Statewide Air Pollution Research Center (SAPRC) staffs believe that chlorine scavengers would prevent chlorine sensitized photooxidation from occurring to any appreciable extent (SAPRC, 1986). The Singh experiments are not directly comparable to what would occur under normal ambient conditions

because of the continuous irradiation that was employed (continuously for 5 to 7 days), as opposed to only about one-half day under ambient conditions. The ARB staff decided, however, to review the 1985 ambient carbon tetrachloride and perchloroethylene monitoring data from the ARB toxic monitoring network to determine if any correlation could be found between the two concentrations. Data for the months of May through September was used because these months have the longest insolation periods of the year.

Based on the ARB staff analysis of the monitoring data, no correlation between carbon tetrachloride and perchloroethylene concentrations was found. Where a correlation factor of 1 indicates a perfect match between perchloroethylene and carbon tetrachloride concentrations, the ARB staff estimated correlation factors of 0.0001 and 0.0008 for Northern and Southern California which indicate no correlation. Figure III-3 and III-4 summarizes the scatter plots that were derived from the analysis of the data for those two areas.

3. Removal Mechanisms for Carbon Tetrachloride in the Atmosphere

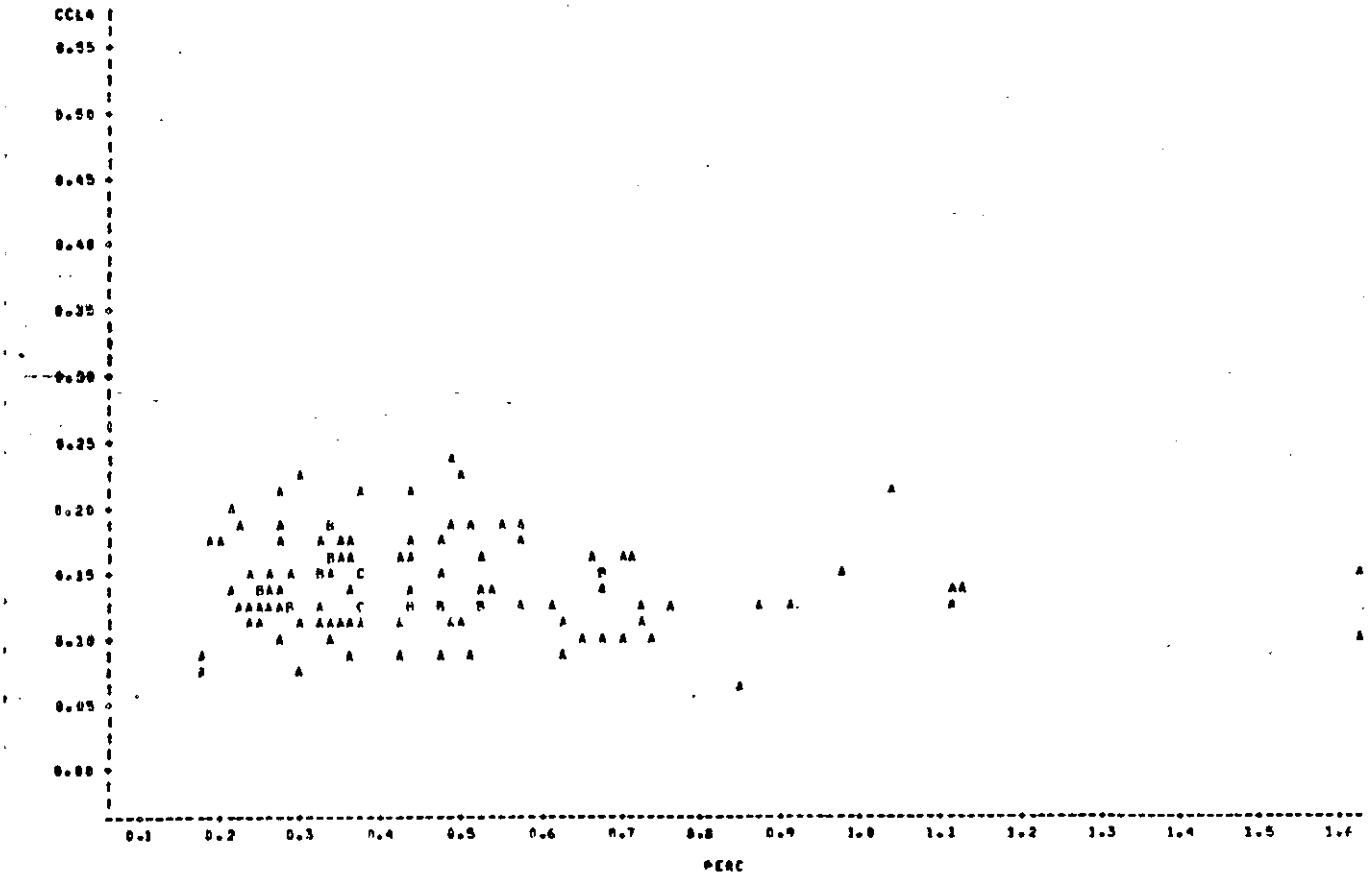
In general, gas phase reactions with radicals, primarily hydroxyl radicals, are the most important tropospheric removal mechanisms for many organic compounds once they are emitted in the troposphere. Other removal mechanisms which may be important for organic compounds are photolysis, absorption into the oceans, adsorption onto particulate matter, wet deposition, and absorption and decomposition in biological systems. However, these removal mechanisms are very slow when it comes to removing carbon tetrachloride from the troposphere. Because of its slow removal rate from the troposphere, carbon tetrachloride accumulates in this region

Figure III-3

Results of Carbon Tetrachloride to Perchloroethylene

Correlation Analysis - Northern California

Correlation Factor = 0.0001



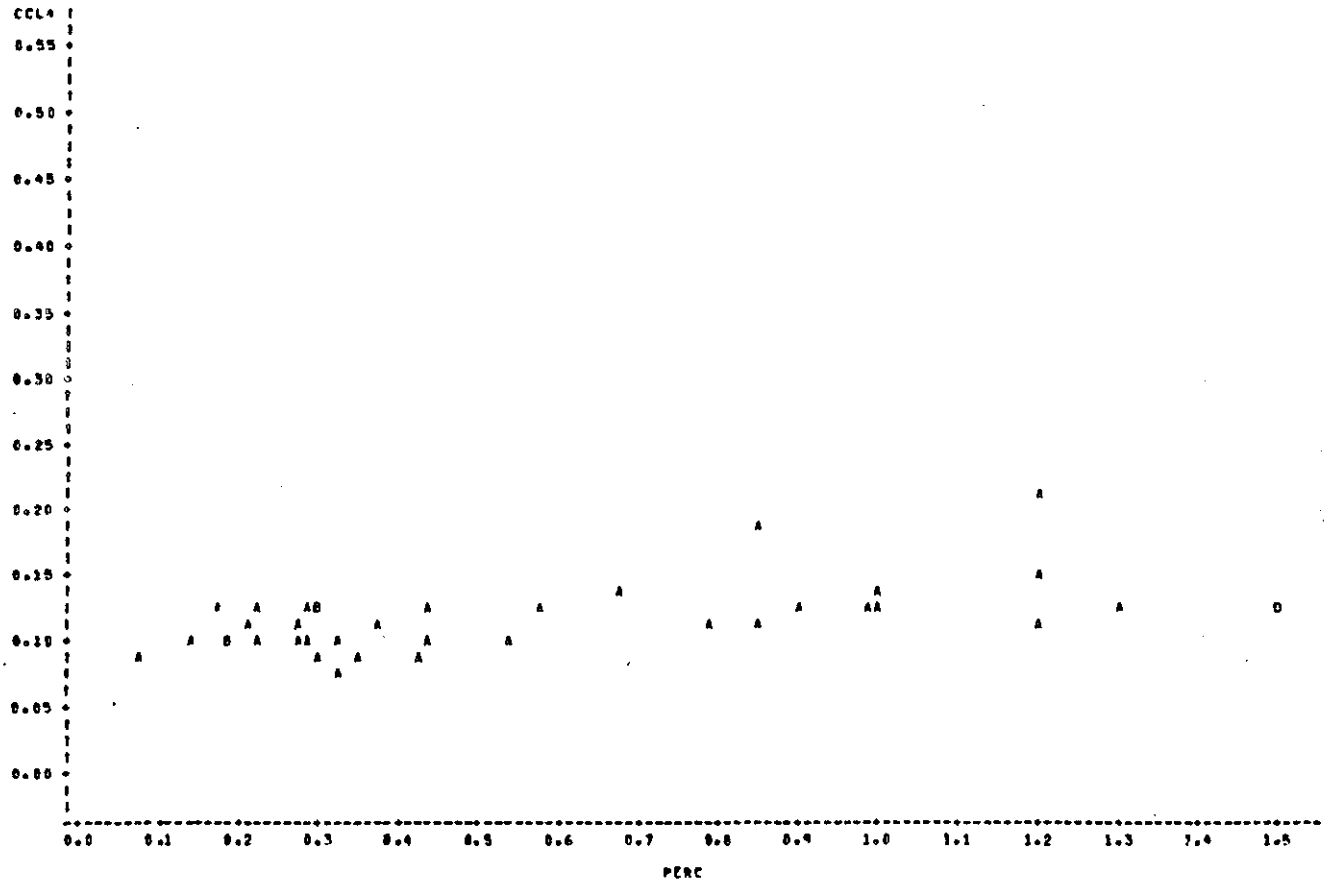
Legand: A = 1 observation, B = 2 observation, etc.

Figure III-4

Results of Carbon Tetrachloride to Perchloroethylene

Correlation Analysis - Southern California

Correlation Factor = 0.0008



Legand: A = 1 observation, B = 2 observation, etc.

of the atmosphere. Estimates of the atmospheric lifetime for carbon tetrachloride have ranged from 18 to over 100 years (Galbally, 1976; Singh, et al., 1976; Cox, et al., 1976; Borchers, et al., 1983; EPA, 1987). However, the ARB staff believes that the best estimate, based on the extensive Atmospheric Lifetime Experiment, is approximately 50 years (Simmonds, et al., 1983). This is in agreement with a recent estimate where the atmospheric lifetime of carbon tetrachloride was calculated to be 48 years (Golombek and Prinn, 1986). Table III-3 summarizes the various atmospheric removal mechanisms which are discussed in terms of first order removal rates and estimated removal times. The estimated atmospheric lifetimes, the removal rates, and removal times were summarized from available information obtained as of May 1987.

Of the identified removal mechanisms, diffusion from the troposphere to the stratosphere is the major pathway by which carbon tetrachloride is removed from the troposphere. Once in the stratosphere, carbon tetrachloride becomes reactive in the presence of the short wavelengths of ultraviolet light (Simmonds, et al., 1983; Atkinson, et al., 1976; Lillian, et al., 1975; Galbally, 1976). The initial process in the stratospheric photolysis of carbon tetrachloride at a wavelength of about 225 nanometers involves the detachment of one chlorine atom yielding a trichloromethyl radical and a chlorine atom (National Research Council, 1978; Rebbert and Ausloos, 1976).

$$CCl_4 + h\nu \longrightarrow .CCl_3 + Cl$$

The chlorine atoms can then react with ozone in the stratosphere, thus, contributing to the depletion of ozone.

$$Cl + O_3 \longrightarrow ClO + O_2$$

$$ClO + O \longrightarrow Cl + O_2$$

TABLE III-3

Atmospheric Removal Mechanisms and Their Estimated Removal Times

Removal Process	Removal Time[1/] τ (years)	Removal Rate $1/\tau$ ($year^{-1}$)	Reference
Stratospheric Photolysis	50	2.0×10^{-2}	Simmonds, et al., 1983
	59	1.7×10^{-2}	NAS, 1976
	40-111	$0.9 - 2.5 \times 10^{-2}$	Galbally, 1976
	30-50	$2 - 3.3 \times 10^{-2}$	Molina and Rowland, 1974
Gas Phase Reactions			
Reactions with $O(^1D)$	667-2000	$0.6 - 1.8 \times 10^{-3}$	Galbally, 1976
Reactions with OH	>330	3×10^{-3}	Cox, et al.,1976
	>8	$<1.3 \times 10^{-1}$	Howard and Evenson, 1976
Absorption into oceans	95-286	$3.5 - 10.5 \times 10^{-3}$	Galbally, 1976
Biological Removal	333-1000	$1.0 - 3.0 \times 10^{-3}$	Galbally, 1976
Adsorption on Silicates	NR[2/]	NR	Ausloos,et al.,1977
Wet Deposition	NR	NR	Ohta, et al.,1976

1/ The removal time is an estimate of the time required for a given amount of compound to decrease 1/e (0.368) of its original value at time zero.

2/ NR means not reported.

Ozone is very important because it absorbs harmful, high-energy, cancer-causing ultraviolet radiation below 290 nanometers from reaching the earth's surface. Depletion of ozone will allow the ultraviolet radiation to reach the earth's surface which can lead to increased skin cancers in humans.

In support of the stratosphere as a sink, atmospheric measurements of the stratospheric profile of carbon tetrachloride show that its concentration decreases rapidly with altitude (Seiler, et al., 1978; Pierotti, et al., 1980; Borchers, et al., 1983). Simmonds reports that Golombek estimated the stratospheric lifetime of carbon tetrachloride to be 7 1/2 years with an overall atmospheric lifetime of approximately 50 years (Simmonds, et al., 1983).

Absorption into the oceans is believed to be the second most important atmospheric removal mechanism for carbon tetrachloride (Simmonds, et al., 1983; Galbally, 1976). The ocean as a removal mechanism is supported by Liss and Slater who have estimated that from the troposphere, 16 tons per year of carbon tetrachloride is removed to the ocean (Liss and Slater, 1974). In deriving that estimate, Liss and Slater applied Fick's first law of diffusion and Henry's law to the atmospheric/oceanic interface. They also had to estimate gas and liquid phase resistances and utilized Henry's Law constants given by Lovelock, as well as atmospheric and oceanic carbon tetrachloride concentrations estimated by Lovelock (Liss and Slater, 1974). Galbally has estimated that tropospheric removal times by the oceans range from 95 to 286 years (Galbally, 1976). Since carbon

tetrachloride is highly resistant to hydrolysis with a half-life of 70,000 years, other oceanic removal processes are probably occurring. Although these removal processes have not been identified, it is speculated that carbon tetrachloride bioaccumulates in marine organisms with subsequent incorporation into sediments (Singh, 1976; NAS, 1976).

In the troposphere, no other removal mechanisms have been shown to be more rapid for carbon tetrachloride than the two mechanisms discussed above. Photolysis is not a significant removal mechanism for carbon tetrachloride in the troposphere because the short wavelengths of ultraviolet light (around 225 nanometers) required for photolysis are absorbed by ozone in the stratosphere and therefore, do not reach the troposphere (Rebbert and Ausloos, 1976; Atkinson, 1986). In addition, gas phase reactions with methyl radicals, hydrogen atoms, and ground state oxygen atoms are not important tropospheric removal mechanisms for carbon tetrachloride (Winer, 1986; Galbally, 1976). These species are not energetic enough to degrade carbon tetrachloride at a significant rate (Winer, 1986).

The most important identified tropospheric gas phase reaction for carbon tetrachloride involves hydroxyl radicals. The uppper-limit rate constants for the reaction of carbon tetrachloride with hydroxyl radicals have been estimated at 4×10^{-15} cm^3/molecule-sec (absolute rate constant) and 1×10^{-16} cm^3/molecules-sec (relative rate constant) (Howard and Evenson, 1976; Cox, et al., 1976). Assuming an average tropospheric hydroxyl radical concentration of 1×10^6 molecules/cm^3, the lower limit atmospheric lifetime for carbon tetrachloride was estimated to be between 8 and 330 years, respectively. However, the upper limit rate constant which gave the lower limit lifetime estimate of 8

years for carbon tetrachloride is questionable because there was an initial drop in the hydroxyl radical concentration, possibly due to a wall effect (Howard and Evenson, 1976). Thus, the actual lower lifetime estimate for carbon tetrachloride due to reaction with hydroxyl radicals is expected to be longer than 8 years.

The reaction of carbon tetrachloride with excited oxygen atoms ($O(^1D)$) is not expected to be an important atmospheric removal mechanism (Galbally, 1976; Atkinson, et al., 1976; Atkinson, 1986). Galbally estimated the atmospheric removal time of carbon tetrachloride due to reaction with $O(^1D)$ at over 650 years (Galbally, 1976). Although $O(^1D)$ is an extremely reactive species, its tropospheric concentration is too low for it to be an important removal mechanism (NAS, 1976). In the stratosphere, where the concentration of $O(^1D)$ is significantly higher than in the troposphere, the degradation of carbon tetrachloride resulting from its reaction with $O(^1D)$ is minor compared to stratospheric photolysis. Atkinson determined an upper limit relative rate constant of 4.2×10^{-10} cm^3/molecules-sec for the reaction of carbon tetrachloride with $O(^1D)$ (Atkinson, et al., 1976). Using this rate constant and a stratospheric $O(^1D)$ concentration of one molecule $O(^1D)/cm^3$, the upper limit stratospheric lifetime of carbon tetrachloride due to reaction with $O(^1D)$ is 75 years. However, the determination of the rate constant reported by Atkinson was complicated by the photolysis of carbon tetrachloride at a rate approximately the same as carbon tetrachloride's reaction with $O(^1D)$. Thus, the rate constant results reported by Atkinson could contain uncertainties (Atkinson, et al., 1976).

A potential removal mechanism which has not been quantified is adsorption onto particulate matter. It has been demonstrated in the laboratory that carbon tetrachloride adsorbed on silica sand or fused quartz decomposes when irradiated with wavelengths above 310 nm (Ausloos, et al., 1977). These wavelengths do reach the troposphere. Limited ambient monitoring in the Saharan troposphere also indicated lower concentrations of carbon tetrachloride in dust cloud samples relative to non-dusty samples (Pierotti, et al., 1978). Although this data suggests that a tropospheric removal mechanism may be acting, it has yet to be conclusively verified and therefore, could not be accounted for in this discussion.

Wet deposition is not expected to be a major tropospheric removal mechanism for carbon tetrachloride. For three compounds including carbon tetrachloride, Ohta demonstrated that wet deposition increased with the compounds' solubility in water (Ohta, et al., 1977). Since carbon tetrachloride is only slightly soluble in water, wet deposition is probably not as important as it is for compounds with greater water solubilities. If carbon tetrachloride is removed by wet deposition, it would be expected to volatilize and re-enter the troposphere.

Another minor tropospheric removal mechanism that has been proposed involves absorption and microbial action in soil and vegetation (NAS, 1976). Galbally estimated the tropospheric removal time of carbon tetrachloride by land biota to be in excess of 333 years (Galbally, 1976).

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APPENDIX A

Atmospheric Lifetime Experiment (ALE)

A. Atmospheric Lifetime Experiment

In 1978 Cunnold, Alyea, and Prinn discussed two different methods for determining the atmospheric lifetimes of chlorofluorocarbons. One method, the "inventory technique", requires knowledge of the atmospheric content and emission history to determine the lifetime. The other method, the "trend technique", requires knowledge of the atmospheric accumulation rate and emission history to determine the lifetime. The "trend technique" is deemed to be the more reliable due to the relative unimportance of absolute measurement accuracy and systematic errors in emissions data; however, the "trend technique" required 3 to 5 years of data with observations made at least daily. Cunnold (et al., 1978) proposed that a remote-station, data-gathering network be implemented.

Based on the above study, Prinn (et al., 1983) began an experiment entitled the "Atmospheric Lifetime Experiment" (ALE), which utilizes the following five globally distributed coastal measurement stations: (1) Adrigole, Ireland, 52°N, 10°W; (2) Cape Meares, Oregon, 45°N, 124°W; (3) Ragged Point, Barbados, 13°N, 59°W; (4) Point Matatula, American Samoa, 14°S, 171°W; and (5) Cape Grim, Tasmania, 41°S, 145°E. Because most of the industrial emissions of chlorofluorocarbons occur in the northern hemisphere at midlatitudes, it was considered highly desirable that two stations operate at these latitudes to avoid the biases that could result from reliance on any one station alone. Each of the ALE stations is intended to be representative of one of the four equal mass subdivisions of the global atmosphere; 0° to 30°N, 30° to 90°N, 0° to 30°S, and 30° to 90°S.

All five ALE stations are equipped with the same microprocessor-controlled Hewlett Packard 5840A dual-channel electron-capture gas chromatograph (Prinn, et al., 1983). Outside air is drawn into each of the instruments by means of a noncontaminating metal bellows pump along a stainless steel line that is securely attached to a large pole so that the air intake is at least 2.0 m above the roof of the instrument building. Separate analysis of a calibration standard as close in concentration to ambient as possible, and under the same conditions, is performed routinely within one hour of the ambient air analysis. Measurement runs along with their accompanying calibration runs are done three to four times daily on the average. At most sites a local caretaker or trained technician makes a daily visit to the station to verify routine performance of the instruments, and each station is visited at least quarterly by the station scientist for detailed servicing of the instrument and for replacement of the calibration gas tank. Considerable care is taken to maintain 1% precision of analysis at ambient levels.

The field calibration standards are prepared at the Cape Meares station by cryogenically liquefying clean ambient air into 35-liter, aircraft-surplus, breathing-oxygen tanks of type-304 stainless steel, passivated by an electropolish (Rasmussen and Lovelock, 1983). The determination of concentrations in the tanks relative to the primary standard is carried out both before and after the use of the tank at a particular site, with each determination consisting of at least six separate analyses. Decline of carbon tetrachloride concentrations in the tanks from heterogeneous surface reaction has been estimated to be 0.15 $\pm$

0.20% per year. Absolute calibration of standards for carbon tetrachloride concentration has been determined by coulometry; the method of exponential dilution for absolute calibration proved to be unreliable for carbon tetrachloride, due to adsorption of the compound onto the glass ampoule by which the compound was introduced to the dilution chamber. The accuracy of absolute calibration for carbon tetrachloride determined by coulometry alone is estimated to be 4%, but 11% is believed to be the more reasonable estimate according to Simmonds (et al., 1983).

Simmonds (et al., 1983) presented ALE results for carbon tetrachloride based on 3 years of data taken from July 1978 to June 1981. The average concentration of carbon tetrachloride in the lower troposphere was 118 pptv (121 pptv in the northern hemisphere), with the average of monthly standard deviations being less than 2 pptv, and was increasing by 2.1 pptv per year. Using a two-dimensional atmospheric transport model consisting of eight tropospheric boxes and one stratospheric box (Cunnold, et. al., 1983), the atmospheric lifetime (1/e-life) of carbon tetrachloride was calculated by the "inventory technique" to be 57 years. Using an optimal estimation technique, incorporating the two-dimensional model, the atmospheric lifetime was calculated by the "trend technique" to be 50 years. The maximum likelihood combination of these two lifetime estimates is 52 years (Simmonds, et al., 1983) and is estimated to be accurate within 30 percent (Prinn, 1986). The inaccuracy of lifetime estimates for carbon tetrachloride is due primarily to incomplete knowledge of emissions history.

Table A-1

Summary of the ALE Monitoring Results

Month	Adrigole, Ireland			Cape Meares, Oregon			Ragged Point, Barbados			Point Matatula, American Samoa			Cape Grim Tasmania		
	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N
July 1978	-	-	-				114.6	2.7	144	110.7	1.8	61	113.8	2.3	54
Aug. 1978	-	-	-				116.0	2.3	200	111.1	2.0	125	113.1	1.8	124
Sept. 1978	-	-	-				115.3	3.0	165	111.4	1.6	126	113.7	1.6	72
Oct. 1978	-	-	-				114.3	3.5	111	111.2	1.7	106	113.9	1.4	44
Nov. 1978	-	-	-				113.2	3.6	134	113.0	2.3	97	114.3	1.1	70
Dec. 1978	-	-	-				116.6	3.5	131	114.0	1.5	60	113.8	0.8	47
Jan. 1979	-	-	-				118.3	2.8	121	114.9	1.1	18	113.1	1.1	58
Feb. 1979	-	-	-				118.1	2.8	118	113.8	1.5	95	112.6	1.0	92
March 1979	-	-	-				115.9	2.8	94	113.6	1.2	117	112.9	1.3	111
April 1979	-	-	-				-	-	-	114.3	1.5	110	113.2	0.8	115
May 1979	-	-	-				117.9	1.5	80	114.2	1.0	121	113.2	1.1	110
June 1979	-	-	-				118.3	1.5	40	114.2	0.8	115	113.0	1.0	112
July 1979	-	-	-				118.1	1.7	104	114.9	0.9	118	113.0	1.0	94
Aug. 1979	-	-	-				117.9	1.5	123	114.9	0.9	111	112.8	0.9	118
Sept. 1979	-	-	-				117.2	1.6	136	114.8	1.3	99	112.8	0.8	106
Oct. 1979	-	-	-				117.6	1.4	134	115.6	1.1	115	114.1	1.0	94
Nov. 1979	-	-	-				118.5	1.5	96	112.6	1.2	115	114.4	1.1	110
Dec. 1979	126.1	1.7	53	123.4	1.7	55	119.2	1.3	129	115.0	1.5	102	114.5	0.9	85
Jan. 1980	128.2	2.3	61	124.1	1.5	74	119.9	1.5	132	116.5	1.5	99	114.5	1.0	94
Feb. 1980	126.4	2.5	108	123.0	2.2	31	119.6	1.4	105	115.9	1.5	122	114.8	0.9	72
March 1980	124.8	1.7	89	123.5	1.8	10	120.8	1.4	128	115.5	1.4	105	115.3	0.9	117
April 1980	126.3	3.2	104	122.1	0.9	87	120.4	1.5	124	115.7	1.5	115	116.2	1.2	79
May 1980	126.0	2.1	61	122.1	0.8	98	120.5	1.3	137	116.0	1.0	116	116.8	0.9	88
June 1980	125.8	1.8	114	122.0	0.8	114	120.9	1.1	147	116.0	0.8	94	116.6	0.8	85
July 1980	125.9	1.6	110	121.7	1.1	91	120.9	1.4	129	116.2	0.7	117	115.3	1.1	105
Aug. 1980	125.7	1.5	119	121.3	0.9	82	121.2	1.9	47	116.4	0.8	117	115.2	0.7	102
Sept. 1980	125.2	1.9	109	122.6	1.1	112	120.2	1.4	125	116.3	1.2	100	116.1	1.1	74
Oct. 1980	125.2	2.0	79	123.7	1.1	126	120.6	1.7	126	116.1	0.7	17	114.9	1.2	81
Nov. 1980	127.2	1.6	79	124.2	1.2	123	121.2	1.9	118	116.8	0.9	63	116.5	1.5	101
Dec. 1980	127.3	2.5	66	123.9	1.3	119	121.7	1.9	117	117.3	1.1	98	116.4	0.5	96
Jan. 1981	128.3	1.9	120	125.0	1.9	132	121.7	1.4	138	117.6	1.3	42	116.6	0.6	54
Feb. 1981	129.4	2.3	66	123.8	1.2	111	121.8	1.3	119	118.3	1.1	4	115.1	0.6	46
March 1981	132.1	2.4	101	124.1	0.7	128	121.7	1.5	99	117.8	1.9	54	115.7	0.6	88
April 1981	131.5	2.0	53	124.4	0.8	113	122.6	1.6	110	118.0	1.0	136	115.8	0.6	80
May 1981	132.3	2.3	62	125.0	0.9	123	122.7	1.5	123	117.4	1.2	123	116.3	0.6	99
June 1981	127.8	2.0	78	125.0	0.9	115	122.9	1.4	110	117.7	0.9	111	116.9	0.7	62

Legend:

$\bar{x}$ = carbon tetrachloride concentration in parts per trillion (ppt)

σ = standard deviation (ppt)

N = number of samples

The atmospheric lifetime of carbon tetrachloride, as determined by the Atmospheric Lifetime Experiment, is in close agreement with the value of 50 years obtained by Golombek (1986) based on stratospheric photodissociation using a three-dimensional model. This agreement implies that stratospheric photodissociation, as was previously suspected, is the major atmospheric removal process for carbon tetrachloride.

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2. Cunnold, D. M., R. G. Prinn, R. A. Rasmussen, P. G. Simmonds, F. N. Alyea, C. A. Cardelino, A. J. Crawford, P. J. Fraser, and R. D. Rosen, 1983. "The Atmospheric Lifetime Experiment, 3. Lifetime Methodology and Application to Three Years of $CFCl_3$ Data," Journal of Geophysical Research, Vol. 88, C13, pp. 8379-8400, American Geophysical Union, Washington, D.C.

3. Golombek, A., and Prinn, R., 1986. "A Global Three-Dimensional Model of the Circulation and Chemistry of $CFCl_3$, CF_2, Cl_3CCl_3, CCl_4, and N_2O," Journal of Geophysical Union, Washington, D. C.

4. Prinn, R. G., P. G. Simmonds, R. A. Rasmussen, R. D. Rosen, F. N. Alyea, C. A. Cardelino, A. J. Crawford, D. M. Cunnold, P. J. Fraser, and J. E. Lovelock, 1983. "The Atmospheric Lifetime Experiment, 1. Introduction, Instrumentation, and Overview," Journal of Geophysical Research, Vol. 88, C13, pp. 8353-8367, American Geophysical Union, Washington, D. C.

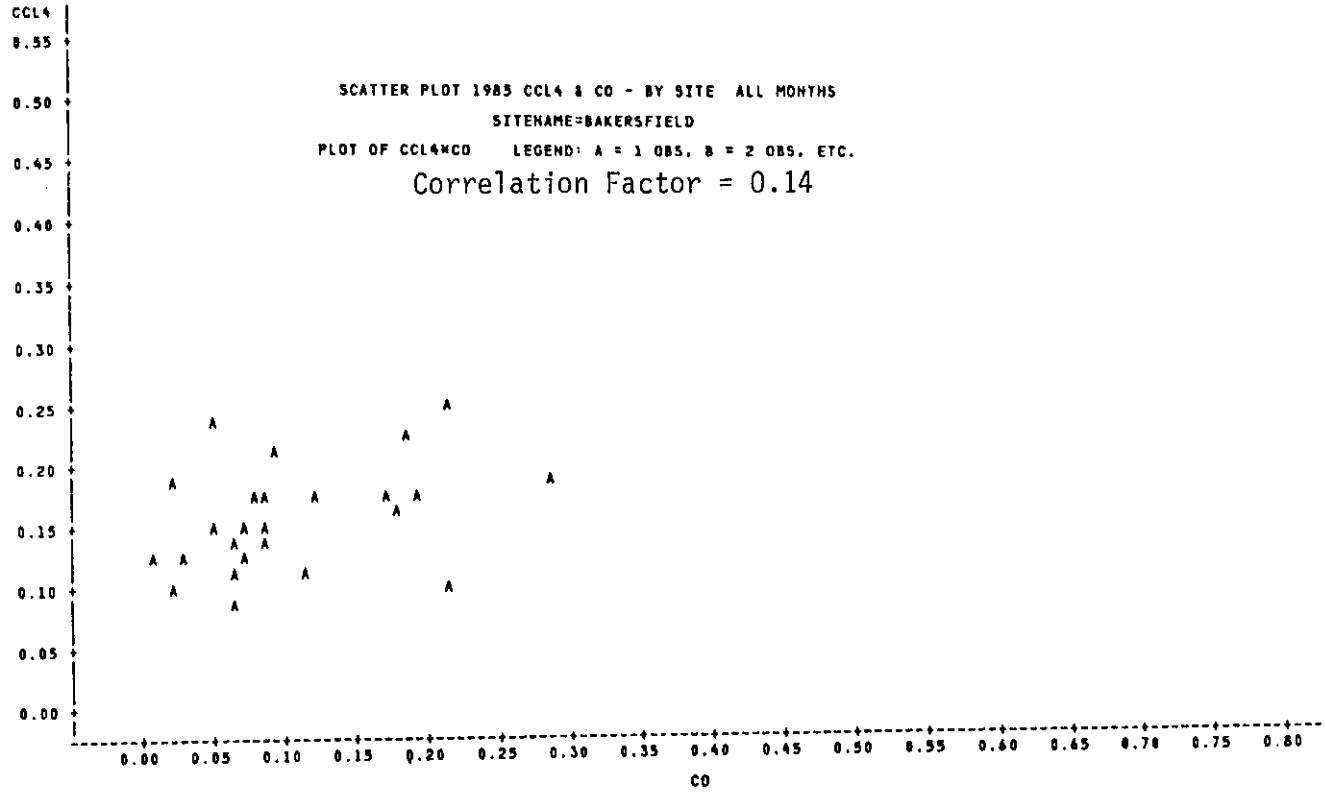
5. Rasmussen, R. A., and J. E. Lovelock, 1983. "The Atmospheric Lifetime Experiment, 2. Calibration," Journal of Geophysical Research, Vol. 88, C13, pp. 8369-8378, American Geophysical Union, Washington, D.C.

6. Simmonds, P. G., F. N. Alyea, C. A. Cardelino, A. J. Crawford, D. M. Cunnold. B. C. Lane, J. E. Lovelock, R. G. Prinn, and R. A. Rasmussen, 1983. "The Atmospheric Lifetime Experiment, 6. Results for Carbon Tetrachloride Based on 3 Years Data," Journal of Geophysical Research, Vol. 88, C13, pp. 8427-8441.

APPENDIX B

Plots From the Carbon Monoxide Versus Carbon Tetrachloride Correlation Analysis

FIGURE B-1



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-2

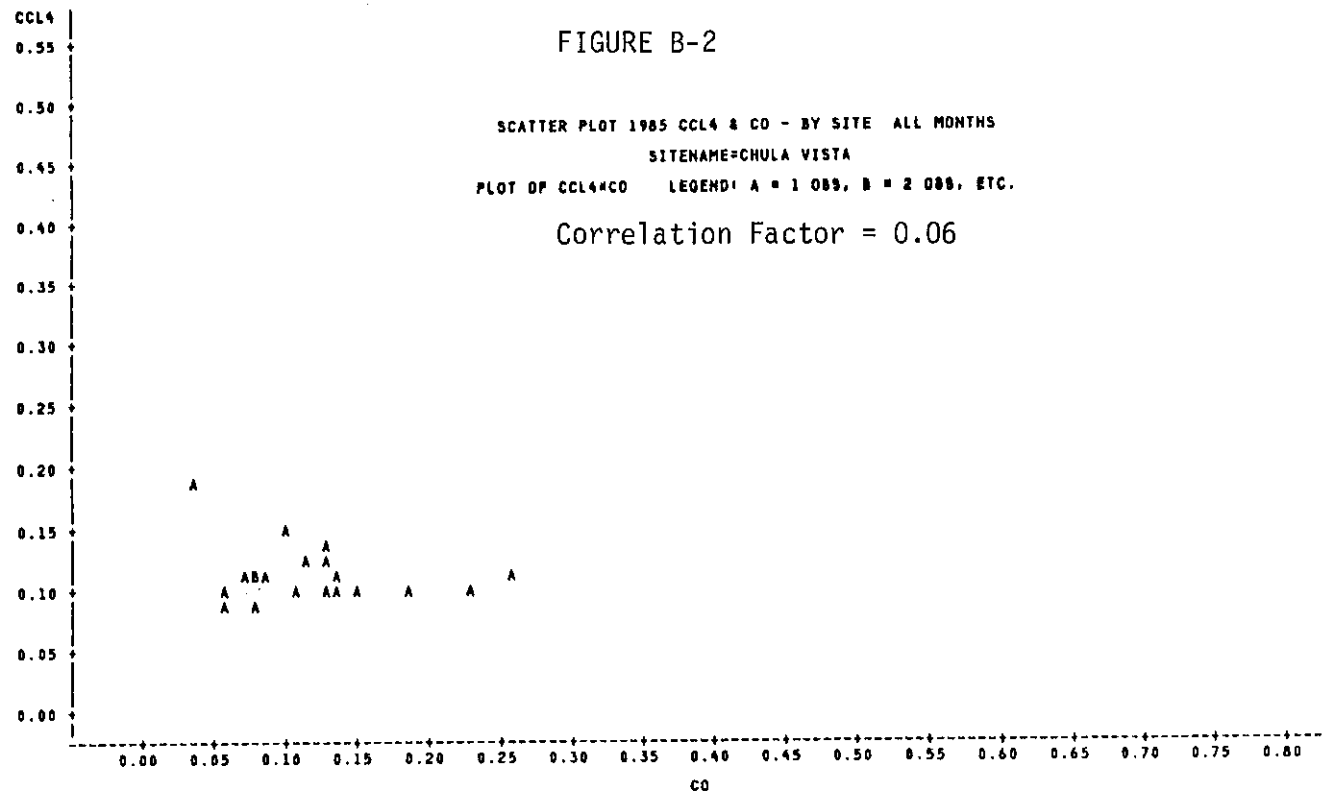
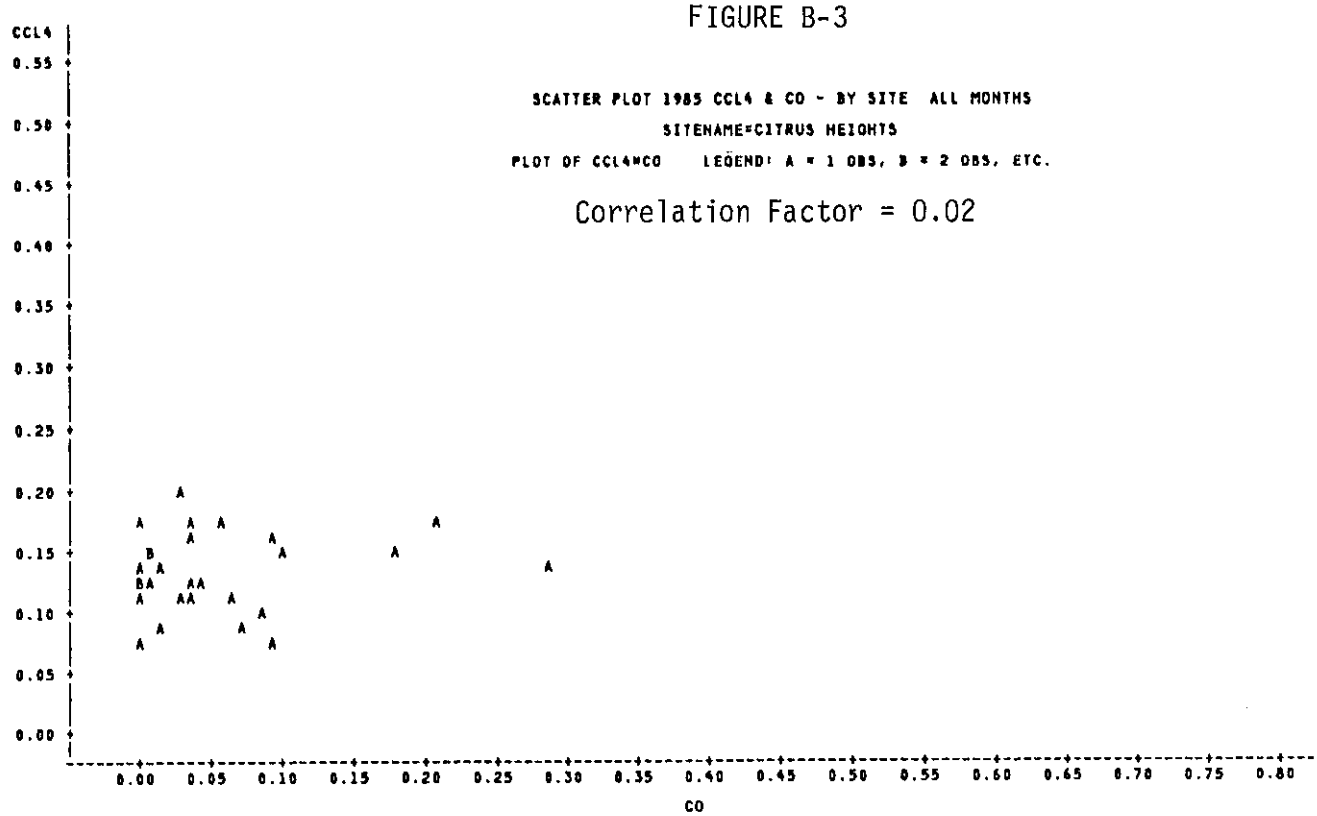


FIGURE B-3



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-4

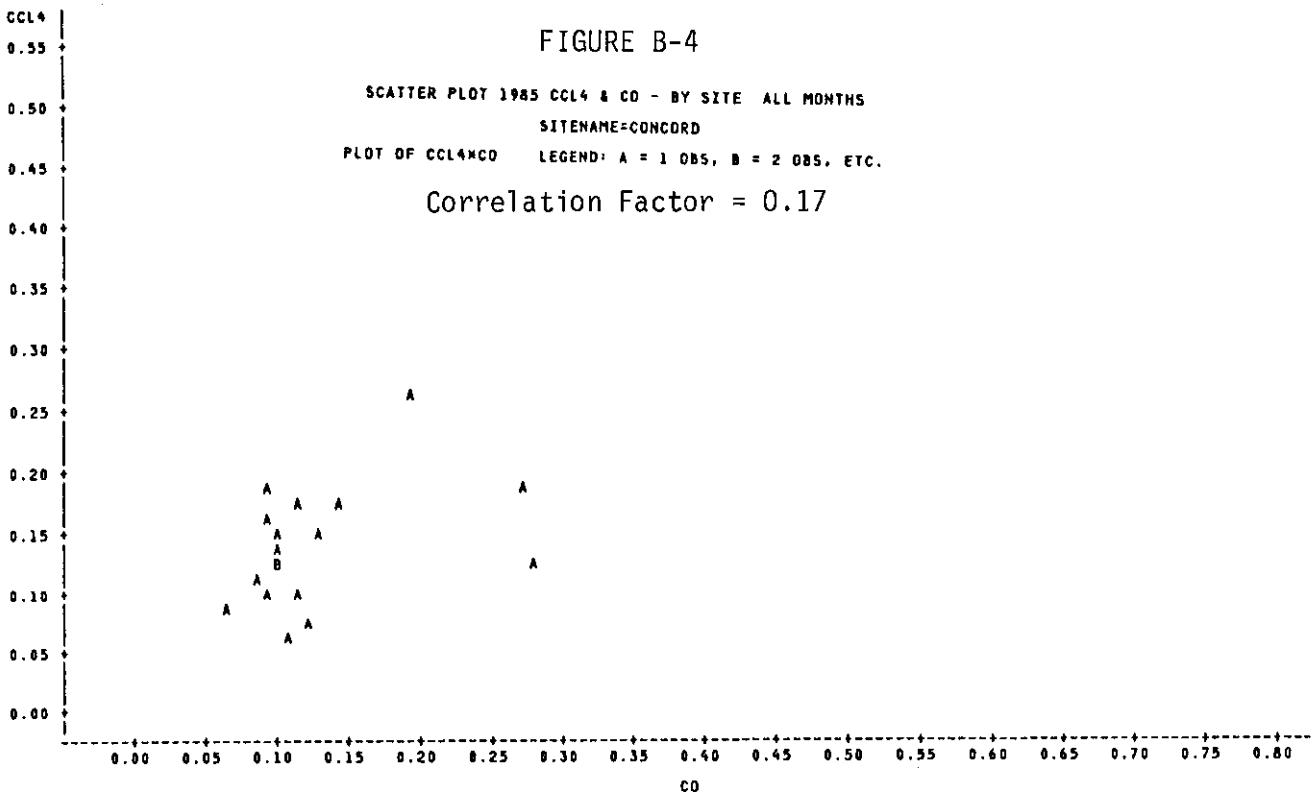
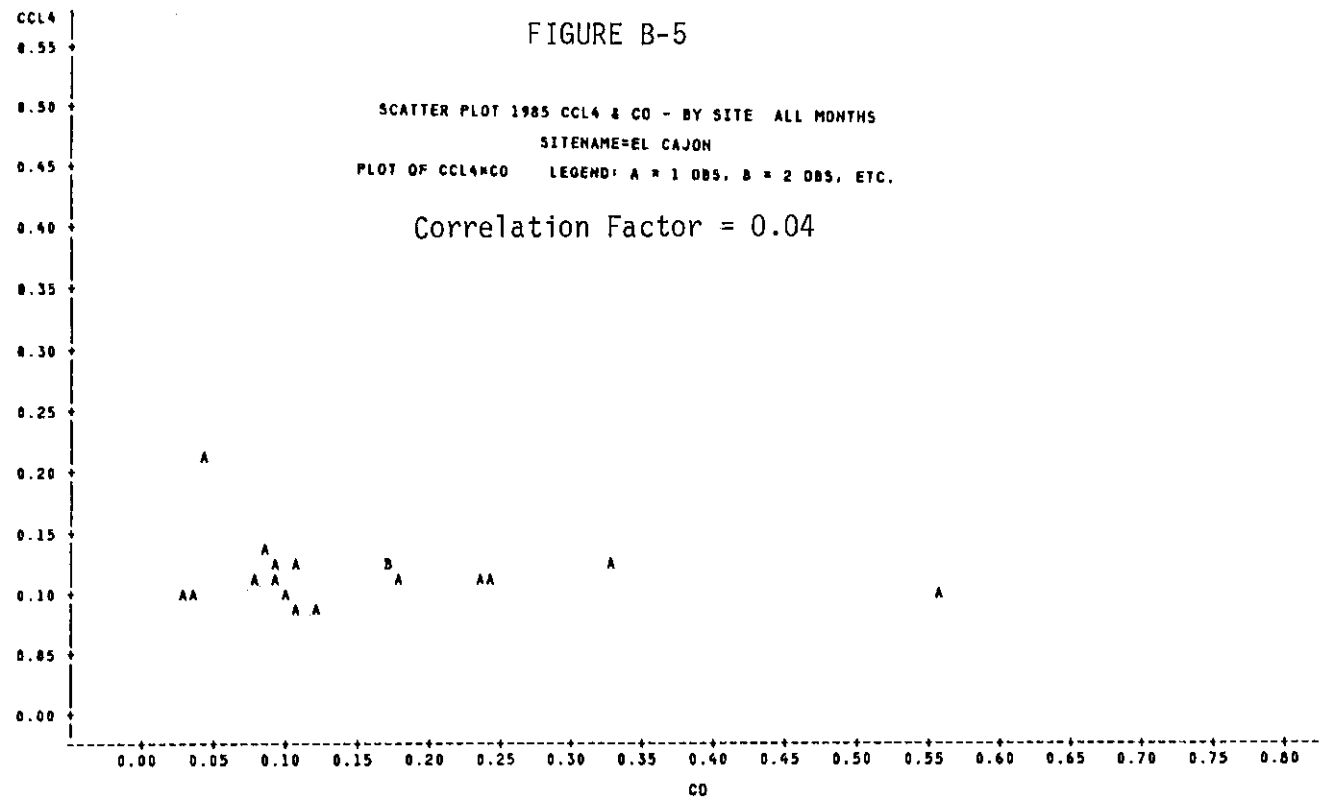


FIGURE B-5



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-6

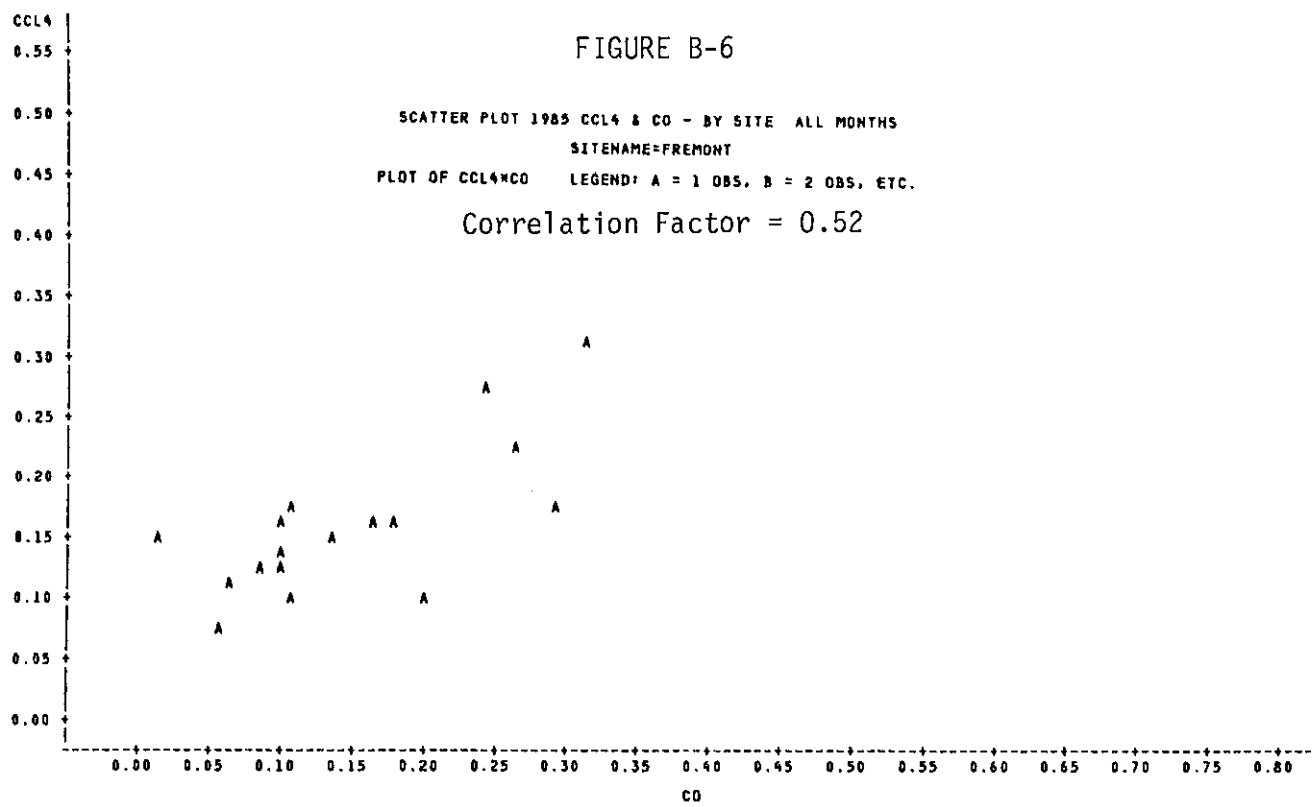
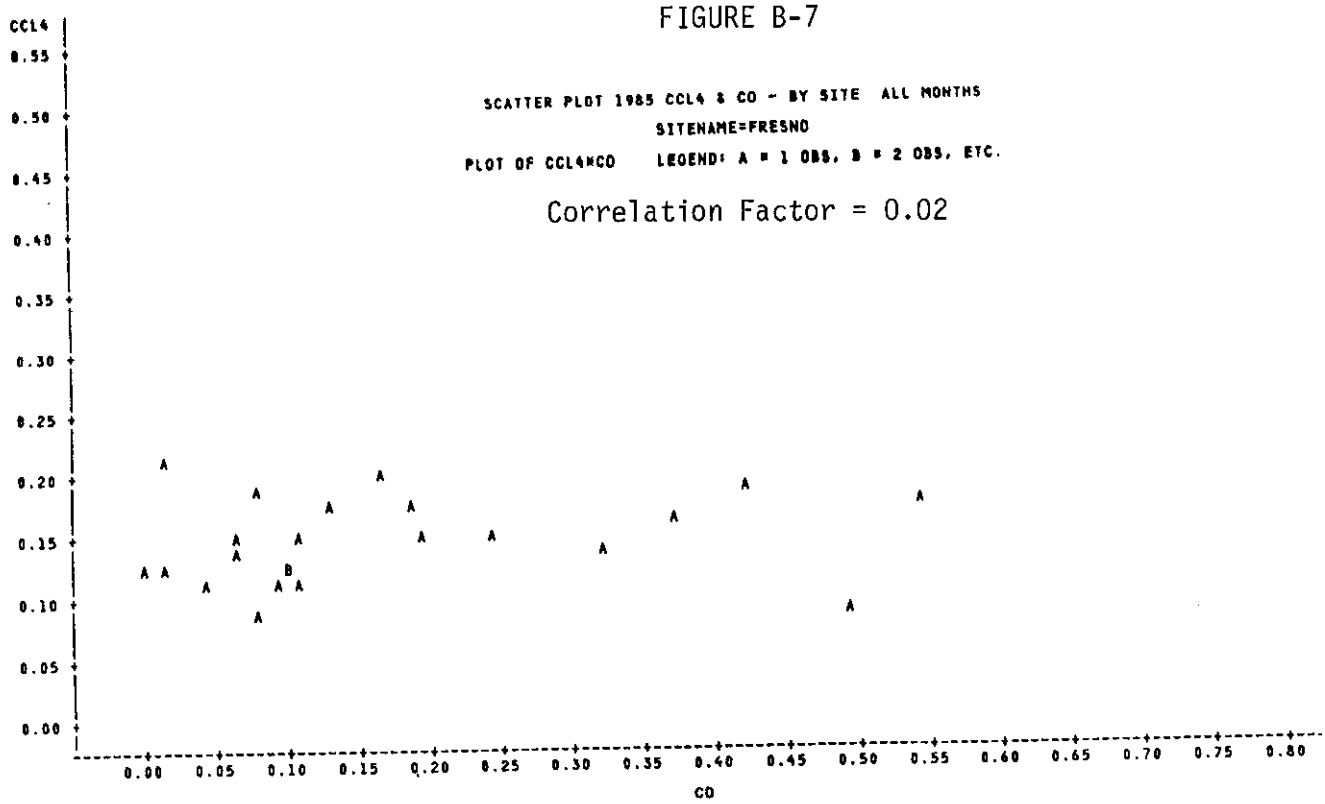
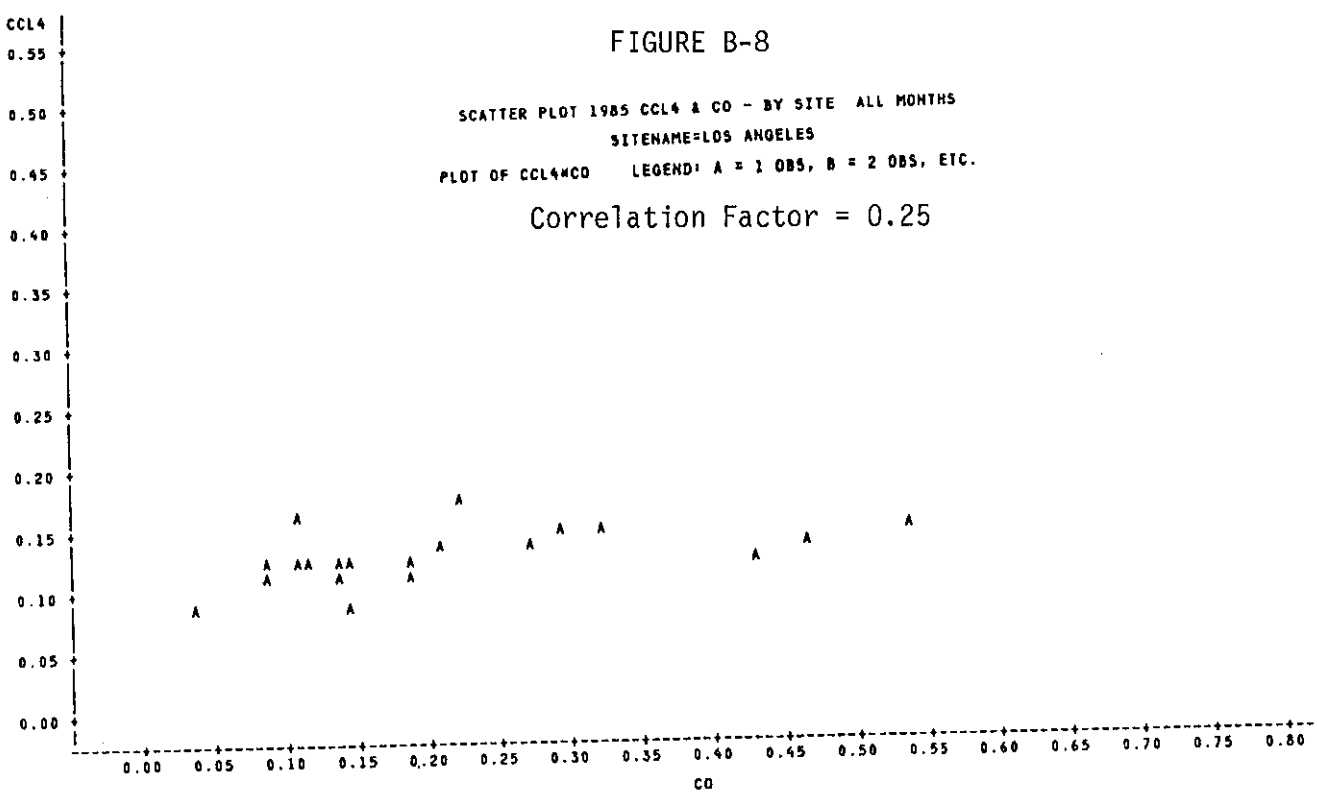


FIGURE B-7



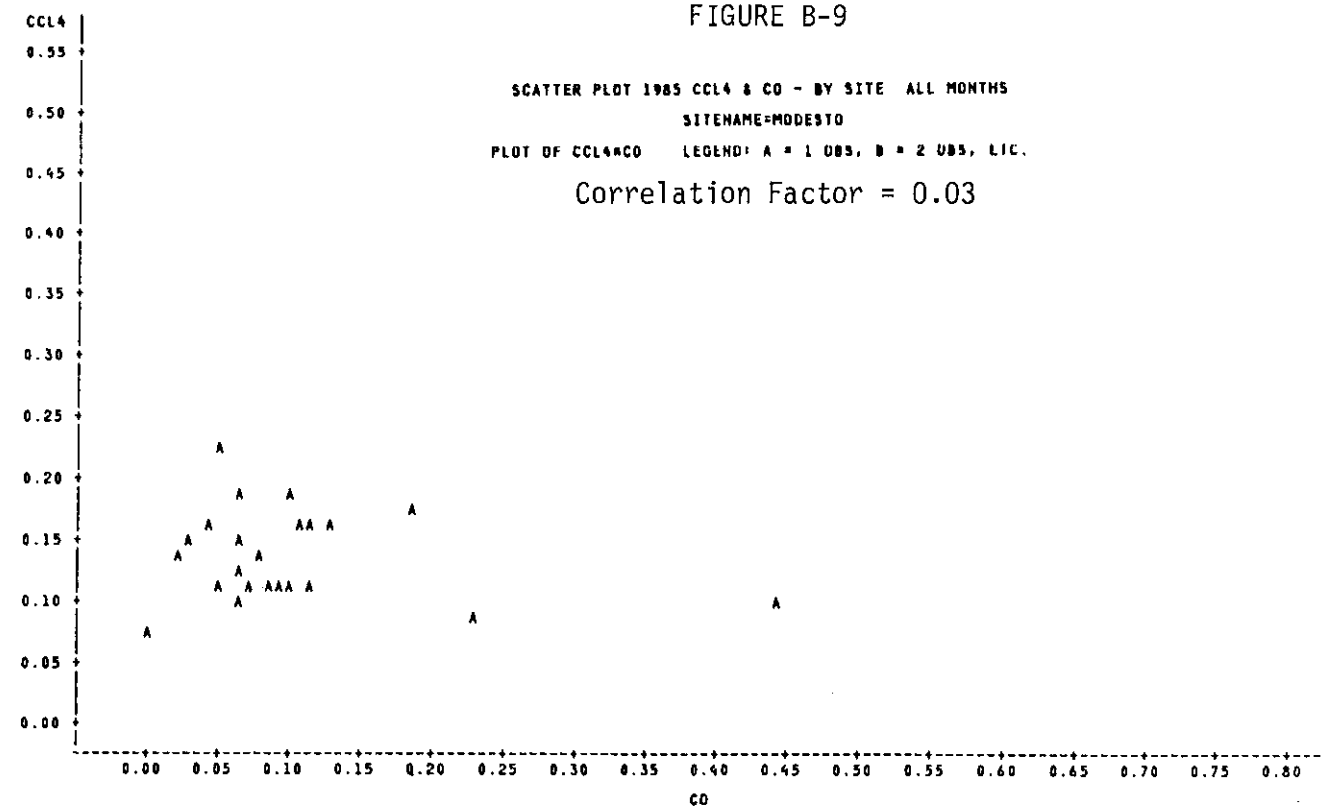
NOTE: 2 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-8



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-9



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-10

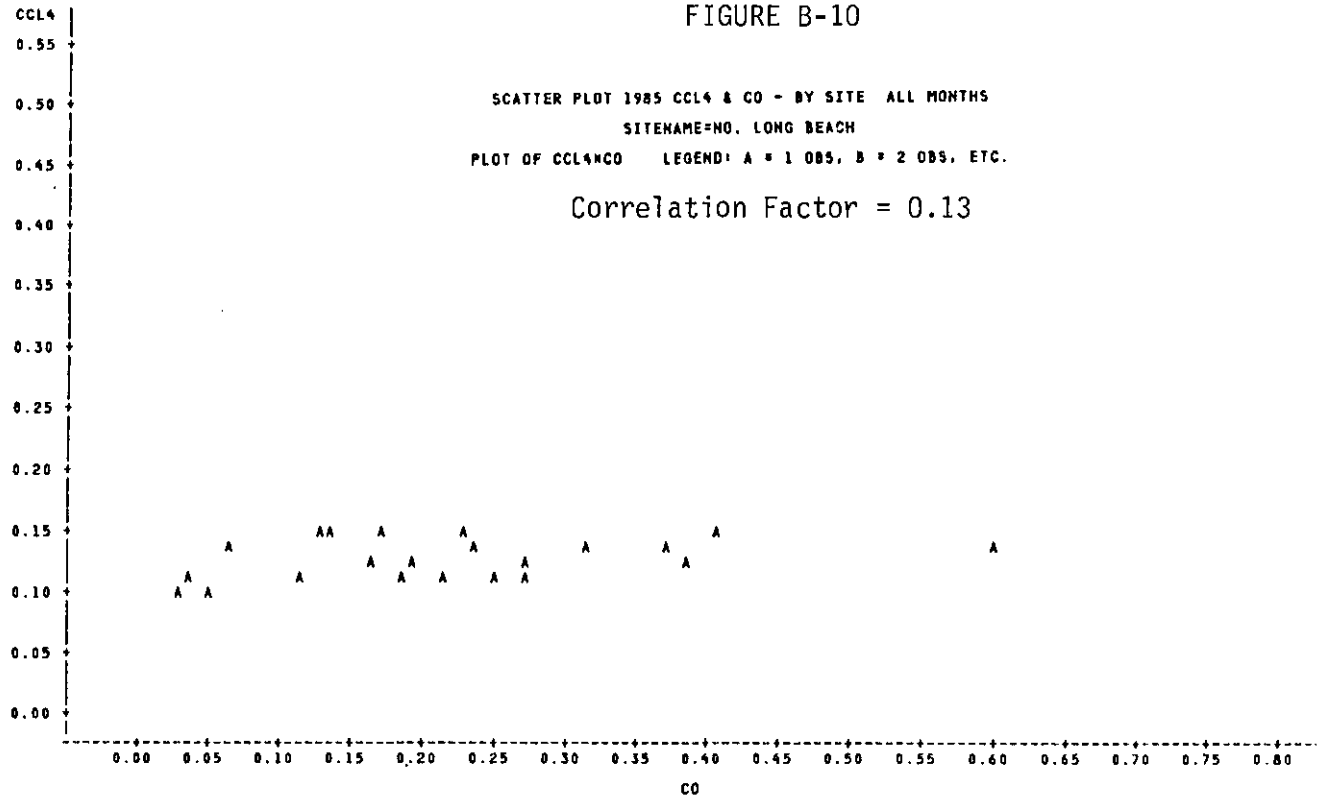
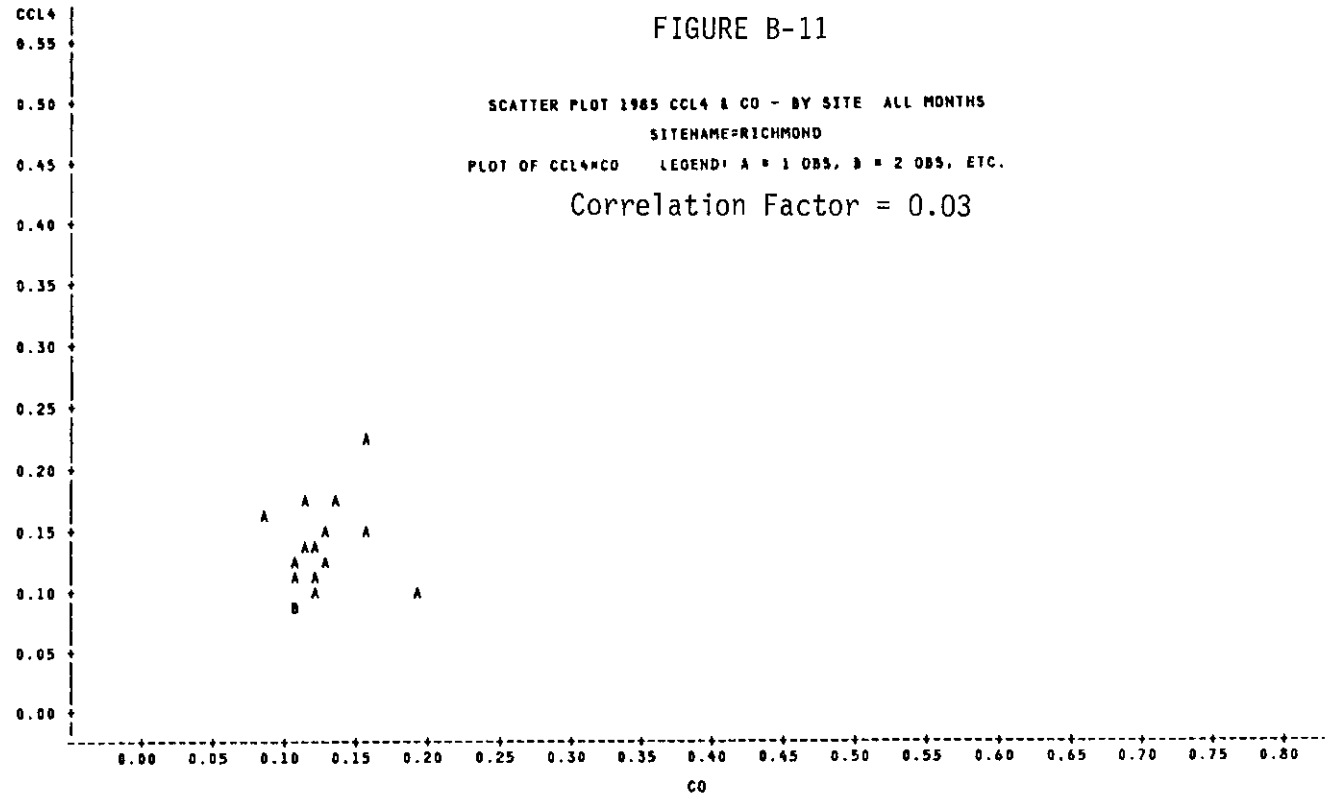
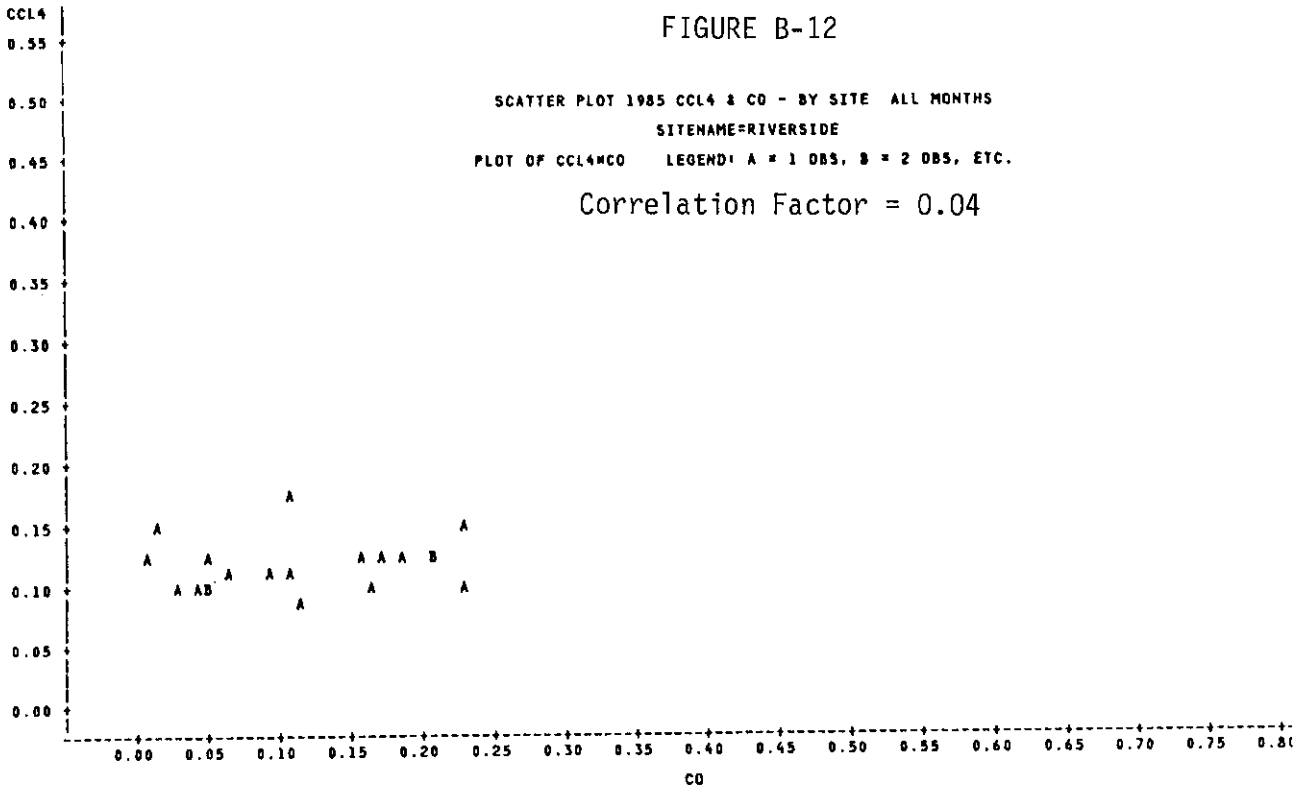


FIGURE B-11



NOTE: 1 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-12



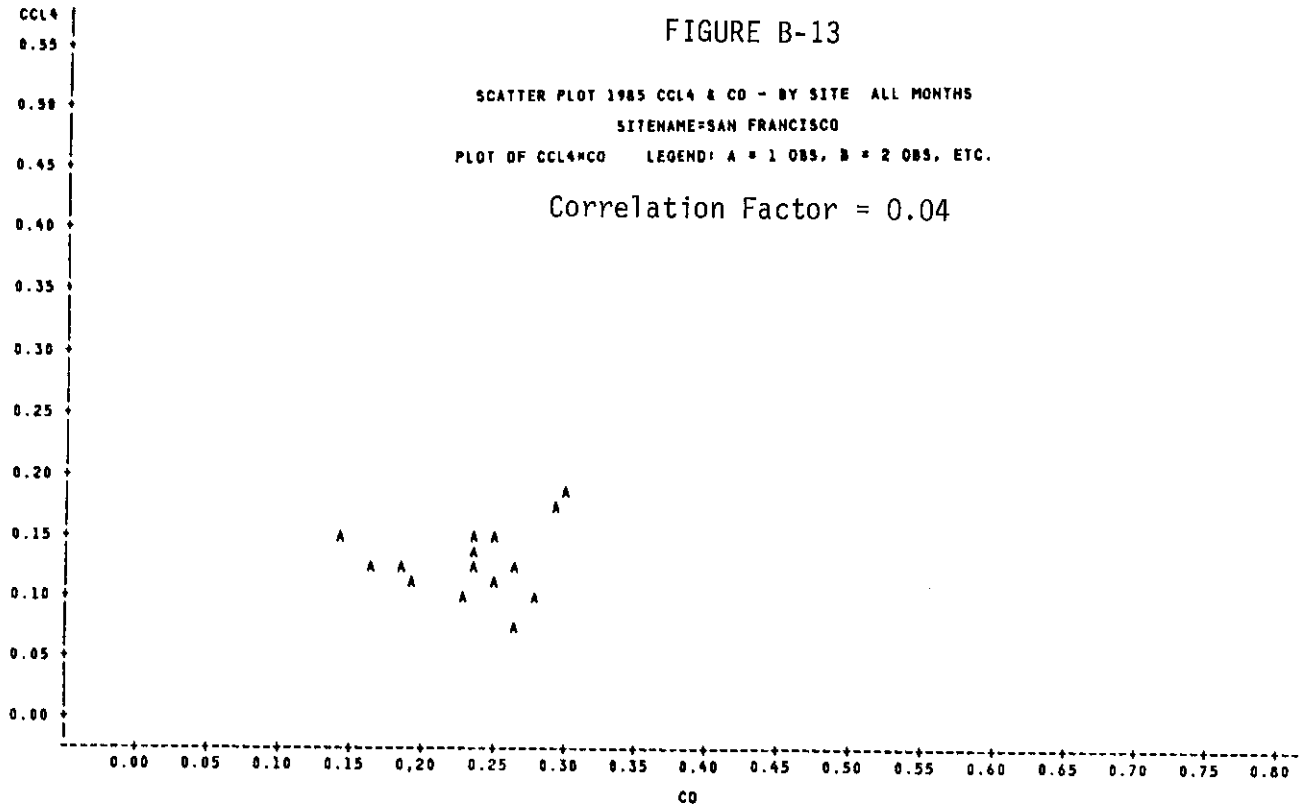


FIGURE B-13
SCATTER PLOT 1985 CCL4 & CO - BY SITE ALL MONTHS
SITENAME=SAN FRANCISCO
PLOT OF CCL4*CO LEGEND: A = 1 OBS, B = 2 OBS, ETC.
Correlation Factor = 0.04
CCL4
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80
CO

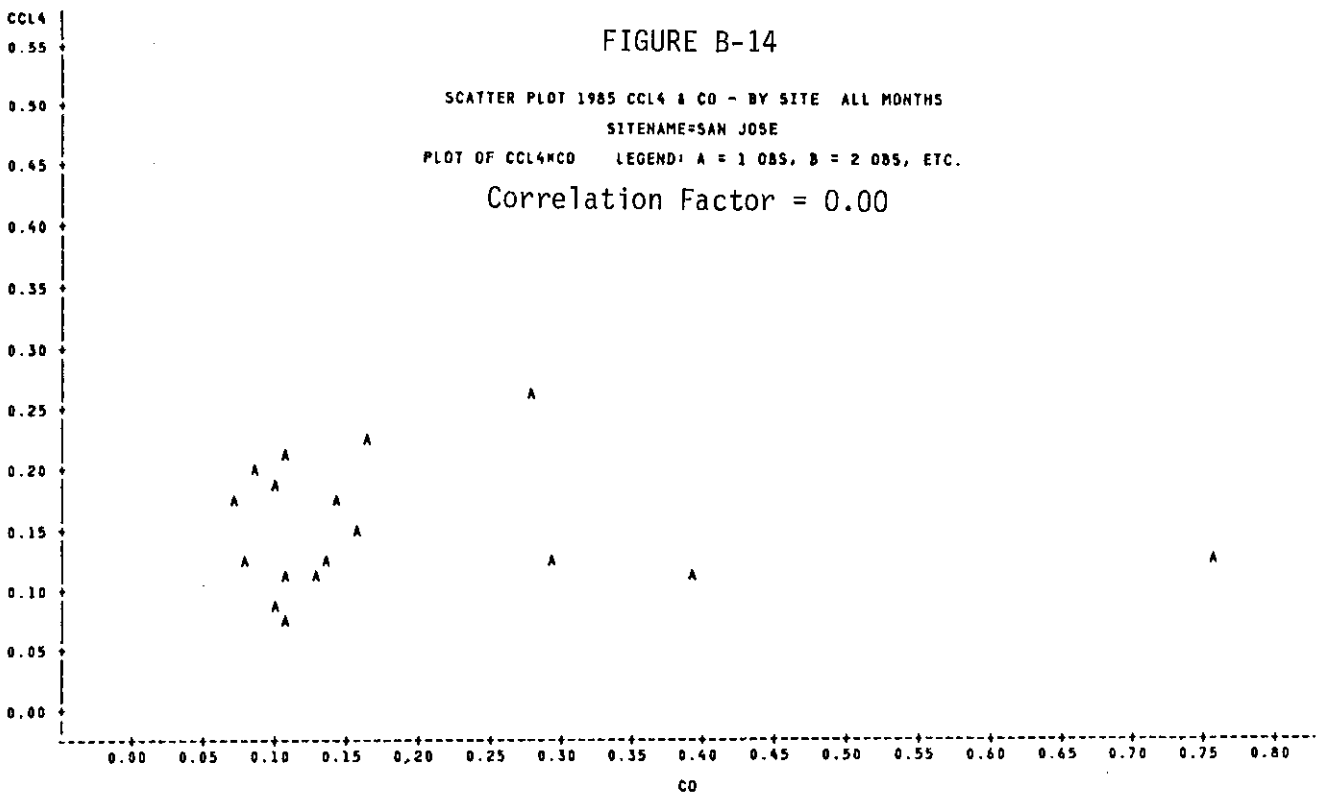
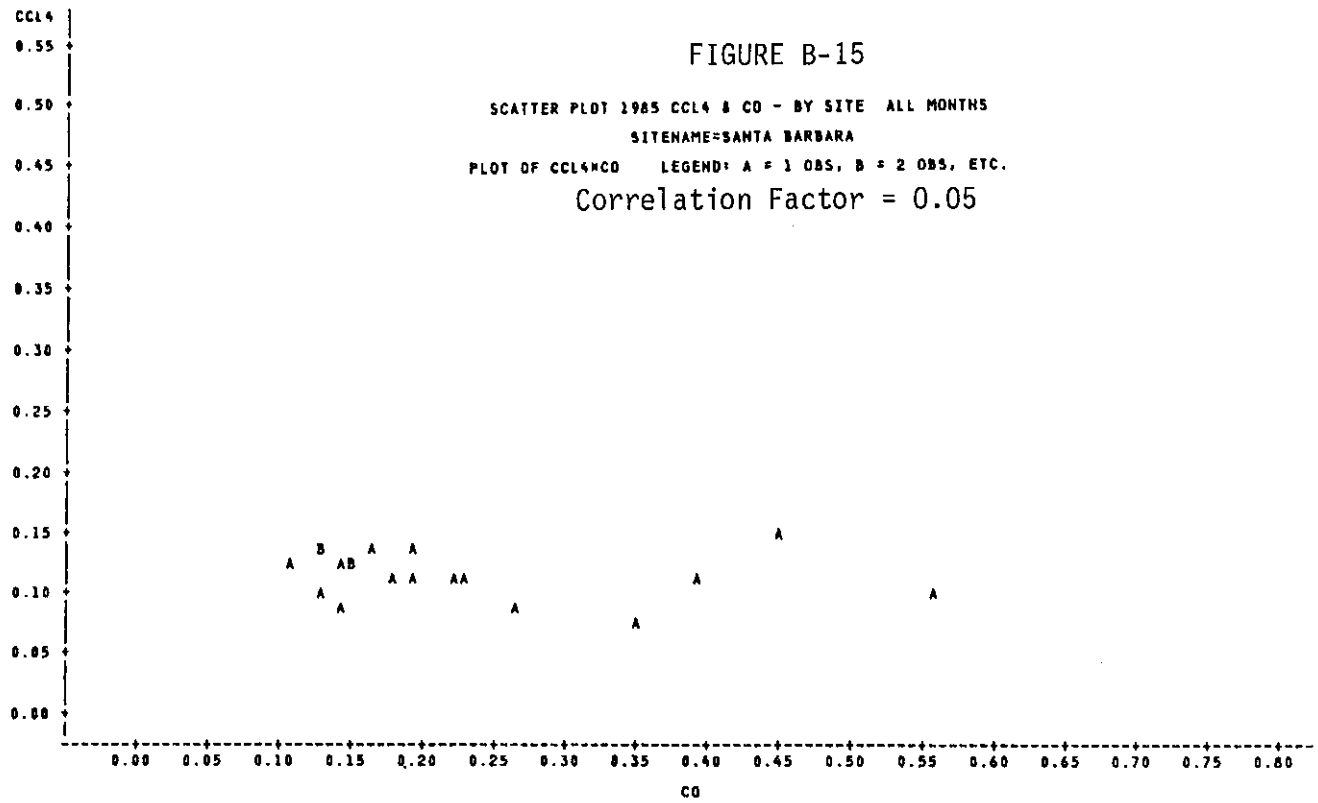
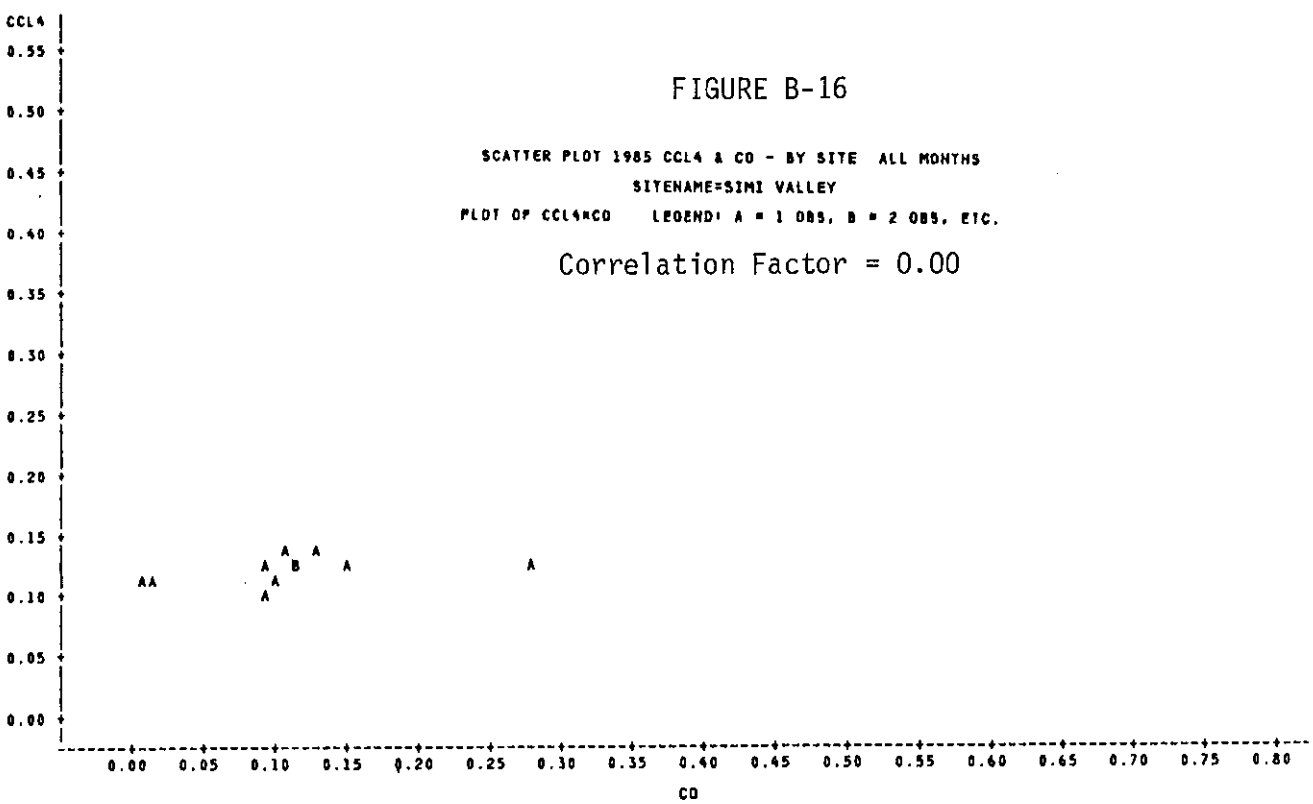


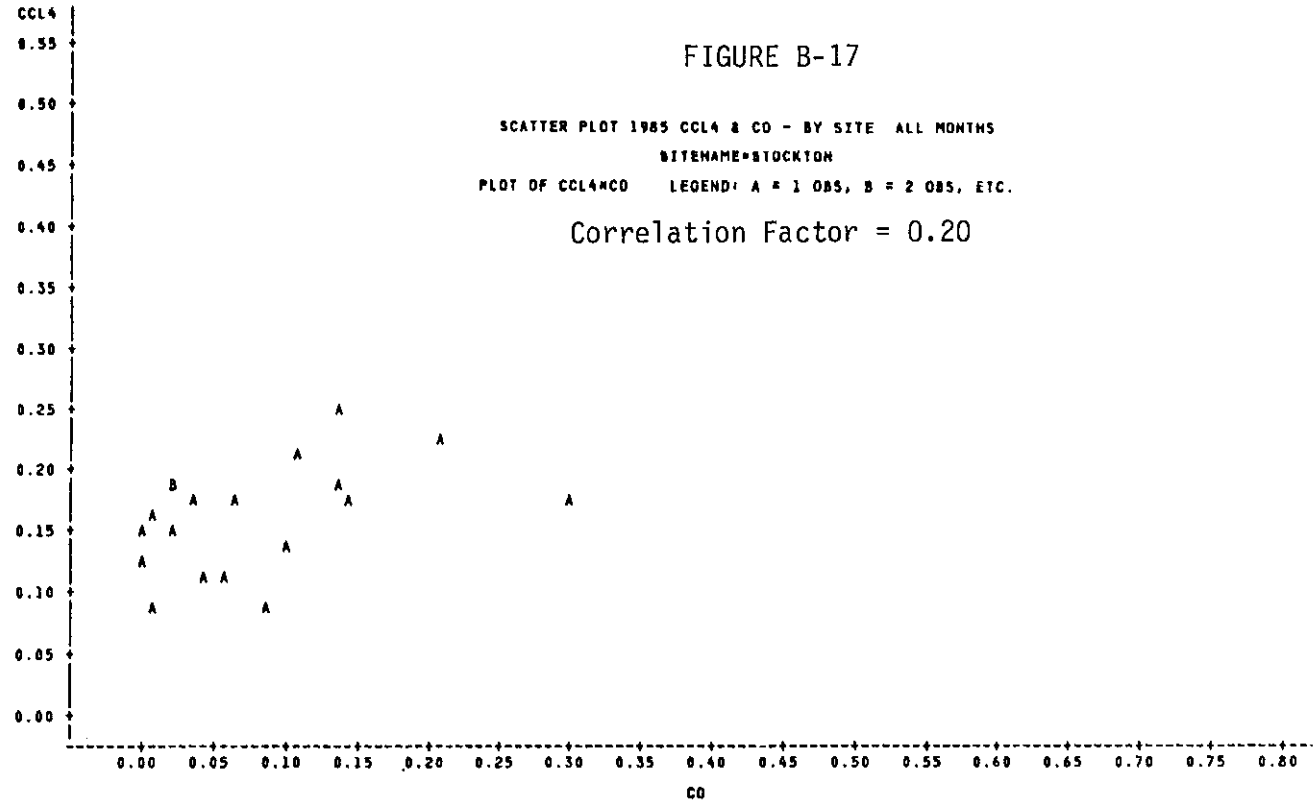
FIGURE B-14
SCATTER PLOT 1985 CCL4 & CO - BY SITE ALL MONTHS
SITENAME=SAN JOSE
PLOT OF CCL4*CO LEGEND: A = 1 OBS, B = 2 OBS, ETC.
Correlation Factor = 0.00
CCL4
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80
CO





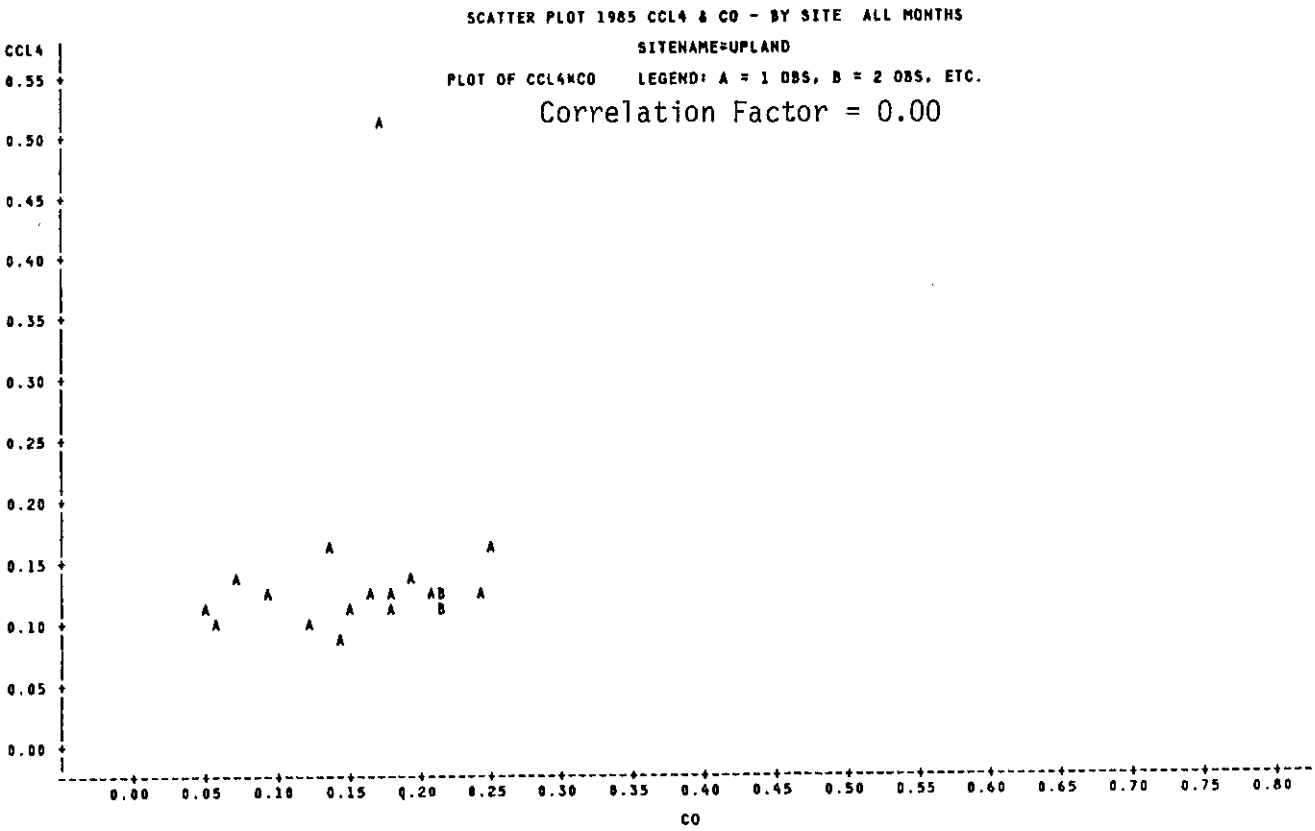
NOTE: 9 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-17



NOTE: 3 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

FIGURE B-18



APPENDIX C

Calculations and Assumptions of Annual Intakes of Carbon Tetrachloride

APPENDIX C

Sample Calculations of the Amount of Carbon Tetrachloride Inhaled or Ingested Annually.*

I. INHALATION OF CARBON TETRACHLORIDE

A. AMBIENT EXPOSURE

Assumptions of exposure for an adult

1. Ambient and indoor carbon tetrachloride concentrations are equivalent.

2. Average carbon tetrachloride concentrations in California range from 0.13 ppb to 0.60 ppb (0.82 ug/m^3 to 3.8 ug/m^3). The 0.13 ppb is the annual average concentration in California as determined from the ARB monitoring data. The 0.60 ppb (3.8 ug/m^3) is the maximum annual average concentration that is estimated from dispersion modeling analysis for people living near Dow Chemical and the du Pont modeling area.

3. Breathing rate of air is 23 m^3/day

* All estimated annual intakes are rounded off to one significant figure.

Yearly intake of

carbon tetrachloride = (3.8 ug/$m^{3)}$ X (23 m^3/day) X (365 day/year)

= 31,901 ug/year

or

30,000 ug/year

II. INGESTION OF CARBON TETRACHLORIDE

A. EXPOSURE FROM FOOD PRODUCTS

Assumptions of exposure from food for an adult

1. The average concentration of carbon tetrachloride in ready to eat food products is 2 ug/kg.

2. Excluding grain products, ready to eat food products represent 50 percent of the diet. The remaining 50 percent of non-grain foods have no carbon tetrachloride residues.

3. The maximum concentration of carbon tetrachloride in grain products is estimated to be 40 ug/kg.

4. An adult consumes 2 kg of food per day. Of this, grain products represents 0.18 kg.

Yearly intake of

carbon tetrachloride = 0.5 (2 ug/kg X 1.82 kg/day X 365 days/year)

+ (40 ug/kg X 0.18 kg/day X 365 days/year)

= 664 ug/year + 2,628 ug/year

= 3,292 ug/year

or 3,000 ug/year

B. EXPOSURE FROM DRINKING WATER

Assumptions of exposure from drinking water for adult

1. The concentration of carbon tetrachloride in California's drinking water ranges from below 0.5 ug/1 to a maximum of 29 ug/1.

2. An average adult consumes 2 liters of water per day.

Sample calculations

Yearly intake of

carbon tetrachloride = (29 ug/1 X 2 1/day X 365 days/year)

= 21,170 ug/year

or 20,000 ug/year

III. DISCUSSION OF ASSUMPTIONS

In estimating exposure to carbon tetrachloride from different exposure routes, several assumptions were made. The inhalation rate of 23 m^3/day and water consumption rate of 2 l/day were based on EPA estimates (U. S. EPA, 1984). The amount of cereal consumed by an adult per day in North America was also based on an EPA estimate (U. S. EPA, 1985). Total food consumption by an adult was based on a World Health Organization estimate (U. S. EPA, 1975).

REFERENCES

1. U. S. EPA, 1984. "Draft Document of Carbon Tetrachloride (Technical Report)," JRB Associates, Inc., McLean, VA. PB 84-209832.

2. U. S. EPA, 1985. "Health Assessment Document for Carbon Tetrachloride," EPA-600/8-82/001F EPA, Cincinnati, OH.

3. U. S. EPA, 1975. "Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride," EPA/600/6-75/004. EPA, Research Triangle Park, N.C.

APPENDIX D

SUMMARY OF INDOOR/OUTDOOR CARBON TETRACHLORIDE MONITORING STUDIES

Introduction and Conclusion

This appendix summarizes the available information comparing indoor (mostly in homes) and outdoor ambient carbon tetrachloride concentrations. Based on a steady state mass balance model, the indoor concentration is expected to equal or exceed the outdoor concentration if indoor sources are present. Some of the monitoring results support this conclusion; however, other results did not. The ARB staff reviewed each of the studies in an attempt to determine which of the results are the most reliable. After the review, the ARB staff could not establish with certainty if the indoor and outdoor carbon tetrachloride concentrations were significantly different due to uncertainties within each of the studies. However, the ARB staff believes that in California the monitored indoor and outdoor concentrations should be equal or similar.

Expected Concentrations

Carbon tetrachloride can enter the indoor environment in two ways. It can be released by indoor sources or it can infiltrate into the indoors as a contaminant of outdoor air. Similarly, it can be removed when contaminated indoor air is exchanged by exfiltration or ventilated to the outdoors. Carbon tetrachloride could also be removed from the indoor air by removal processes unique to the indoor environment if such processes were present.

The steady-state mass balance model of time averaged indoor concentration for a non-reactive gas is:

$$Ci = Co + (S - R)/Va$$

where:

Ci = indoor concentration (mass/volume)

Co = outdoor concentration (mass/volume)

S = indoor source strength (mass/time)

R = indoor removal rate (mass/time)

V = building volume (volume)

a = effective fractional air exchange rate (/time)

For carbon tetrachloride, there are no known indoor removal processes, so the indoor removal rate (R) is assumed to be zero. Also, because of a Consumer Products Safety Commission (CPSC) ban, consumer products containing carbon tetrachloride are not in widespread use, so the indoor source strength or S is also zero in many cases. Therefore, the indoor concentration will often equal the outdoor concentration (Ci = Co). In cases where there are elevated indoor concentrations, indoor sources can cause or influence these concentrations. Some indoor sources of carbon tetrachloride include drinking water, consumer products, and commercial products that contain carbon tetrachloride. At this time, there is not sufficient information to determine the contribution of these sources to the elevated indoor concentrations.

The above model assumes steady state equilibrium between sources and removal processes of carbon tetrachloride. Therefore, monitored indoor concentrations can only be expected to follow the steady state model where the outdoor concentration, indoor source strength, indoor removal rates, and air exchange rate are constant. The results for samples with averaging times greater than a few hours should also follow this model,

since typical air exchange rates are 0.2 to 2.5 air changes per hour due to infiltration alone.

For carbon tetrachloride, there are no known physical reasons to explain average indoor concentrations lower than outdoor concentrations. In a few instances, lower averaged indoor concentrations were reported in some of the studies. For short sample averaging times, such an anomaly could be explained if the homes were near emission sources since outdoor concentrations could be influenced by meteorological factors such as inversions and changes in wind direction. These effects would be felt more slowly in the indoor environment and thus, indoor concentrations could be either higher or lower. With sampling times longer than a few hours, or in areas remote from sources, indoor concentrations lower than outdoor concentrations would be explained only by removal processes unique to the indoor environment or by experimental error.

Available Monitoring Data

Carbon tetrachloride and other compounds have only been recently measured in the indoor (mostly homes) and outdoor environments. The ARB staff reviewed the available studies in an attempt to determine the relationship between indoor and outdoor carbon tetrachloride concentrations. Due to uncertainties and differences in each of the studies, the ARB staff could not establish with any degree of certainty, the relationship between indoor and outdoor carbon tetrachloride concentrations. Some of the uncertainties and differences include: 1) limited number of samples taken in some studies; 2) large percentage of the samples below the limit of quantitation (LOQ); 3) no quality assurance

results reported in some studies; 4) for studies that did report quality assurance results, uncertainties were sometimes large relative to differences between reported indoor and outdoor concentrations; and 5) there were major differences in the purpose and design of the studies.

Generally, compounds in the ambient concentration range of carbon tetrachloride (in the low ppb range) are difficult to measure. Accurate determination of a small difference between two concentrations requires precise measurements. While high precision of measurements is necessary, biases of measurement in the same direction, whether high or low, is less critical in assessing the differences in measurements. Therefore, interlaboratory differences in accuracy, for instance due to different calibration standards, are not as important provided the precision of measurements is acceptable. An accurate comparison of monitored results also requires that measurements be made under the same conditions. This would include similar indoor and outdoor sampling methods and analytical procedures which is not always the case in the studies. Therefore, differences between the monitored results are expected.

An analysis of the monitoring studies reviewed by the ARB staff is presented below and the monitoring results are summarized in Table D-1.

U.S. EPA, 1985a - Northrop Services, Inc.

Near Research Triangle Park in North Carolina, a study of indoor and outdoor concentrations of various compounds was conducted for the Environmental Protection Agency (EPA) by Northrop Services, Inc. (U.S. EPA, 1985a). It was reported that the mean indoor and outdoor carbon tetrachloride concentrations for homes in the study were similar. The ARB

Table D-1
Summary of Indoor/Outdoor Monitoring Studies

Site Media	Source	Percent of Samples Measurable	Percent RSD of Duplicate Samples[a,b] Median	Percent RSD of Duplicate Samples[a,b] Maximum	Number of Samples	Concentration[b] (ppb) Minimum	Median	Mean	Maximum	Ninetieth Percentile
North Carolina	EPA									
summer indoor	Final	100.	2[d]	5[d]	15	.09		0.14	0.23	
winter indoor	Report	100.	2	5	16	.11		0.14	0.16	
outdoor	1985	100.	2	5	12	.13		0.15	0.16	
New Jersey (TEAM)	EPA									
overnight personal	Interim	31.	24[e]	97[e]	346					0.9
overnight outdoor	Report	53.	15[e]	50[e]	81					0.3
	1984									
LA. Feb. 1984 (TEAM)	EPA Updated									
overnight personnel	Draft	95.	15	63	117		0.10	0.12		0.17
overnight outdoor	Report	97.	28	71	24		0.10	0.11		0.19
LA. May, 1984 (TEAM)										
overnight personal	"	99.	9	42	52		0.10	0.10		0.14
overnight outdoor		100	17	51	23		0.10	0.10		0.15
Contra Costa June 1984 (TEAM)										
overnight personal	"	94	12	54	71		0.11	0.16		0.59
overnight outdoor		95	43	43	10		0.05	0.08		0.07
Greensboro, NC (TEAM)	"									
overnight personal		6	--	--	24					
overnight outdoor		NR[f]	--	--	6					
Devils Lake, ND (TEAM)	"									
overnight personal		14	19	27	20					
overnight outdoor		NR[f]	7	13	5					
Greensboro, NC	Hartwell									
overnight personal	Conference	55			20		0.03		2	
overnight outdoor	Paper	45			20				.3	
	1984									
Baton Rouge, LA										
overnight personal	*	48			27				3	
overnight outdoor		52			27		0.02		4	
Houston, TX										
overnight personal	*	100			10		0.2		0.6	
overnight outdoor		100			10		0.3		0.5	
No. Italy, Nonurban	DeBartoli									
indoor	Final	94			16	.16	0.9	1.0	1.9	2
outdoor	Report	88			16	.16	0.8	1.1	4.5	3
	1985									

a Percent Relative Standard Deviation of duplicate sample pairs = $\frac{\text{Standard deviation}}{\text{Mean}} \times 100\%$

b Blank entries were generally not reported by authors. In some cases median and mean values are omitted where percent measurable was low. Maximum values are reported where upper percentiles were not available, but should be used with caution.

c Concentration greater than 90 percent of measured concentrations (or estimated population exposures in case of TEAM study).

d Analytical precision for repeat runs on the same sample based on references 9 and 10.

e From draft report.

f Not reported by author due to small sample size.

staff believes that these mean concentrations could also be similar to the global background concentrations of 0.11 to 0.15 ppb (0.69 to 0.94 ug/m^3) which have been estimated by other researchers.

In this study, short duration samples (less than 2 minutes) were collected inside and outside the homes, using evacuated Summa polished stainless steel canisters. Whole air samples were analyzed using cryogenic preconcentration and subsequent capillary chromatography with simultaneous flame ionization and electron capture detection. The authors have previously demonstrated high precision (2 percent relative standard deviation) with these methods for carbon tetrachloride (Pliel, et al., 1985). The ARB staff believes that this may be one of the more precise studies reviewed.

Twenty-six homes were sampled, with five homes overlapping the summer and winter seasons. The results of the study are as follows:

Table D-2

Summary of Northrop Services Inc. Study

Season	# of Samples Taken	Mean Carbon Tetrachloride Concentration (ppb)	Mean Carbon Tetrachloride Concentration (ug/m^3)	Range of Concentrations (ppb)	Range of Concentrations (ug/m^3)
Summer-indoor	15	0.14	0.90	0.09-0.23	0.58-1.5
Winter-indoor	16	0.14	0.90	0.11-0.16	0.70-1.0
Outdoor-combined seasons	12	0.15	0.96	0.13-0.16	0.83-1.0

Both the summer indoor maximum concentration of 0.23 ppb (1.5 ug/m^3) and indoor minimum concentration of 0.09 ppb (0.58 ug/m^3) are outside the range of outdoor measurements. It is not known whether outdoor samples

were collected at the same time and location as these indoor samples. The higher maximum indoor concentration does show the possibility of elevated indoor concentrations, but sampling times were very short; therefore, comparison of the results must be made with caution.

TEAM Studies - Research Triangle Institute

Under contract with EPA, Research Triangle Institute conducted a series of Total Exposure Assessment Methodology (TEAM) studies. The studies were conducted to estimate the frequency distributions of 20 organic compound concentrations (including carbon tetrachloride) in personal and outdoor air in different cities around the United States. Earlier results were compiled during pilot studies and methods development work in Beaumont, Texas and Chapel Hill, North Carolina. More detailed monitoring studies were later conducted in New Jersey and California. The results have been compiled in a final interim report for the first season of monitoring in New Jersey (U.S. EPA, 1984a). The monitoring data from a later New Jersey study and a comparison study in Greensboro, North Carolina and Devils Lake, North Dakota, and the California study are contained in two final draft reports (U.S. EPAa, Undated; U.S. EPAb, Undated). Additional information were also obtained from conference papers and a journal preprint (Pellizzari, et al., 1984; Hartwell, et al., 1984a; Hartwell, et al., 1984b; Wallace, 1986).

Since the TEAM study measured personal exposure rather than indoor concentrations, a description of the study design and sampling procedures may be helpful. Participants were probabilistically selected to represent

the target population. In order to better define the upper percentiles of personal exposure, individuals with suspected high occupational exposure were over-selected for monitoring. Results were then statistically weighted to adjust for that over-selection.

Each study participant wore a personal sampler for twenty-four hours. Two twelve hour samples were collected daily on tenax tubes from approximately 7 p.m. to 7 a.m. and 7 a.m. to 7 p.m. When sleeping, the participant placed the sampler on top of a night stand or dresser in the bedroom. Although instructed to continue normal activities, some participants may have postponed certain activities outside the home until after the monitoring study due to the physical constraints of the personal samplers.

The 12 hour overnight personal exposure monitoring results provide a surrogate for indoor monitoring since participants are more likely to be home during this period. Simultaneous outdoor (backyard) samples were also collected using the same method for some of the participants. The fraction of participants with simultaneous outdoor sampling was about 0.25, 0.2, 0.5 and 0.14 in New Jersey, Los Angeles first and second seasons, and Contra Costa respectively. Therefore, the overnight personal samples and the outdoor samples provided the basis for comparison of indoor and outdoor concentrations.

1. New Jersey TEAM Study

The New Jersey TEAM study was a large study in which many indoor and

outdoor samples were taken (U.S. EPA, 1984a). A summary of the New Jersey TEAM study is presented below:

Table D-3

Summary of the New Jersey TEAM Study

Environment	# of Samples Taken	Ninetieth Percentile Concentration (ppb)	Ninetieth Percentile Concentration (ug/m^3)	% of Samples Below LOQ
Indoor	346	0.90	5.75	69
Outdoor	81	0.32	2.06	47

A large percentage of the indoor and outdoor samples were below the limit of quantitation (LOQ). Because of this, an analysis estimated median of indoor and outdoor concentrations would not give a useful or reliable comparison. The ARB staff believes that a more useful comparison can be made by reviewing estimated concentrations at the ninetieth and ninety-fifth percentiles.

For the ninetieth and ninety-fifth percentiles, overnight personal air concentration exceeded overnight outdoor concentration by 0.58 ppb and 1.27 ppb (3.7 and 8.1 ug/m^3) respectively. This may be attributable to the presence of unspecified indoor sources of carbon tetrachloride, the result of sampling and analytical uncertainties, the result of the limited number of outdoor samples taken compared to the larger number of personal (indoor) samples collected. The ARB staff feels that indoor sources of carbon tetrachloride are unlikely because of the CPSC ban on consumer products containing carbon tetrachloride, but possible presence of such sources could not be ruled out. The other two factors could also have caused discrepencies in the monitoring data, but the ARB staff could not estimate to what extent. Thus, the ARB staff

was not able to compare with any degree of certainty of indoor and outdoor measurements from this TEAM study.

2. Los Angeles TEAM Study

Compared to the New Jersey TEAM study, the Los Angeles TEAM study had a much lower LOQ which resulted in over 95% of samples above the LOQ (U.S. EPAa, Undated). Elevated median overnight indoor (personal air) carbon tetrachloride concentrations similar to the New Jersey study were not measured in the Los Angeles TEAM study. At the ninetieth and ninety-fifth percentiles, the Los Angeles indoor and outdoor concentrations were similar.

The results of the Los Angeles TEAM study are summarized as follows:

Table D-4

Summary of the Los Angeles TEAM Study

Study Period	# of Samples	Median Concentration (ppb)	Median Concentration (ug/m^3)	% of Samples Above LOQ	Median Duplicate % RSD
Feb. 1984					
Indoor	117	0.11	0.65	95	15
Outdoor	24	0.11	0.65	97	28
May 1984					
Indoor	52	0.10	0.65	99	42
Outdoor	23	0.11	0.64	100	51

The Los Angeles TEAM data appeared to indicate that homes in the study had a median indoor carbon tetrachloride concentration similar to the median outdoor concentration. However, the maximum relative standard deviation (RSD) of duplicate field samples was high. The maximum RSD was 63 and 71% in the February study and 42 and 51% in the May study for indoor and

outdoor field samples respectively. This causes some doubt as to the precision and accuracy of the reported monitoring results. The ARB staff feels that even though these results show similar indoor and outdoor median concentrations for this area, this conclusion could not be supported on the basis of this study alone.

3. Contra Costa TEAM Study

In the Antioch-Pittsburg area, a TEAM study was conducted during June 1984 (U.S. EPAa, Undated). As with the Los Angeles TEAM study, the low LOQ resulted in a majority of the measured samples being above the LOQ. The results of this TEAM study are presented below:

Table D-5

Summary of Contra Costa TEAM Study

Environment	# of Samples Taken	Median Concentration (ppb)	Median Concentration (ug/m^3)	% of Samples Above LOQ	Median Duplicate % RSD
Indoor	71	0.14	0.11	94	12
Outdoor	10	0.05	0.33	95	43

The median overnight personal air concentration was similar to that found in the Los Angeles TEAM study. The median outdoor concentration, estimated from 10 samples, was much lower than the median outdoor concentration measured in the Los Angeles TEAM study (0.05 ppb versus 0.11 ppb). The percent relative standard deviation (RSD) for the one pair of duplicate outdoor field samples taken for this study was 43 percent. It is difficult to assess the precision of the monitored results since the absolute standard deviation is unknown; however, outdoor median concentration lower than the estimated global background level makes the

results suspect. For these reasons, comparisons between the outdoor and personal air concentrations in Antioch-Pittsburg area are not conclusive.

4. Other TEAM Studies

As stated earlier, some monitoring data were also collected in TEAM studies in Devils Lake, North Dakota and Greensboro, North Carolina (U.S. EPAb, Undated). The ARB staff believes that the small number of outdoor samples and the low percentage of indoor and outdoor samples that were measurable make comparison of indoor and outdoor measurements unreliable.

Hartwell used the TEAM study methodology to survey halogenated hydrocarbon exposures in the cities of Greensboro, North Carolina, Baton Rouge, Louisiana, and Houston, Texas. The results were presented in a brief conference paper which included median and maximum values and the percent of samples measurable for both indoor and outdoor sites (Hartwell, et al., 1984a). As with some of the earlier TEAM studies for carbon tetrachloride, low percentage of measurable samples resulted due to the high LOQ (except in Houston) and maximum values higher than later TEAM studies were reported. The ARB staff believes that the Los Angeles-Contra Costa TEAM study monitoring results may be the most reliable because of the improvements made since the earlier TEAM studies. Therefore, the Hartwell study results are not sufficient for determining the relationship between indoor and outdoor concentrations.

5. De Bartoli, 1985

In Northern Italy, De Bartoli conducted a study in which paired

samples were collected inside and outside of 14 residences and 1 office, in 9 towns, villages, and rural areas. The table below summarizes this study:

Table D-6

Summary of the De Bartoli Study

Environ-ment	# of Samples	Median Concentration (ppb)	Median Concentration (ug/m^3)	Range of Conc. (ppb)	Range of Conc. (ug/m^3)	% of Samples Above LOQ
Indoor	16	0.9	6	<0.16-1.9	<1-12	94
Outdoor	16	0.8	5	<0.16-4.5	<1-29	88

The reported median indoor and outdoor concentrations appear to be similar (0.9 ppb versus 0.8 ppb). However, these median concentrations and the concentrations of other compounds reported in the study are generally an order of magnitude higher than those which have been reported elsewhere. This would suggest that indoor and outdoor emission sources are contributing to the reported median concentrations or that the experimental uncertainties are biasing the results to the high side. As stated earlier, the precision of measurements is more critical in assessing the differences between indoor and outdoor concentrations than the accuracy of the measurements. If the median concentrations and the measurements have the acceptable precision, then the median indoor and outdoor concentrations could be assumed to be similar.

The De Bartoli monitoring data was further reviewed by the ARB staff. Individual pairs of indoor and outdoor measurements for an area in many cases were not similar and for some pairs, higher outdoor concentrations than indoor concentrations were noted by the ARB staff. However, when the results were averaged, the mean concentrations were coincidentally

similar. This type of analysis was not possible for the other studies because the only information that was available for comparison was summary results such as mean values, median values, and like percentiles. The ARB staff concluded that from the review of this study, it cannot be determined if there are actual similarities between indoor and outdoor concentrations.

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TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CARBON TETRACHLORIDE

PART B:

HEALTH EFFECTS OF CARBON TETRACHLORIDE

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1.0 EXECUTIVE SUMMARY

DHS estimates that approximately 50% of inhaled carbon tetrachloride (CTC) is absorbed by the body. Numerous studies have suggested that CTC is metabolized to a highly reactive trichloromethyl radical which can then react with cellular components to produce acute and chronic toxicity.

Accidental acute human exposures, at concentrations at least five orders of magnitude greater than expected ambient levels, and animal experiments have shown that CTC can produce liver and kidney damage and numerous effects on the nervous system. Chronic exposure to CTC, in occupational settings where CTC concentrations are three to four orders of magnitude higher than current ambient levels, has produced neurological effects and elevation of serum liver enzymes indicating liver damage. Long-term animal exposure to similarly high levels of CTC has produced liver and kidney damage. At current ambient CTC levels, however, no acute or noncarcinogenic chronic effects are expected to occur.

Reproductive effects developed in male animals in response to very high concentrations of CTC. Dosing of pregnant rats with high concentrations of CTC resulted in embryo- and fetotoxicity. Experimental data are inadequate to assess potential human reproductive risk from ambient CTC exposures.

Radiolabeled CTC given to laboratory animals binds to DNA as well as other cellular components. Thus, CTC is potentially genotoxic. However, tests for mutagenicity using standard bacterial and yeast assays and other methods for detecting chromosomal damage have been predominantly negative. This

apparent lack of effect may reflect the inability of those assays to test adequately halogenated hydrocarbons such as CTC or may indicate that CTC is not strongly mutagenic.

Examination of human case reports and epidemiological studies has not shown that CTC causes cancer in humans. However, the carcinogenicity of CTC has been clearly demonstrated in three animal species, which has led the International Agency for Research on Cancer (IARC) to conclude that there is sufficient evidence of carcinogenicity in animals and that, in the absence of adequate data in humans, it is reasonable for practical purposes to regard CTC as if it presents a carcinogenic risk to humans. In the major animal cancer studies CTC was administered orally in a solution with olive or corn oil. None of the studies was conducted by inhalation. In these studies CTC produced malignant tumors in the liver in up to 100% of the animals, and the tumors began to appear 16 weeks after the beginning of the study. On the basis of this experimental work, DHS staff concurs with the findings of IARC. In addition, DHS staff has not found compelling evidence demonstrating the existence of a carcinogenic threshold for CTC.

The DHS recommends adopting portions of the risk assessment performed by the Environmental Protection Agency (EPA), which applied a multistage model to the results of several of the animal studies. For one of the studies time-to-tumor information was incorporated into the multistage model. DHS staff suggests the use of increased lifetime carcinogenic risk values from exposure to carbon tetrachloride ranging from 10 to 42 cancer cases per million people continuously exposed over their lifetimes to 1 microgram CTC

per cubic meter of air (1 $\mu g/m^3$). This range is based on the carcinogenic potencies estimated from two animal studies.

The range of risk values represents several sources of uncertainty, including statistical uncertainty due to the small numbers of animals used in the bioassays and the variability in the animals' response in experiments using different species and protocols. Other general sources of uncertainty, which did not directly affect the magnitude of the above range of risks, include the choice of the animal-to-human scaling factor, the choice of the extrapolation models, and the large range of extrapolation (three to five orders of magnitude) from the orally administered CTC concentrations used in the animal experiments to current ambient levels.

The lifetime risk values given above represent a range of conservative estimates and are unlikely to be exceeded by the actual risk. A lifetime excess risk of 10-42 per million population must be viewed in the context of the overall probability of developing cancer, which is on the order of 250,000 cases per million population (25%) over a lifetime.

Based on the findings of carcinogenicity and the results of the risk assessment, DHS staff finds that ambient CTC is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

2.0 PHARMACOKINETICS

2.1 Routes of exposure

Carbon tetrachloride (CTC) is lipophilic and is readily absorbed orally and via inhalation. There is some dermal absorption. Acute oral exposure in humans is primarily restricted to accidental ingestion or suicide attempts. However, it was formerly used as an anthelmintic,[1] and medicinal doses occasionally resulted in toxicity (Von Oettingen 1964). Information regarding oral administration is provided below for comparative purposes and to supplement inhalation data. Chronic oral exposure occurs from consumption of contaminated food and water. The major routes of occupational exposure are inhalation and dermal. The toxicokinetics have been reviewed previously by Von Oettingen (1964), Browning (1965), Swinyard (1975), Bergman (1979), Torkelson and Rowe (1981) and others.

2.2 Absorption

2.2.1 Inhalation

Inhalation absorption was first studied by Lehmann and Hasegawa (1910) using rabbits. They reported that the absorption rate decreased from 34.7 to 4.7%, during a 3-hour exposure to 50 mg/L (≈8000ppm). Following exposure of dogs to 15,000 and 20,000 ppm CTC, Von Oettingen et al. (1949, 1950) found

[1] An agent destructive to worms. Recommended oral doses were 2-3 ml for adults, and 0.13 ml per year of age for infants and children up to 15 years old.

that blood CTC levels reached equilibrium in approximately 5 hours. However, exposure to such high concentrations would induce severe toxicity that could result in decreased absorption.

McCollister et al. (1950, 1951) exposed three monkeys via inhalation to an average of 46 ppm of ^{14}C-labelled CTC for 2 to 6 hours. The absorption reportedly occurred at an average rate of 1.34 mg/kg/hour, or 30% of the total weight of CTC inhaled. They observed that absorption of the material ranged from 26 to 37%. The highest absorption rate was obtained during the longest exposure. Equilibrium of CTC between the air and blood was not reached during the course of the experiment. Consequently, absorption following a longer exposure until equilibrium was reached would be expected to be above 37%.

In a human inhalation study by Lehmann and Schmidt-Kehl (1936), individuals were exposed to CTC vapors for up to 30 minutes. The amount of CTC absorbed was calculated from the difference of the amount available and the amount exhaled. Thus the amount of CTC absorbed was estimated indirectly. They reported a range of absorption of 57 to 64%. This study used from 2 to 14 subjects, although the actual number was unspecified. Extrapolating from the primate studies of McCollister et al. (1950, 1951), it is unlikely that equilibrium was attained using such short exposure periods in the human studies.

The above noted primate and human studies, even with their limitations, represent the two best estimates for absorption reported in the literature. The staff at DHS believe that these two studies, with their shortcomings,

should be given equal weight in estimating an absorption value for humans. The human study is lacking due to incomplete documentation of exposure of the subjects and the indirect absorption method used. The primate study directly measured absorption; however, it is not clear how similar human exposure would be. Consequently, the reported absorption coefficient values were given equal weight in estimating a 50% absorption coefficient that will be utilized in the quantitative risk assessment in Section 9.0. Although the studies on which this value is based are not ideal, the staff at DHS believes that 50% is the best estimate and that a more precise absorption calculation would change the unit risk estimates by less than a factor of two.

2.2.2 Dermal

Two monkeys were exposed dermally to vapor concentrations of 485 and 1150 ppm for approximately four hours (Beamer et al. 1950, McCollister et al. 1951). CTC blood levels indicated that absorption by this route was relatively low and was not of practical significance. Stewart and Dodd (1964) studied the dermal absorption of CTC in human subjects. Three subjects immersed their thumbs for 30 minutes in a beaker of CTC, and expired air samples were analyzed. CTC was detected in the alveolar air samples within ten minutes and it continued to rise for up to 30 minutes post-exposure. Although absorption of vapor by the dermal route is insignificant, dermal absorption of liquid CTC could result in toxicity.

2.2.3 Oral

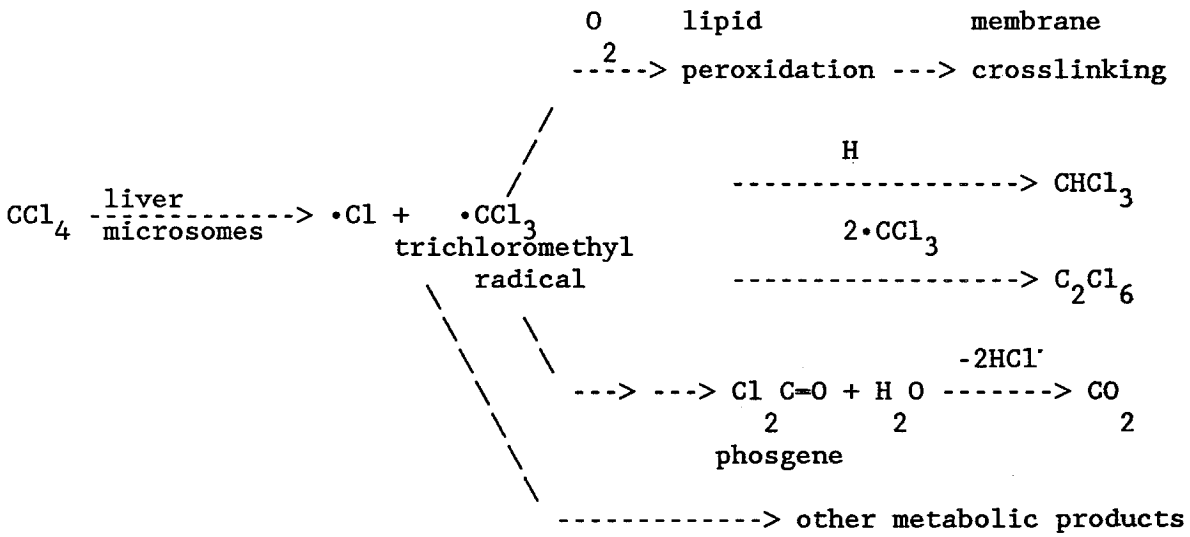
Essentially 100% of an oral dose is absorbed. Gastrointestinal absorption of CTC (3 ml) was studied by Robbins (1929), who demonstrated that it was readily absorbed from the small intestine and that the rate was enhanced by alcohol and fats. The oral absorption in rats was subsequently studied by Recknagel and Litteria (1960), who determined that peak blood concentration occurred 1.5 hours following administration.

2.3 Distribution

The distribution of carbon tetrachloride in animals varies with the route of administration, concentration, and the duration of exposure (Von Oettingen 1964); however, as would be predicted from CTC's solubility properties, most of the compound accumulates in tissues with high fat content, such as adipose tissue, liver and bone marrow (Robbins 1929, McCollister et al. 1950, 1951). Fowler (1969) examined the distribution and metabolism of CTC following oral administration to rabbits of 1 ml/kg. The highest concentrations of CTC were found in the fat, followed by the liver, kidney and muscle. CTC metabolites (i.e. chloroform and hexachloroethane) were also detected in fat, liver, kidney and muscle. In a study on CTC accumulation, adipose tissue concentrations appeared to reach a steady state CTC concentration after one week of repeated 3-hour exposures of rats to 10, 50, or 100 ppm CTC (Shimizu et al. 1973). Following a two-week exposure of rats to 100 ppm $^{14}CCl_4$, Paustenbach et al. (1986a) found that the fat, liver, adrenals and lung contained the highest concentrations of $^{14}CCl_4$.

2.4 Metabolism

The metabolism of CTC has been investigated in the rat, rabbit, dog and human. Close to half of the absorbed CTC is excreted unchanged, but the remainder is metabolized to carbon dioxide, chloroform, hexachloroethane, urea, carbonate and a number of unidentified substances present in tissues, in feces or in urine. Carbonyl chloride (phosgene) is also a postulated metabolite. The metabolic products are thought to be produced via the formation of a trichloromethyl radical. A basic metabolic scheme has been postulated as follows:



Paustenbach et al. (1986b) exposed rats to 100 ppm $^{14}CCl_4$ for 1 to 2 weeks. They found that 1 to 2 % of the CCl_4 was present as CO_2 in the expired air. The rate of elimination of $^{14}CO_2$ was slower than that of $^{14}CCl_4$ in the expired air. The investigators concluded that the late appearance of $^{14}CO_2$ was probably due to stored $^{14}CCl_4$, which was slowly released from the fat

and then metabolized. Radiolabeled compound in the feces was not identified, but is presumed to be a metabolite.

McCollister et al. (1950, 1951) exposed monkeys to radiolabeled CTC vapor by inhalation. An estimated 40% of the absorbed material was exhaled unchanged, while 11% was exhaled as carbon dioxide. In the blood, a number of unidentified radiolabeled materials were isolated and classified as "alkaline volatiles," "acid volatiles," or as "non-volatiles." In the urine, some of the labeled carbon was in the form of urea and carbonate, but 95% was a nonvolatile, unidentified compound.

The production of chloroform following administration of CTC was demonstrated in the rat (Ahr et al. 1980), in the rabbit (Fowler 1969) and in the dog (Butler 1961). Chloroform production from CTC was also demonstrated <u>in vitro</u>, using mouse tissue homogenates (Butler 1961). Fowler (1969) identified hexachloroethane, which was assumed to have formed from the dimerization of the trichloromethyl radical. Reynolds et al. (1984) measured CTC, chloroform and CO_2 exhalation following oral $^{14}CCl_4$ administration (0.1 to 26 mmoles/kg). They reported that as the dose was increased, the proportions of CO_2, chloroform and CTC changed: $^{14}CO_2$ declined from 28 to 0.7 %, chloroform levels remained under 1 %, and expired $^{14}CCl_4$ levels increased from 19 to 89%. This suggests that saturation of CTC metabolism had occurred. The authors suggested that the decrease in CO_2 production, along with an increase in hepatotoxicity, is

consistent with the presumption that the trichloromethyl radical reacts with other biomolecules when the CO_2 pathway is saturated.

Durk and Frank (1984) showed that CTC metabolism increased when the oxygen partial pressure was lowered. This resulted in an increase in the amount of lipid peroxidation as measured by the exhalation of ethane and pentane. However, the total time course of CTC metabolism was limited due to the concomitant destruction of cytochrome P-450. It has also been demonstrated that hyperbaric O_2 treatment alters CTC metabolism as measured by a decrease in the conversion of CCl_4 to CO_2 and $CHCl_3$ (Burk et al. 1986). Thus, the metabolism of CTC and the production of various metabolites appear to be highly dependent on the experimental conditions.

The mechanism of carbon tetrachloride hepatotoxicity has been extensively studied and reviewed (Ahr et al. 1980, Castro and Diaz Gomez 1972, Comporti 1985, Farber 1985, Ray and Moore 1986, Recknagel and Glende 1973, Recknagel 1983, Shah et al. 1979, Slater 1966, Slater et al. 1985, Smith and Sandy 1985, Smuckler and James 1984, Yalcin et al. 1986). The general view is that CTC may act via the formation of a trichloromethyl radical intermediate ($\bullet CCl_3$) following loss of a chlorine atom (Butler 1961, Kubic and Anders 1981, Sagai and Tappel 1982, Gee et al. 1981, Link et al. 1984). The irreversible incorporation of CTC into total lipids and phospholipids was shown in liver, kidney, lung, brain and other tissues (Ciccoli et al. 1978). The binding of CTC to lipid and protein has been shown to occur <u>in vivo</u> (Castro and Diaz Gomez 1972, Ciccoli et al. 1978).

Several studies have suggested the stimulation of lipid peroxidation as a possible mechanism of toxicity of CTC (see Slater et al. 1985). Link et al. (1984) isolated and identified a group of monomeric trichloromethyl fatty acid residues. They suggested that the binding of trichloromethyl radicals to lipids may result in membrane lipid cross-linking, which could ultimately disrupt cellular function. Yalcin et al. (1986) reported that CTC injections caused significant increases in hepatic lipid peroxide levels and significant decreases in glutathione peroxidase activity, glutathione transferase activity and hepatic glutathione levels. The reports of lipid peroxidation do not preclude the trichloromethyl radical from also binding with other biological molecules, such as proteins, to initiate biochemical toxicity.

Other studies have investigated the disturbance of Ca^{++} homeostasis as a possible mechanism for CTC hepatotoxicity (Moore and Ray 1983, Ray and Moore 1986, Recknagel 1983, Smith and Sandy 1985). Intracellular calcium releases may initiate hepatotoxic changes (Ray and Moore 1986). In addition to the above evidence for binding of carbon tetrachloride metabolites to proteins and lipids, there is also evidence of binding to DNA; this is discussed in the section on genotoxicity.

2.5 Elimination

Following inhalation, ingestion, or injection, unmetabolized CTC is predominantly excreted via the lungs (McCollister et al. 1951, Reynolds et al. 1984, Robbins 1929). Excretion of CTC appears to be biphasic and the second phase is relatively slow; thus, accumulation of CTC with repeated

exposure can result in chronic intoxication. Monkeys exhaled CTC for 29 days after exposure (McCollister et al. 1950, 1951). Studies based on rats would tend to underestimate the tendency of CCl_4 to accumulate in humans since rats eliminate CCl_4 faster (Paustenbach et al. 1986a, Stewart et al. 1961).

The predominant route for elimination of CTC metabolites appears to be the feces. In rats this represented 32 to 62% of the total CTC dose (Paustenbach et al. 1986b). However, the substances containing the radioactivity detected in the feces have not been identified and are only presumed to represent metabolic end products. In contrast, elimination in the urine represented 4 to 8% of the excreted dose, while elimination as CO_2 in the exhaled air was approximately 2% of the total dose. The remainder of the dose (32 to 59%) was exhaled as unchanged CTC. In an earlier study, when CTC was administered by injection to rats, 85% of CTC was exhaled unchanged in 18 hours (Paul and Rubenstein 1963).

The percent of excretion by exhalation has not been quantified in human studies (Stewart and Dodd 1964, Stewart et al. 1961, Lehmann and Schmidt-Kehl 1936). In the Stewart et al. (1961) experiments, individuals inhaled CTC (11 or 49 ppm) for up to 180 minutes. CTC was detected (0.3 ppm) in the expired air up to 5.5 hours post-exposure. However, the limit of detection was only 0.1 ppm and it was not stated whether samples were taken after 5.5 hours.

3.0 ACUTE TOXICITY

The narcotic effects of CTC were first reported in 1867 (Sansom) and descriptions of its toxicity appeared in the early 1900's (Lehmann 1911). Over 611 cases of acute CTC poisoning, many of which were fatal, have been reported in the literature (Beattie et al. 1944, Bjarnason et al. 1968, Dupont et al. 1975, Ruprah et al. 1985, Von Oettingen 1964). The NOAEL (no observed adverse effect level) for a 3-hour acute exposure of humans is 10 ppm (Stewart et al. 1961). This concentration is at least 4 orders of magnitude greater than expected ambient levels, providing enough of a margin of safety so that the acute toxic effects would not be expected to occur in the general population.

3.1 Local effects

Applied to the skin, CTC causes reddening, blistering, inflammation and pain. Ingested orally it can irritate mucous membranes, produce a burning sensation and stimulate peristalsis. Exposure to the vapor can produce irritation of the eyes, nose and throat. The NOAEL for irritation of mucous membranes for humans is 49 ppm for a 70-minute exposure (Stewart et al. 1961).

3.2 Systemic effects

CTC produces acute systemic toxicity following ingestion or inhalation, including inhalation of vapors in a poorly ventilated area. The major effects are nervous system depression, hepatic damage, and renal tubular

destruction. Symptoms of toxicity may appear after a delay of two to three days. Pulmonary toxicity has been reported (Anttinen et al. 1985, Boyd et al. 1980). Hemolysis and other circulatory disturbances have been observed (Schulze and Kappus 1980, Von Oettingen 1964).

The CNS symptoms following exposure to CTC are nausea, vomiting, headache and/or dizziness. In severe cases, CTC may produce vertigo, mental confusion, incoordination, stupor, convulsions, coma or death. Suppression of the medullary centers may result in vasodilation and a fall in blood pressure.

CTC is hepatotoxic in animals (Adams et al. 1952) and in humans (Dupont et al. 1975), and the effects appear rapidly. In humans, alterations in lipid metabolism in the liver may be observed 30 minutes following administration. Histological changes may be observed within one hour. Within 24 hours a characteristic centrilobular necrosis of the liver is present. Early signs of injury may appear as altered enzymatic levels, such as increased serum glutamic oxaloacetic transaminase (SGOT), or enlargement of the liver (Beattie et al. 1944). Relative to lethality, hepatotoxicity is an extremely sensitive endpoint. In acute exposures, hepatotoxicity (median toxic dose) has been reported at concentrations 1/230 to 1/280 of the median lethal dose (Klaasen and Plaa 1966, Lundberg et al. 1986).

The kidney is a major target of CTC toxicity. Necrosis and tubular degeneration have been observed in laboratory animals (Chandler and Chopra 1925). In mild poisoning incidents in man, CTC can produce reversible

oliguria for several days (Dudley 1935 a.b.). In severe cases, there may be complete anuria, hypertension, acidosis and pulmonary edema.

In humans, 317 ppm is an estimated toxic concentration for a 30-minute exposure (NIOSH 1984). A 70-minute exposure of 6 individuals to 49 ppm altered normal metabolism (depressed serum iron and elevated urinary urobilinogen) of three of the subjects (Stewart et al. 1961). In the same study, no effects were observed following an exposure to 10 ppm for 180 minutes. Thus, based on information for humans, a NOAEL for acute exposures up to 3 hours is 10 ppm.

The severity of effects from CTC depends more on the concentration inhaled than on the length of exposure. Using rats, experiments examining the relative effects of concentration versus length of time, investigators found higher concentrations over shorter exposures produced more toxic effects than lower concentrations over a longer period (David et al. 1981, Uemitsu et al. 1985).

4.0 SUBCHRONIC AND CHRONIC TOXICITY

Toxic effects, other than genotoxicity, reproductive effects and carcinogenicity, following both subchronic and chronic exposures to CTC are discussed in this section. Chronic toxicity has been observed following dermal (animal studies), oral (animal studies) and inhalation exposure (animal studies and human cases). The slow excretion rate of CTC results in its accumulation, increasing the potential for toxicity following repeated exposure. Subchronic and chronic exposures affect the same target tissues as acute exposure: the nervous system, the liver and the kidney (Higgins and Stasney 1936, Lehmann and Schmidt-Kehl 1936, Cameron and Karunaratne 1936, Smyth et al. 1936, Edwards 1941, Edwards and Dalton 1942, McCord 1946, Prendergast et al. 1967, Kanics and Rubenstein 1968, Shimizu et al. 1973, Merkur'eva et al. 1979).

Toxic effects have been reported following chronic inhalation exposure to 5 ppm or greater. The longest animal study reported lasted 10 1/2 months. A NOAEL based on histopathologic and gross toxicity for a prolonged exposure of the rat is 1 to 5 ppm (depending on the study, Prendergast et al. 1967, Adams et al. 1952). NOAEL's for other species have not been determined, but are below 1 ppm. There appears to be a reasonable margin of safety to expect that histopathologic or gross toxicity would not occur in the general population since current ambient levels are 4 orders of magnitude below the LOEL (low effect level). However, a recent gavage study examining biochemical markers of hepatotoxicity indicates that CTC has a very shallow dose-response curve, spanning over 2 orders of magnitude. Consequently, although it is unlikely that any biochemical liver changes would occur from

exposure to current ambient levels, animal studies have not been conducted that establish NOAEL for this endpoint.

4.1 Animal Studies

4.1.1 Subchronic

A subchronic inhalation study was conducted on carbon tetrachloride by Prendergast et al. (1967) using the rat, guinea pig, rabbit, dog and monkey (see Table 1). The most susceptible species in terms of mortality was the guinea pig; twenty percent of the animals died during the 515 mg/m^3 exposure (≈ 80 ppm). Weight loss was reported in all species except the rat. Severe liver damage was observed in rats, guinea pigs and monkeys following 24 hour/day exposures to 61 mg/m^3 (≈ 10 ppm) for 90 days. At the 6.1 mg/m^3 (≈1 ppm) exposure, slight growth depression and histopathological changes were observed in all species except the rat. Thus, from this study for subchronic exposures the NOAEL for the rat would be 1 ppm, but the NOAEL for rabbit, dog and monkey would be below 1 ppm. It is important to note that the animals in this study were more sensitive to CTC than those animals in the chronic studies (See below). Consequently, in the present document, the NOAEL for chronic exposure is primarily based on the results of this subchronic study.

Hayes et al. (1986) conducted a 90-day gavage exposure of CD-1 mice (20 animals of each sex per dose group) to 12, 120, 540 or 1200 mg/kg in corn oil. There were no effects on mortality, body weight, hematological endpoints or urinalysis endpoints. There were significant increases in

TABLE 1. SUMMARY OF DESIGN OF SUBCHRONIC AND CHRONIC INHALATION STUDIES

Study	Species	(N)[1]	Concentration (ppm)	Exposure Design	Length	Effects Observed
Smyth et al. 1936	rat	24	50,100,200,400	8h/d, 5d/w	10.5m[2]	Sciatic nerve damage, cirrhosis above 50 ppm
	guinea pig	24	50,100,200,400	"	"	High mortality, nerve damage.
	guinea pig[3]	16	25,50,100,200	"	"	Mortality.
	monkey	4	50,200	"	"	Fatty infiltration, sc nerve damage at 200.
Adams et al. 1952	rat	30[4]	100,200,400	7h/d, 5d/w	37w	Mortality, liver and kidney (> 100) patholo
	rat	30[4]	25,50	"	"	Fatty degeneration.
	rat	40[4]	10	7h/d, 5d/w	27w	Fatty degeneration.
	rat	48	5	7h/d, 5d/w	29w	No effects observed.
	guinea pig	10[4]	25	"	26w	Decreased growth, cirr
	rabbit	4[4]	25,50,100	"	36w	Cirrhosis.
	rabbit	4[4]	10	"	"	No effects observed.
	monkey	2	100	"	40w	Fatty degeneration.
	monkey	2	50	"	"	Decreased growth.
	monkey	1	25	"	30w	No effects observed.

TABLE 1. (cont.) SUMMARY OF DESIGN OF SUBCHRONIC AND CHRONIC INHALATION STUDIES

Study	Species	(N)[1]	Concentration (ppm)	Exposure Design	Length	Effects Observed
Prendergast et al. 1963	rat	15	≈80	8h/d, 5d/w	6w	Liver and lung pathology.
	guinea pig	15	≈80	"	"	Mortality, weight loss, liver and lung pathology.
	rabbit	3	≈80	"	"	Weight loss, liver and lung pathology.
	dog	2	≈80	"	"	Weight loss, liver and lung pathology.
	monkey	3	≈80	"	"	Mortality, weight loss, liver and lung pathology.
	rat	15	≈10	continuous	90d	Depressed growth, enlarged liver, fatty infiltration.
	rat	15	≈1	continuous	90d	Lung inflammatory changes.
	guinea pig	15	≈10	"	"	Mortality, depressed growth, enlarged liver, fatty infiltration.
	guinea pig	15	≈1	"	"	Decreased weight gain, lung inflammatory changes.
	rabbit	2	≈10	"	"	Depressed growth, enlarged liver.
	rabbit	3	≈1	"	"	Lung inflammatory changes, decreased weight gain.
	dog	2	≈10	"	"	Depressed growth, histological liver changes.
	dog	2	≈1	"	"	Lung inflammatory changes, decreased weight gain.
	monkey	3	≈10	"	"	Emaciated appearance, loss of hair.
	monkey	3	≈1	"	"	Decreased weight gain.

[1] N refers to the number of animals per dose group.
[2] h refers to hours, d to days, w to weeks, m to months
[3] This group of guinea pigs had 1.2g of calcium lactate added to daily diet.
[4] Half of the animals were male.

serum lactate dehydrogenase (LDH), serum glutamic-pyruvic transaminase (SGPT), and serum glutamic-oxaloacetic transaminase (SGOT) at all dose levels relative to controls. The serum glucose was decreased at all dose levels relative to controls. There was a significant increase in liver weight and spleen weight at all dose levels relative to control animals. At levels of 120 mg/kg and above, animals exhibited a significant increase in thymus weight. Hepatotoxicity was evident at all dose levels and was reported to be dose-dependent. Although the study used a 100-fold dose range with no observed mortality, a NOAEL was not obtained.

A 90-day subchronic oral toxicity study of CTC was conducted by Bruckner et al. (1986). Rats (15 to 16 per group) were gavaged daily with 0, 1, 10, or 30 mg/kg CTC in corn oil. Administration of 1 mg/kg did not affect clinical chemistry indices, weight gain, tissue weights or liver morphology. The 10 mg/kg dose level produced mild centrilobular vacuolization, but no evidence of necrosis, fibrosis or other serious degenerative changes. Animals in the 30 mg/kg dose group had increased sorbitol dehydrogenase (SDH), ornithine-carbamyl transferase (OCT) and glutamic-pyruvic transaminase (GPT) levels. They exhibited a decrease in weight gain and an increase in liver weight to body weight ratios. The livers had extensive degenerative lesions, periportal fibrosis, bile duct hyperplasia and some hyperplastic nodules. The authors concluded that 1 mg/kg represented a NOAEL for rats, 10 mg/kg represented a LOAEL, and that, although cirrhosis and hyperplastic nodules are commonly seen in livers of animals with hepatic tumors, the existence of a causal relationship is unclear.

To compare the relative toxicity of the inhalation versus the oral route, the results of the 90-day subchronic studies in rats of Prendergast et al. (1967) and Bruckner et al. (1986) can be compared. In the Prendergast et al. (1967) study a NOAEL was observed at 6.1 mg/m^3 (1 ppm). Assuming that 50% of the inhaled dose is absorbed and that a rat breaths 0.144 m^3 of air per day, the daily dose of CTC is: (0.5) (6.1 mg/m^3) (0.144 m^3/day) ÷ 0.350 kg rat = 1.25 mg/kg per day. This value is comparable to the 1 mg/kg per day NOAEL observed in the Bruckner et al. (1986) study.

4.1.2 Chronic

The first major study on chronic exposure to carbon tetrachloride was conducted by Smyth et al. (1936) as summarized in Table 1. They also examined workers exposed to CTC (discussed below). Extensive mortality occurred in the guinea pigs, such that only the 25 and 50 ppm groups survived an average of 40 or more exposures. Only two rats succumbed from CTC at the 400 ppm exposure. Growth retardation was reported in guinea pigs (25 ppm), in rats (400 ppm) and in monkeys (200 ppm). The rats (100 ppm and above) and guinea pigs (50 ppm and above) exhibited liver cirrhosis while the monkeys showed signs of fatty degeneration. Kidney damage was also reported in the rats and guinea pigs. Many of the guinea pigs and monkeys exposed to 200 and 400 ppm exhibited sciatic nerve damage, while rats exhibited it at all exposure levels.

Adams et al. (1952) studied rats, rabbits, guinea pigs and a few rhesus monkeys (see Table 1). Survival rates at 100 ppm and above were 50% or less for the rats and guinea pigs. Although precise information is not provided, apparently animal mortality was observed at exposure levels above 50 ppm for rats and

guinea pigs. Four or fewer animals were used in the rabbit and monkey dose groups preventing clear evaluation of the responses. They found that chronic exposure of guinea pigs, rats and rabbits (at 100 ppm or greater) produced growth depression, increased liver weights, centrilobular fatty degeneration and cirrhosis of the liver, and degeneration of the tubular epithelium of the kidneys. Rats exhibited hepatic effects above the 5 ppm exposure. The guinea pigs reportedly had a statistically significant increase in liver weight at the 5 ppm level. For the monkeys, growth depression (50 and 100 ppm) and hepatic toxicity (100 ppm) were observed. The NOAEL is reported in rats to be 5 ppm for the 7 hour/day exposure. The NOAEL for the guinea pigs was not attained in this study, but would be below 5 ppm. The NOAELs for rabbits and monkeys cannot be determined in this study due to the few animals tested.

4.2 Human Cases

Signs and symptoms of chronic CTC poisoning include fatigue, headache, anxiety, giddiness, muscular twitching, jaundice, hypoglycemia, lack of appetite, nausea, diarrhea, dull pain in the kidney region, dysuria, proteinuria, blurred vision, and eye irritation. Studies of exposed workers have reported the presence of gastrointestinal/hepatic disturbances, cirrhosis, aplastic anemia, and neurological disturbances (Browning 1965, Kazantzis and Bomford 1960, McDermott and Hardy 1963, Stewart and Witts 1944, Straus 1954).

NIOSH has recommended a time-weighted average (TWA) occupational standard of 2 ppm (10-hour workday, 40-hour workweek with air sample taken over a period not to exceed 1-hour duration) based on reports of liver and eye changes in workers chronically exposed and animal studies (NIOSH 1975, 1984). They stated that

this concentration is expected to be low enough to prevent chronic liver injury in humans. The American Conference of Government Industrial Hygienists (ACGIH) recommended a 5 ppm TWA threshold limit value (TLV) based on exhibition of fatty infiltration in chronically exposed laboratory animals to 10 ppm CTC (ACGIH 1984). The current CAL-OSHA standard for CTC is also 5 ppm.

Based on the highest average ambient concentration reported by ARB, current ambient levels are three orders of magnitude below the current occupational standards.

5.0 GENOTOXICITY

Radiolabeled $^{14}CCl_4$ has been shown to bind covalently to macromolecules, including DNA, *in vitro* and *in vivo*. Most research has shown that it is first metabolized to the trichloromethyl radical, possibly at the nuclear membrane, prior to alkylation. Almost all bacterial mutagenicity tests have been negative. A weak positive response was reported in yeast. Negative responses were reported in an *in vitro* study using a rat liver epithelial cell line. Negative or weak responses were observed in four studies examining unscheduled DNA synthesis. CTC has been shown to be a strong inducer of chromosomal rearrangements. Based on these results, DHS staff have concluded that carbon tetrachloride has genotoxic potential.

5.1 Covalent Binding to DNA

As indicated in Section 2.1, much of the carbon tetrachloride absorbed by any route is exhaled unchanged; however, some is apparently metabolized to form trichloromethyl radical. This highly reactive intermediate has been found to covalently bind with macromolecules. Furthermore, metabolically activated carbon tetrachloride was found to bind with DNA *in vivo* (Diaz Gomez and Castro 1980a, Rocchi et al. 1973) and *in vitro* (Diaz Gomez and Castro 1980a, Direnzo et al. 1982, Levy and Brabec 1984, Rocchi et al. 1973). The *in vivo* test species were Swiss and A/J mouse strains, and Wistar and Sprague-Dawley rats. The *in vitro* systems included rat mitochondrial DNA, mouse liver DNA, and calf thymus DNA. An *in vitro* study (Diaz Gomez and Castro 1981) indicated that the trichloromethyl radical interacted with all four DNA bases, but bound preferentially to guanine and

adenine. Consequently, carbon tetrachloride could produce a genotoxic response following metabolic activation.

5.2 Mutagenicity test systems

The ability of CTC to produce a mutagenic response has been examined using several test systems. The sole positive result was reported in an abstract by Cooper and Witmer (1982), who observed that Salmonella strain TA100 exhibited a weak mutagenic response under low oxygen tension, with rabbit liver S9 as the activation system. Negative reponses were reported with strains TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538, TA1950 using rat liver S9 for metabolic activation (Barber et al. 1981, Braun and Schoneich 1975, De Flora et al. 1984, Simmon et al. 1977, Uehleke et al. 1977).

EPA considered these negative results inconclusive because the rat liver S9 could be an inadequate activation system for CTC; there could have been scavenging of reactive intermediates by microsomal protein or lipid; or there may have been evaporation of CTC from the test systems (EPA 1984). Other halogenated hydrocarbons as a class have reportedly produced false negatives in the Ames Salmonella assay (McCann and Ames, 1976). The bacterial test systems may not be appropriate for testing the mutagenic response of CTC because of the lack of a nuclear membrane. Nuclear protein fractionation studies using rat liver (Diaz Gomez and Castro 1980b) indicate that metabolic activation of CTC occurs preferentially in the nuclear membranes, providing the reactive intermediates access to DNA. Thus, the bacterial test system may not be an appropriate mutagenicity model.

CTC was analyzed for its mutagenic potential in yeast (Callen et al. 1980). The D7 strain of Saccharomyces cerevisiae yeast was examined for gene conversion at the trp-5 locus, mitotic crossing over at the ade-2 locus, and gene reversion at the ilv-1 locus. The yeast strain contained an endogenous cytochrome P-450 dependent monooxygenase activation system, thus avoiding a number of the pitfalls cited in the bacterial studies. The authors concluded that CTC induced mutations in yeast. However, since positive mutagenic responses were observed only under conditions of extreme (90%) cytotoxicity, DHS staff believes that these results are unreliable.

5.3 Chromosomal Effects

Gualandi (1984) examined the ability of CTC to induce gene mutations and chromosomal rearrangements in a diploid strain of Aspergillus nidulans. When assayed for mutagenicity, CTC produced negative results in the plate incorporation assay and produced a 2- to 3-fold increase of suppressor mutants in the growth-mediated assay. In contrast, CTC was shown to be a strong inducer of chromosomal rearrangements compared to controls. This study indicates, that although CTC lacked strong mutagenic activity in the assay, it was genotoxic by virtue of its induction of chromosomal rearrangements.

In a study using an epithelial-type cell line derived from rat liver, CTC did not produce chromatid or chromosomal aberrations (Dean and Hodson-Walker 1979). In this test system, CTC was not observed to be mutagenic, but this may have been due to the high cytotoxicity of CTC to the cell line used. The exposure concentrations used in the chromosome assay were based on a

predetermined "growth inhibiting dose." Thus the dose levels for CTC were very low. For example, the CTC doses (0.005 to 0.02 μg/ml) were less than 1/2500 of the dose levels of other substances examined in the test series: 2-acetylaminofluorene, propylene oxide and cyclophosphamide.

5.4 Other Test Systems

Amacher and Zelljadt (1983) tested CTC's ability to produce *in vitro* morphological transformation of Syrian hamster embryo (SHE) cells. CTC produced a weakly positive response as indicated by the transformation of one to three of the test colonies. No transformed colonies were observed in the solvent controls. These results are consistent with other data suggesting that CTC is potentially genotoxic.

Sina et al. (1983) developed an alkaline elution rat hepatocyte assay to measure DNA single-strand breaks (SSBs). In the test system, CTC produced a 3- to 5-fold greater number of SSBs than the controls; a positive response suggesting potential genotoxicity of CTC. The authors concluded that the test system correlates well (85 to 92%) with mutagenic and carcinogenic activity for the 91 compounds tested.

In a study by Brambilla et al. (1986), CTC was used as an agent to stimulate rapid hepatic growth for testing effects of 2-acetylaminofluorene (2-AAF). However, administration of CTC alone increased the level of DNA fragmentation. Furthermore, the concurrent administration of 2-AAF and CTC produced more than an additive effect on DNA fragmentation. This study indicates that CTC may affect DNA stability.

CTC produced a positive genotoxic response in a test system of De Flora et al. (1984). CTC was assayed in a DNA-repair test with E.Coli strains proficient and deficient in DNA repair. The genotoxic effect was ascertained by increased killing or growth-inhibition of bacteria lacking specific DNA-repair mechanisms, compared with the isogeneic repair-proficient strains. Although the test indicates genotoxicity it does not assay for mutagenicity.

CTC produced negative results in tests for unscheduled DNA synthesis (UDS). Mirsalis et al. (1980 and 1982) treated F-344 rats in vivo with CTC and reported no increase in measured UDS in vitro using primary hepatocyte cultures. Although some known hepatocarcinogens (dimethylnitrosamine and acetylaminofluorene) were positive in the test system, other known mutagens (benzo[a]pyrene and 7,12-dimethyl benz[a]anthracene) tested negative. In another in vivo study (Craddock and Henderson 1978) rat hepatocyte nuclei were examined for induction or changes in de novo replication. A positive effect was reported at 17 hours after treatment; the authors felt that the latency indicated that the repair replication was a secondary effect and not a direct reaction with DNA. Perocco and Prodi (1981) examined the effect of CTC on scheduled and unscheduled DNA synthesis in vitro using human lymphocytes. They reported that CTC inhibited scheduled DNA synthesis (SDS) but produced low values of UDS.

In summary, carbon tetrachloride appears to have genotoxic potential based on its ability to form reactive intermediates that can covalently bind to DNA, to induce chromosomal rearrangements in vitro, to cause SSBs and to produce morphological transformation of SHE cells. CTC has demonstrated

very little, if any, mutagenic activity based on the standard bacterial mutagenic assays, a yeast assay, and determinations using unscheduled DNA synthesis. However, the negative mutagenicity test results may be a result of the inadequacy of the activation systems of some of the assays, the inappropriateness of using a bacterial test system as a model and the high cytotoxicity of CTC in the test systems. The absence of positive results in the standard mutagenicity assays indicates that although CTC is potentially genotoxic, it probably does not induce point mutations.

6.0 REPRODUCTIVE TOXICITY

Inhaled carbon tetrachloride causes degenerative changes in the testes and reduced testicular weight in laboratory animals. In one study CTC reduced fertility in rats (Smyth et al. 1936). In pregnant female rats exposed to concentrations of 300 ppm, CTC crossed the placenta and produced developmental abnormalities in the fetus. The teratogenic potential of CTC has not been adequately tested.

The NOAEL for reproductive effects caused in rats is 100 ppm (Adams et al. 1952). This level is nearly six orders of magnitude above the highest recorded ambient levels of CTC; therefore, reproductive effects are not expected to occur in the general population due to exposure to CTC.

6.1 Male Reproductive Effects

A number of studies demonstrate decreased weight in testes and accessory reproductive organs or other pathological changes. The most sensitive study that considered male reproductive effects was by Adams et al. (1952). Rats and guinea pigs were repeatedly exposed to CTC ranging from 5 to 400 ppm (See Table 1 for details). At 200 ppm and above rats exhibited decreased weight of the testes compared to controls and germinal elements of the testes showed moderate to marked degeneration, with some seminiferous tubules exhibiting complete atrophy of germinal elements. At 400 ppm guinea pigs exhibited some minor nonspecific pathological changes in the testes. No decrease in testicular weight or histological effects were observed in rats at concentrations of 100 ppm or below, or in guinea pigs at concentrations of 200

ppm or below. Rabbits and monkeys were also studied by Adams et al. (1952), but there were only one or two animals in each dose group so the numbers were too small to draw reliable conclusions.

Chatterjee (1966) and Kalla and Bansal (1975) reported similar male reproductive effects caused by CTC in rats. In both studies 4800 mg/kg CTC were administered intraperitoneally for 10 to 20 days. The relative weights of the testes and accessory reproductive organs were decreased compared with controls. Histological examination indicated testicular atrophy, disruption of normal architecture, and marked abnormalities in spermatogenesis, including azoospermia. Both studies reported an increase in pituitary weight; however, the relevance of this finding cannot be determined without actual measurement of serum gonadotrophins. The route of administration (intraperitoneal instead of inhalation) and high dose make the interpretation of these results difficult.

These three studies indicate that CTC can produce adverse male reproductive effects. A similar decrease in testicular weight was observed in two species by two exposure routes. Although the results indicate a decline in the spermatogenic process, only one investigator has tested the reproductive ability of affected animals (Smyth et al. 1936, described below).

6.2 Study on Fertility

In a multigeneration study, Smyth et al. (1936) found that 200 and 400 ppm CTC diminished the number of litters and decreased the number of offspring per litter in rats, compared to controls. Up to 3 generations were observed for fertility following repeated 8-hour/day, 5-day/week exposure of both sexes to 50, 100, 200 and 400 ppm CTC over 10.5 months. It was not clear if the decline in fertility resulted from effects of CTC on males, females, or both.

6.3 Placental Transport

Dowty and Laseter (1976) reported that CTC (as well as other halogenated hydrocarbons) can cross the human placenta and accumulate in the fetus. Blood samples were recovered from the umbilical cord and from paired maternal blood of 11 women after vaginal delivery. The authors indicated that exposure to CTC and other halogenated hydrocarbons may have occurred in drinking water. Carbon tetrachloride levels were higher in cord blood than in the maternal blood. In animal studies, CTC was shown to cross the placenta of pregnant rats and to produce fetotoxicity (Sundareson 1942, Bhatacharyya 1965, Schwetz 1974). Maternal toxicity was produced in these studies, which could increase fetal toxicity. However, several investigators have shown that for CTC there does not appear to be a direct correlation between the severity of maternal toxicity and the severity of reproductive effects in the rat fetus (Wilson 1954, Schwetz et al. 1974). Sundareson (1942) reported that direct injections of CTC into fetuses *in utero* produced maternal toxicity, indicating that CTC can traverse the placenta in either direction.

6.4 Developmental Toxicity

Several studies have suggested that CTC is embryotoxic in rats; these are summarized in Table 2. The presence or absence of maternal toxicity is also indicated. Administration of CTC to pregnant rats prior to the 12th day of gestation produced a failure to implant or increased intrauterine mortality (Sundareson 1942). CTC produced a decrease in the viability and in the number of pups per litter when compared to controls (Gilman 1971). In rabbits, CTC administered on days 4 and 5 of gestation produced cellular degeneration in the embryonic discs, and the trophoblasts contained very large nuclei with prominent nucleoli (Adams et al. 1961). The latter study indicates that CTC can produce embryotoxicity prior to implantation.

CTC is fetotoxic in rodents. When administered after the 12th day of gestation CTC was associated with premature delivery, increased postnatal mortality, and liver degeneration and necrosis in the fetus (Sundareson 1942, Bhattacharyya 1965). Schwetz et al. (1974) reported that CTC inhalation by pregnant rats produced a significant decrease in fetal body weight and crown-rump length when compared to controls. Furthermore, CTC can diffuse into mother's milk and cause liver damage in the nursing neonate (Bhattacharyya 1965).

Two studies reported the absence of teratogenic effects. In a preliminary inhalation study, Gilman (1971) reported no teratogenic effects were observed in the offspring. Schwetz et al. (1974) also reported the absence of

TABLE 2. SUMMARY OF STUDIES ON DEVELOPMENTAL TOXICITY

Study	Species	(N)[2]	Dose	Day of Gestation Exposed	Fetal Effects	Maternal Toxicity[1]
Briese 1938	rat	60	nr	1-21	Anemia	yes
Sundareson 1942	rat	1-22	200-2400 mg/kg	19-20	Death, liver degeneration	yes
Adams et al. 1961	rabbit	nr[3]	4800-8000 mg/kg	4-5	Embryonic degeneration	no
Bhatacharyya 1965	rat	nr	1600,3200 mg/kg	19-20	Liver necrosis	nr
Gilman 1971	rat	25	≈250 ppm 8 hours/day	10-15	Fetotoxicity	nr
Schwetz et al. 1974	rat	22	300 ppm 7 hours/day	6-15	Fetotoxicity	yes
	rat	23	1000 ppm 7 hours/day	6-15	Fetotoxicity	yes

[1] Maternal toxicity was evidenced by anemia, hepatotoxicity, reduced food consumption and increased SGPT activity.

[2] Number of female animals per dose group.

[3] Not reported.

teratogenicity in the rat as a result of CTC inhalation. However, significant increases in total skeletal anomalies (300 ppm), the presence of subcutaneous edema (300 ppm), and evidence of sternebral anomalies (1000 ppm) suggest that fetotoxicity rather than teratogenicity was associated with prenatal CTC exposure in the rat. The experiments cited above do not meet current EPA criteria for a test of teratogenic potential. EPA study design guidelines require that three dose levels be administered, that a nonrodent species be studied, and that positive controls be used (EPA 1984).

The studies on embryo- and fetotoxicity suggest that, in rodents, CTC exposure exhibited only limited potential for teratologic change. Additional studies in at least one more rodent and in a nonrodent species are needed prior to conducting an adequate human health risk assessment for prenatal and neonatal CTC exposure.

7.0 CARCINOGENICITY

Carbon tetrachloride has been shown to produce liver tumors in mice, rats and hamsters by the oral, subcutaneous and rectal routes. No inhalation studies have been conducted. These bioassays were not designed for use in a quantitative risk assessment: the studies were either preliminary in nature or CTC was administered to animals as a positive control; furthermore, there was high noncancer mortality in most of the experiments. Human case reports and epidemiological studies have not provided sufficient information to draw any inferences about a causal association between carbon tetrachloride exposure and cancer in humans. Consequently, CTC is considered to be an animal carcinogen and a potential human carcinogen. IARC's evaluations of carcinogenicity (1972, 1979) concluded that there was sufficient evidence that CTC was carcinogenic in experimental animals and that CTC should be regarded as a potential human carcinogen.

Mouse Studies

At least eight studies on chronic CTC administration have reported the development of hepatic tumors in six different strains of mice. Tumors have been reported in both males and females, by oral and rectal administration. The results of seven of these experiments are summarized in Table 3.

Edwards (1941) and Edwards and Dalton (1942) administered CTC by gavage to four different strains of mice (1 to 6 months of age) two to three times a week for 8 to 23 weeks. Both sexes were used in the study, but the olive

TABLE 3. MOUSE BIOASSAYS

Strain	Vehicle[1]	Dose (mg/kg)	Tumor Incidence % (N)[2]	Tumor	Reference
A m,f[3]	none	0	1 (200)	hepatoma	Edwards 1941
f	olive oil	≈2100	100 (54)	hepatoma	
A m	olive oil	0	0 (44)		Edwards & Dalton 1942
A f		≈260	71 (58)	hepatoma	
m,f		≈2100	98 (64)	"	
A m,f	olive oil	0	0 (28)[4]		Eschenbrenner and Miller 1943
		≈160	38 (63)	hepatoma	
		≈315	38 (63)	"	
		≈625	42 (59)	"	
		≈1250	53 (60)	"	
		≈2500	55 (60)	"	
A[5] m,f	olive oil	0	0 (10)		Eschenbrenner and Miller 1946
		≈40	0 (10)		
		≈80	70 (10)	hepatoma	
		≈159	63 (8)	"	
A[6] m,f	olive oil	0,≈10	0 (10)		Eschenbrenner and Miller 1946
		≈20	100 (10)	hepatoma	
		≈30	100 (10)	"	
		≈40	100 (9)	"	
B6C3F1	corn oil	0	4 (157)	hepatocellular carcinoma	NCI 1976 a,b, 1977
m,f		1250	100 (89)		
		2500	97 (93)	" "	
C m	olive oil	0	0 (16)		Edwards & Dalton 1942
f		≈2100	83 (41)	hepatoma	
C3H m	none	0	0 (17)		Edwards 1941
	olive oil	≈2100	88 (143)	hepatoma	
C3H m	olive oil	0	4 (23)	hepatoma	Edwards & Dalton 1942
		≈2100	88 (143)	hepatoma	
L m,f	none	0	1 (152)	hepatoma	Edwards et al. 1942
	olive oil	≈2100	47 (73)	hepatoma	
Y m,f	none	0	2 (129)	hepatoma	Edwards & Dalton 1942
	olive oil	≈2100	60 (15)	hepatoma	

[1] All animals were administered CTC by gavage.
[2] N refers to the number of animals in the treatment group.
[3] m refers to male and f refers to female animals.
[4] Animals dosed at various intervals were combined; there were 5-12 per group.
[5] Administered 30 doses over 120 days.
[6] Administered 120 doses over 120 days.

oil vehicle was administered only to male control animals of strains A, C and CH3. The animals were 1 to 5 months old at the beginning of the study. One experiment in the study indicated the latency for tumor development in mice was 8 weeks. To assess the tumor-producing ability of CTC, animals were necropsied 12 to 21 weeks after the last treatment. For those animals exposed to approximately 2100 mg/kg of CTC the incidence of hepatoma was 88.2 percent; specific strain incidences are presented in Table 3. Whether the CTC-induced hepatomas were malignant was not established histologically in the study. The animals were dosed on a nondaily schedule for a maximum of 16 weeks and sacrificed as young as 4 months of age. Since tumor expression is a function of both dosage and the latency period, any risk assessment based on these studies, with their short observational periods, will underestimate the true carcinogenic risk. The data for strains A, C and CH3 (Edwards and Dalton 1942) were used in the DHS and EPA (1984) risk assessments of CTC. In another experiment Edwards and Dalton (1942) administered 1, 2 or 3 doses of carbon tetrachloride (≈260 to 2100 mg/kg) followed by long-term observation. The doses were hepatotoxic, but when the animals were examined 12 months later no tumors were observed. This experiment indicates that at these dose levels an acute exposure may not be tumorigenic in Strain A mice. Edwards et al. (1942) also reported CTC-induced tumors in an inbred L strain of mice, but these data were not used in the risk assessment since there were no vehicle controls, the dosing schedule was irregular and there was a relatively short exposure period relative to lifespan.

Eschenbrenner and Miller (1943, 1946) extensively examined tumor production in Strain A mice. In the first study they administered 30 doses of CTC at

intervals of one to five days. All animals were examined for tumors at 150 days following the first dose. Centrilobular liver necrosis was observed at all exposure levels. They reported that the incidence of hepatomas was increased as the time interval between doses increased. In Table 3 results for the different interval groups were combined. These data were not used in the risk assessment because the number of animals in the control groups was small (5 to 6), there was high animal mortality (39% of the controls), there was a short 30-day exposure period for animals and also a relatively short period of time prior to necropsy (21 weeks after first dose).

In a second study Eschenbrenner and Miller (1946) administered the same total quantity of CTC, either in 30 doses at four-day intervals or in 120 doses on consecutive days. This study was conducted to determine the effect of liver necrosis on tumor development; they found that mice receiving the smaller dose over 120 days (a so-called "non-necrotizing" dose) developed tumors at roughly the same or greater rate as those animals that received necrotizing doses (30 large doses at 4-day intervals). The 1943 study implied that a larger interval between doses increased tumor production. The 1946 study showed that the total length of the exposure period (i.e., 120 versus 30 days), not the time between doses, may have been the major determining factor in the production of tumors. There were too few animals in the study to determine a statistically significant effect, and consequently this study could not be used in a quantitative risk assessment. Other problems with using these data for risk assessment include the short exposure period, the short observation period to necropsy and the high mortality in all treated and control groups.

The 1946 study attempted to address the question of whether liver necrosis was a precondition of tumor production. The results indicated that massive liver necrosis was not a required precondition for the production of tumors with CTC. However, the study did not address the question of whether an hepatotoxic dose was a precondition for tumor production. Based on the work of Hayes et al. (1986), it is likely that hepatotoxic effects occurred in the animals dosed in the 1946 study. However, this does not answer the question of whether hepatotoxicity is a required precondition for tumor production by CTC. As indicated by Williams and Weisburger (1986) the carcinogenic mode of action of carbon tetrachloride remains to be clarified.

The three NCI mouse bioassays used carbon tetrachloride as a positive control (NCI 1976a,b, 1977, Weisburger 1977) and excess mortality was a severe problem in the studies. Mice were dosed by gavage for 5 days a week for up to 78 weeks and they were to be sacrificed at 92 weeks; however, only 14% of the animals survived to 78 weeks and less than 1% survived to 92 weeks. This compares with 66% of the controls surviving the 92-week experiment. All animals were necropsied, regardless of the time of death, and hepatocellular carcinoma was found in almost every treated animal. Carcinomas were observed as early as 16 weeks for the low-dose female group. The high mortality and virtual 100% tumor response are the more serious limitations of this study. The data from this study, however, were used in the DHS and EPA (1984) risk assessments.

7.2 Rat Studies

Several studies reported the production of malignant tumors in rats following subcutaneous injections and oral administration of carbon tetrachloride. Tumor production in rats has been demonstrated in at least four strains, and in both sexes. The results of these studies are summarized in Table 4.

Reuber and Glover (1967) injected Buffalo rats subcutaneously twice a week for up to 12 weeks. Control animals were given corn oil. The animals were 0.6, 4, 12, 24 or 52 weeks old at the beginning of the study. Newborn rats died in approximately 8 days due to hepatic and renal necrosis. Animals were sacrificed and necropsied following exposure at 12 weeks. They reported hepatic hyperplasia, hyperplastic nodules and a few cases of hepatic carcinoma.

In a later study, Reuber and Glover (1970) compared the carcinogenicity of CTC in 12-week-old male rats from the Japanese, Osborne-Mendel, Wistar, Black and Sprague-Dawley strains. The animals were subcutaneously injected twice a week for up to 105 weeks, depending on survival. Corn oil was administered to controls. All of the Sprague-Dawley strain died within 16 weeks, and all of the Black strain died within 18 weeks. Although hyperplastic nodules were reported in these two strains, no carcinomas were observed. The absence of carcinoma is possibly due to the poor survival; the latency period reported for carcinoma in this study was 68 weeks. Hyperplastic nodules and hepatic carcinoma were reported in the other three strains. Other lesions reported were hemangiomas, carcinomas of the thyroid

TABLE 4. RAT BIOASSAYS

Strain		Route	Dose (mg/kg)	Tumor Incidence %	(N)[1]	Tumor	Reference
Buffalo	m,f	sc	0	0	48		Reuber & Glover 1967
	m		≈2060	2	40-56	carcinoma	
				12	"	hyperplas. nodule	
	f	sc	≈2060	5	"	carcinoma	
				40	"	hyperplas. nodule	
Japanese	m,f	sc	0	0	12		Reuber & Glover 1970
			2080	80	15	hepatic carcinoma	
				13	15	hemangioma	
				20	15	thyroid carcinoma	
				7	15	leiomyosarcoma	
				20	15	hyperplas. nodule	
Osborne-Mendel	m	sc	0	0	12		Reuber & Glover 1970
			2080	62	13	hepatic carcinoma	
				8	13	hemangioma	
				23	13	thyroid carcinoma	
				31	13	hyperplas. nodule	
Wistar	m	sc	0	0	12		Reuber & Glover 1970
			2080	14	33	hepatic carcinoma	
				14	58	hyperplas. nodule	
Black[2]	m	sc	0	0	12		Reuber & Glover 1970
			2080	41	17	hyperplas. nodule	
Sprague-Dawley[2]	m	sc	0	0	12		Reuber & Glover 1970
			2080	12	17	hyperplas. nodule	
Osborne-Mendel[2]	m,f	oral	0	0	40		NCI 1976a,b 1977
	m		47	4	50	hepatic carcinoma	
				4	50	neoplastic nodule	
			94	4	50	hepatic carcinoma	
				2	50	neoplastic nodule	
	f		80	8	50	hepatic carcinoma	
				4	50	neoplastic nodule	
			159	2	50	hepatic carcinoma	
				6	50	neoplastic nodule	

[1] Size of dose groups at beginning of study.
[2] Incidence rates may not be comparable due to high mortality rate during study.

gland, and subcutaneous leiomyosarcoma. Cirrhosis was reported in all animals. Due to the small group size, poor survival of several strains and the incomplete reporting of total dosage, and most importantly, the inappropriate route of exposure, (subcutaneous injections may produce high local concentrations and an uncertain whole-body dose) this study cannot be used in a quantitative risk assessment.

As in the mouse studies, NCI used carbon tetrachloride as a positive control in rat bioassays for chloroform, 1,1,1-trichloroethane and trichloroethylene (1976a,b and 1977, Weisburger 1977). The Osborne-Mendel rats were administered a time-weighted average dose of CTC by gavage for 78 weeks. All surviving animals were observed for up to an additional 32 weeks, but only 28% of the animals survived until that time. Thirty-nine percent of the pooled controls[1] survived the 110-week experiment. Hepatic carcinomas were found at both doses in both sexes. A lower incidence was reported in the high-dose females, but this may to have been a result of that dose group's high mortality rate prior to tumor expression. The first hepatocellular carcinoma was observed in the female dose group at 16 weeks and in the male dose group at 26 weeks. Tumors in other tissues were not discussed, although the authors implied that other tissues were examined. The EPA (1984) and National Academy of Sciences (NAS 1978) used this study in their risk assessment estimates; however, DHS staff members consider such use of the NCI study inappropriate because when the data are adjusted for excess mortality there is not a statistically significant association between dose and tumor response.

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[1] Vehicle and non-vehicle controls.

7.3 Hamster study

CTC in corn oil was administered weekly by gavage to Syrian golden hamsters (both sexes) for a total of 30 weeks (Della Porta et al. 1961). The dosages were equivalent to 190 and 380 mg/kg of body weight respectively (EPA 1984).

Following treatment the animals were kept 25 weeks, sacrificed and examined. Only eight of the original 20 animals survived the full 55 weeks. The first animal death occurred at 10 weeks. Historical controls were used in the study and reportedly had not developed any liver-cell tumors (0/254). Carcinomas were not observed in the animals that died prior to the 43rd week (50%), but one or more liver-cell carcinomas were reported in the remaining animals. The high mortality rate and the 100% tumor incidence in surviving animals indicate that tumors may be produced at lower levels in this species. Furthermore, only 20 animals were treated, and it is likely that the animals were infected with a liver disease as many other colonies were in the early 1960's (Dungworth 1986, personal communication). Consequently, even though the hamster appears to be the most sensitive species studied and exhibited a very high tumor incidence rate at the exposure level used, the study was deemed inadequate for quantitative risk assessment.

7.4 Human Case Reports and Studies

The epidemiological data suggesting an association of carbon tetrachloride exposure with human cancer development are inconclusive; exposure data are unavailable and the putative association is confounded by exposure to other potential carcinogens. Several case reports stated that liver cancer developed following a single acute exposure (Tracey and Sherlock 1968, Simler et al. 1964) or a chronic exposure to CTC (Johnstone 1948). However, as with the epidemiological data, exposures were poorly documented, and the information can at best be used qualitatively to corroborate animal test data.

7.4.1 Human studies

Capurro (1979) reported a study on the residents in a rural valley polluted by vapors from a solvent recovery plant for at least 10 years. Chloroform, benzene, methyl isobutyl ketone, trichloroethylene and 26 other organic agents were detected in the air in addition to CTC (Capurro 1973). The author reported four excess cases of lymphoma. Attributing these cancer cases to CTC alone would be inappropriate since exposure to the other contaminants was verified in blood samples of residents.

In a preliminary study of 330 laundry and dry cleaning workers, Blair et al. (1979) examined occupational exposure to CTC and other dry cleaning agents. Information from death certificates indicated an excess of deaths from lung, cervical and liver cancers, and leukemia. Katz and Jowett (1981) studied female laundry and drycleaning workers in Wisconsin. Their results failed

to show an overall increase in malignant neoplasms, but they did report an elevated risk for cancers of the kidney and genitals (unspecified), along with smaller excesses of bladder and skin cancer and lymphosarcoma. However, the use of carbon tetrachloride has been of only minor importance in dry cleaning since the 1950's (DeShon 1978, Garfield 1985 a,b), and quantitative data on exposure to CTC were not presented in these studies.

Hernberg et al. (1984) reported a case-control study on primary liver cancer and exposure to solvents. Of 126 cases, 2 had a history of exposure to carbon tetrachloride, among other solvents. They concluded that there was an association between primary liver cancer and exposure to "solvents" among women, but not for men.

Recently, two reports were published on cancer mortality in a population of rubber workers (Checkoway et al. 1984, Wilcosky et al. 1984). Information on cause of death was reported in an earlier study (McMichael et al. 1974). They examined work history records to estimate the potential exposure experienced by the individuals. They reported a significantly elevated odds ratio relating carbon tetrachloride with lymphatic leukemia (OR=15.3, $p < 0.0001$) and lymphosarcoma and reticulum cell sarcoma (OR=4.2, $p < 0.05$). Attributing these outcomes to CTC alone is inappropriate since different solvents were used simultaneously in a given process area. That is, a high degree of correlation existed between exposure to several solvents and the incidence of lymphatic leukemia (CTC, carbon disulfide, ethyl acetate, acetone, and hexane) and lymphosarcoma (CTC, xylenes, carbon disulfide and hexane). Although carbon disulfide, ethyl acetate, acetone, hexane, and xylenes are not recognized carcinogens, these potentially confounding

exposures, the lack of association of CTC exposures with these cancers in other studies, and the small number of cases (19 of a study population of 6678), preclude any causal inference from this study.

Summary

Animal studies demonstrate that carbon tetrachloride produces hepatocellular carcinomas in the mouse, rat and hamster; human evidence is inconclusive. IARC evaluated CTC and concluded that it is an animal carcinogen. The IARC classification would place CTC in group 2B, indicating that it is probably carcinogenic to humans. DHS staff members concur with this assessment, based on the evidence cited in the preceding subsections. Since there are sufficient animal data to conclude that CTC is a potential human carcinogen, a risk assessment of CTC is presented in Section 9.

The epidemiological studies and human case reports are inadequate to use in a quantitative risk assessment. Thus, the quantitative risk assessment will be based on animal data. Two studies were selected for quantitative risk assessment: Edwards and Dalton (1942), and NCI (mouse) (1976a,b and 1977). These are discussed further in Chapter 9 on quantitative risk assessment.

8.0 SYNERGISM AND ANTAGONISM

8.1 Synergism

A number of substances have been shown to potentiate the noncarcinogenic effects of carbon tetrachloride. Some have been shown to increase its acute toxicity, such as ethanol, fats, polybrominated biphenyls, 2-butanone, 2,3-butanediol, chlordecone, phenobarbital, Mirex, and isopropanol (Curtis et al. 1979, Dietz and Traiger 1979, Klingensmith and Mehendale 1983, Kluwe et al. 1979, Mehendale 1984, Robbins 1929, Strubelt et al. 1978). Other compounds, such as benzo(a)pyrene and p-dimethylaminoazobenzene, may increase the chronic toxicity of CTC (Kotin et al. 1962, Moore and Ray 1983, Protzel et al. 1964, Ueda 1967).

8.1.1 Acute Interactions

The most prominent synergistic effect reported is the potentiation of hepatic toxicity in humans by alcohol (Bjarnason et al. 1968, Von Oettingen 1964). The precise nature of the potentiation has not been elucidated, but interest in the effect has generated numerous studies and a number of mechanisms have been proposed.

Alcohol increased the absorption of carbon tetrachloride from the intestinal tract in dogs (Robbins 1929); however, the effect (liver necrosis and mortality) was so much greater than the effect of CTC alone that the author concluded that "alcohol affects the toxicity in some way other than by changing the rate of absorption."

Klaassen and Plaa (1967) and Cornish and Adefuin (1966) reported that pretreatment with ethanol followed by CTC administration elevated the serum glutamic-pyruvic transaminase (SGPT) in dogs by an order of magnitude, indicating liver dysfunction. Other studies examining ethanol potentiation of CTC toxicity were conducted by Traiger and Plaa (1971), Wei et al. (1971), and Strubelt et al. (1978). In summary, ethanol has been shown to potentiate the acute toxicity of carbon tetrachloride in several animal species, including humans; it is unknown whether such potentiation extends to chronic effects and carcinogenicity.

8.1.2 Chronic Interactions

A study by Ueda (1967) compared the chronic toxicity of CTC and p-dimethylaminoazobenzene (DAB), administered separately and simultaneously. Liver carcinoma and cholangiofibrosis were observed in the DAB treatment group alone. Liver fibrosis and cirrhosis were observed in the CTC treatment group. The combined regimen produced nodular hyperplasia with liver cirrhosis, and greater incidences of liver carcinoma and cholangiofibrosis. DAB did not increase the incidences of liver fibrosis or cirrhosis observed with CTC, although the appearance of cirrhosis occurred earlier. The primary interaction observed was the potentiation by CTC, as a promoter, of DAB's carcinogenic effects.

Liver damage produced by CTC has been shown to change the rate of benzo(a)pyrene metabolism and the profile of metabolites formed (Kotin et al. 1962). When CTC (0.06 ml/100 g b.w.) was injected prior to injection of 200 μg of radiolabeled benzo(a)pyrene, clearance of benzo(a)pyrene was

reduced and there was a decrease in glucuronide conjugation of 3-hydroxybenzo(a)pyrene. Kotin et al. (1962) also studied the effects in mice of chronically administered CTC and benzo(a)pyrene, both separately and together. No tumors were observed in animals treated with CTC alone. However, CTC administration doubled the incidence of tumors present when compared with those animals treated with benzo(a)pyrene alone. A similar enhancement of benzo(a)pyrene tumor production was observed by Protzel et al. (1964), who applied a 0.1% solution of benzo(a)pyrene to the buccal mucosa of mice and periodically injected a 10% solution of carbon tetrachloride. CTC also enhanced 2-acetylaminofluorene (AAF) tumor production, apparently by increasing the metabolism of AAF to the N-hydroxylated metabolite (Weisburger et al. 1963 and 1965).

8.2 Antagonism

A number of compounds reportedly produced a protective effect against carbon tetrachloride toxicity. Beattie et al. (1944) reported that oral administration of methionine prevented a fatality in an acute case of CTC poisoning. In an animal study, calcium lactate (added to the feed at 1.2 g/day) increased the number of CTC exposures (100 and 200 ppm) that guinea pigs were able to tolerate before death (Smyth et al. 1936). Other substances that have reportedly antagonized the effects of CTC include dietary vitamin E, selenium, reserpine, carbon disulfide, diethyldithiocarbamate, chloramphenicol and chlorpromazine (EPA 1984). However, many of these compounds primarily reduce subclinical effects, so it is unclear how effective they would be following human administration.

In summary, the acute toxicity of CTC can be potentiated by a number of substances, including some commonly used drugs and some environmental pollutants. CTC itself has been shown to act as a carcinogenic promoter for several substances. Other compounds have been shown to antagonize the effects of CTC; however, there is not sufficient information to incorporate this into the risk assessment.

9.0 QUANTITATIVE RISK ASSESSMENT

A health assessment document for CTC was recently prepared by the EPA (1984). The document was peer-reviewed by members of the EPA Office of Health and Environmental Assessment (OHEA) and by external reviewers not connected with EPA. The initial purpose of the document was for use by the Office of Air Quality Planning and Standards, although the final scope was expanded to include other areas. The health assessment included quantitative risk estimates for cancer. The quantitative risk assessment section of the document has been modified for use in this report and is included in Appendix A. The staff of DHS believes the EPA (1984) risk assessment, as modified, is a reasonable and appropriate interpretation of the health effects data on CTC, as explained below.

9.1 Noncarcinogenic Risks

The effects of CTC following acute and chronic exposure are presented in Sections 3 to 7. The NOAEL in humans for a 3-hour acute exposure is 10 ppm while the NOAEL for rats for chronic exposure was reported to be 5 ppm. These levels are four orders of magnitude above the highest ambient maximum 24-hour concentrations reported in Part A of this document. However, NOAEL's for other species were not attained when subchronic testing was conducted at 1 ppm. Furthermore, chronic animal studies have not been conducted that establish a NOAEL for biochemical liver changes. Even in the absence of this information, based on the relatively low ambient CTC concentrations, noncarcinogenic, chronic intoxication is not expected to result in the general population from inhalation of carbon tetrachloride.

9.2 Carcinogenic Risks

9.2.1 Thresholds

For toxicologic purposes, a threshold dose is one below which a specified outcome does not occur; however, the self-propagating, clonal nature of tumor growth and development from a single damaged cell suggests that the effective dose for carcinogenesis may be so low as to be indistinguishable from zero. While threshold models (based on detoxification enzyme saturation, the existence of DNA repair mechanisms, recurrent cytotoxicity) have been proposed, none has been convincingly demonstrated.

An "epigenetic mechanism" that could theoretically embody threshold doses has been invoked to explain the carcinogenic action of substances that do not directly produce genetic damage in short-term tests. However, neither short-term tests nor nonlinearities in dose-response curves from animal bioassays can reliably distinguish between "genetic" versus "epigenetic" carcinogenesis, primarily because of the limited sensitivities of the experimental methodologies. In the case of CTC there is evidence suggesting potential genotoxicity (because of binding to DNA) without much evidence of mutagenicity (see Chapter 6). There is also experimental support for CTC acting as a promoter of tumorigenesis (see Chapter 8). On the other hand, in some experiments CTC alone was an effective carcinogen (see Chapter 7). Thus, the mechanism of CTC-induced carcinogenesis has not been elucidated. Since CTC produces its toxicity via production of the trichloromethyl radical, it might be assumed that a threshold exists based on the presence of antioxidants and free radical scavengers. However, as indicated by

Slater et al. (1985) "it is evident that effective scavenging of such species must satisfy a number of demanding criteria," including the ability to penetrate to the precise intracellular locus of metabolic activation. On the other hand, the DNA must compete with other biomolecules that would be damaged by the trichloromethyl radical as well as with the potential noncytotoxic scavengers. Consequently, further study is required to elucidate the effectiveness of the competing processes. DHS staff agrees with the conclusion of the IARC (1983) that there is insufficient evidence at present to justify creating separate classes of carcinogens (based on mechanism) for which different risk assessment methods would be used. Thus, in the absence of compelling evidence to the contrary, DHS treats carcinogenesis as a non-threshold phenomenon.

9.2.2 Risk assessment

The quantitative risk assessment of CTC conducted by EPA is contained in Appendix A. DHS modified the EPA risk assessment by: 1) applying an absorption fraction of 50% instead of 40%; 2) omitting the rat bioassay (NCI 1976 a, b, 1977) and the hamster bioassay (Della Porta et al. 1961) EPA used ; 3) assuming an average inhalation intake of 18 μg/day instead of 20 μg/day; and 4) presenting the range of resulting unit risks instead of the geometric mean. The range of human equivalent excess cancer risk estimates for lifetime inhalation exposure to CTC at 1μg/m^3 determined by DHS is presented in Table 5. Discussion of the differences between the EPA and DHS interpretations follow.

EPA chose an inhalation absorption fraction of 40%. EPA considered three reports in calculation of their inhalation absorption fraction (Lehmann and Schmidt-Kehl 1936, McCollister et al 1951, and Stokinger and Woodward 1958). The Stokinger and Woodward (1958) 30% absorption value represents their interpretation of the literature; however, they did not provide any data to support their conclusion. DHS staff decided to consider only the Lehmann and Schmidt-Kehl (1936) and the McCollister et al. (1951) studies in calculating an inhalation absorption fraction of 50% of the total CTC inhaled.

No animal study in the CTC health effects literature is ideal for use in a quantitative risk assessment. Four studies have sufficient information to estimate unit risk (Della Porta et al. 1961, Edwards et al. 1942, and NCI 1976 a,b, 1977 [rat, mouse]). However, DHS believes that the use of the rat NCI (1976 a,b, 1977) data and the hamster (Della Porta et al. 1961) data, is inappropriate as discussed in Sections 7.2 and 7.3. The NCI study used both vehicle and nonvehicle controls; when only vehicle controls are used and adjustments are made for early mortality, the NCI rat study data do not indicate a statistically significant association between dose and tumor response for either sex at either of the doses tested. Therefore, the NCI rat study constitutes a negative carcinogenic result. The hamster bioassay study was very small, using ten male and ten female animals. Only one dose level was tested. The tumor incidence was compared to 50 male and 30 female vehicle controls that were not concurrent, but they were housed under similar conditions. The report indicates that a number of animal deaths occurred early in the study; however, time-to-tumor information was not available. Also, it is possible that the hamster colony was infected with a

liver disease as many of them were at that time (Dungworth 1987, personal communication). The staff at DHS did not include these data in the risk assessment even though the study represents the most sensitive carcinogenic response to CTC.

Limitations of the two other studies are discussed below. The major limitation of the database is that there is no appropriate inhalation study examining the carcinogenic effects in the literature. Consequently, oral studies have to be used and applied to inhalation exposure. In addition, none of the studies were originally designed for use in a carcinogenic risk assessment model and the quality of the data is not ideal. In these studies emphasis was placed on determining the presence of liver tumors; the presence of other tumors, although mentioned, was poorly documented. This factor may have little influence on the risk assessment since it appears that the liver is the predominant site for CTC-induced tumors.

The NCI mouse study (NCI 1976a,b, 1977) has a number of study design problems. There was considerable animal mortality, requiring that the data be adjusted for the animals dying prior to the observation of the first liver tumor. The tumor response was close to 100% in both dose groups, limiting the interpretation of the dose-response curve. The goodness-of-fit criterion was not satisfied for the multistage model; however, the data provided are sufficient to calculate a time-to-tumor risk estimate.

The major limitations of the Edwards and Dalton (1942) study are the use of only male control mice, the short duration of the experiment, and the irregular dosing schedule. Although the authors did not indicate whether

the hepatomas were benign or malignant, the fact that hepatocellular carcinomas were reported in mice (NCI 1976a,b 1977), rats (NCI 1976a,b 1977, Reuber and Glover 1970), and hamsters (Della Porta et al. 1961) indicates that the hepatomas should be used in a risk assessment.

The EPA risk assessment uses several correction factors in its risk calculations as described below. Corrections for the data are discussed in Appendix A. This includes reasons for combining groups, eliminating inappropriate data points, corrections for surface area, adjustments for experiment duration and time-weighted average approximations of dosage. The EPA then calculated the geometric mean of the risk estimates from each of the four studies.

The DHS risk assessment does not adopt EPA's approach of using the geometric mean. Instead DHS presents the range of the estimates predicted by each of the two studies used. See Table 5.

The exposure level used in the unit risk calculation was 1 $\mu g/m^3$ and it corresponds to an estimated inhaled intake of 18 μg/day. The dose-response curve for the multistage model at these low concentrations is projected to be linear for the 95% upper confidence limit. Thus the upper limit of risk can be estimated by multiplying the unit risk by the exposure concentration. Since there are no inhalation studies, the unit risk is estimated from ingestion studies. The expected daily intake for the inhalation route is calculated using the respiration rate, absorption fraction and the estimated human weight as described on page A-24 of the Appendix. Using an absorption fraction of 50%, an estimated human weight of 60 kg and an estimated

respiration rate of 18 m^3/day, the unit inhalation intake is 4.5 times the unit oral intake. Thus the EPA 95% upper confidence limit excess cancer risk values in Table 2 of the Appendix, are multiplied by a factor of 4.5 to obtain the values in Table 5.

As seen in Table 5 the upper limit estimate for inhalation exposure to $1\mu g/m^3$ ranges from low to high values of 10 to 42 excess cancers per million people exposed continuously for a lifetime. The staff at DHS believes that this range best estimates the excess risk associated with inhalation exposure to CTC based on the available data.

TABLE 5. Human Equivalent Excess Cancer Risk Estimates for Lifetime Inhalation Exposure to 1 $\mu g/m^3$ Carbon Tetrachloride

Data Set	Maximum Likelihood Estimate	95% Upper Confidence Limit	Type of Model
Edwards et al., 1942	3.2×10^{-5}	4.2×10^{-5}	multistage
NCI 1976a,b,. 1977 mouse	8.1×10^{-6}	9.9×10^{-6}	multistage time-to-tumor

REFERENCES

The DHS conducted a search of the CTC literature in the following manner. In October 1985 a bibliography was compiled from several sources including a list of references submitted by the Air Resources Board, the references cited in the US EPA Health Effects document and several on-line literature searches of Toxline and Medline data bases available from the National Library of Medicine. An updated search of Toxline and Medline was conducted in December 1985. In December 1986, references cited in the Public Comments (Part C) were reviewed. In April 1987 an updated bibliographic search was conducted from Toxline, Medline and the Toxic Substances Control Act Test Submissions (from the US EPA) data bases. In addition to these sources, articles pertaining to carbon tetrachloride were obtained when reviewing specific scientific journals and as references in specific journal articles. In May 1987, a revised version of Part B incorporated information from articles published since the May 1986 version.

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APPENDIX

QUANTITATIVE RISK ASSESSMENT FOR

CARBON TETRACHLORIDE

(Source: EPA, 1984)

APPENDIX

Unit Risk Estimates for Cancer

DEFINITION

Unit risk is one index of the relative carcinogenic potential of a chemical. Unit risk is defined here as the lifetime risk to humans of contracting cancer from a daily exposure to a concentration of 1 μg/ℓ in water via ingestion or a daily exposure to 1 μg/m³ in air via inhalation. The main assumptions for such risk estimates are 70 kg bw, 2 ℓ/day consumption of water and 20 m³/day inhalation rate (ICRP, 1975). The unit risk represents only the estimated risk at the stated exposure concentrations. It should not be interpreted as the slope at any exposure level since the shape of the curve in the low-dose region is not known.

The unit risk estimate for CCl_4 represents an extrapolation below the dose-risk range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis. At the present time the dominant view of the carcinogenic process involves the concept that most agents that cause cancer also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal response that is characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide

variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature probably reflecting the effects of multistage processes on the mutagenic response. The linear non-threshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxin in the diet). Some supporting evidence also exists from animal experiments (e.g., liver tumors induced in mice by 2-acetylaminofluorene in the large scale ED_{01} study at the National Center for Toxicological Research and the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because it has the best, albeit limited, scientific basis of any of the current mathematical extrapolation models, the non-threshold model which is linear at low doses has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing the most plausible upper-limit for the risk, i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

The mathematical formulation chosen to describe the dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data. It is constrained to ensure linearity in the low dose region at least for the upper confidence limit by requiring non-negative values for the fitted coefficients. Furthermore, there exists

a procedure for estimating an upper confidence limit on the slope at low extrapolated doses that is based on fitting the data at all experimental dose levels. Other dose-response models have been proposed which are also linear in the low dose region. The procedure recommended by the Carcinogen Assessment Group of EPA, however, involves estimating a most plausible upper limit of the slope at low doses. The other models (discussed later) can be shown to give lower slopes for the same data set than does the linearized multistage model, when extrapolated to the low dose region. Thus, the extrapolation model preferred by the Carcinogen Assessment Group is the multistage model.

EXPERIMENTAL STUDIES USED IN UNIT RISK ESTIMATES

Three oral studies on animals have sufficient information to allow estimation of unit risk. The oral studies are the positive control data for mice and rats used in three of its bioassays (NCI, 1976a,b, 1977), the Edwards et al. (1942) mice data and the Della Porta et al. (1961) hamster data. The incidence data and other pertinent quantitative information on these studies are presented in Table 1. For all studies, male and female data were combined. This was done because of the small sample sizes in the groups segregated by sex. No appropriate inhalation studies or human oral studies were found in the available literature.

Each of these oral studies has one or several characteristics which make it less than ideal for risk estimation for continuous daily exposure over a lifetime. Della Porta et al. (1961) did not report results for a control group, although they did report the incidence rate for vehicle controls in a different study. Moreover, the dose was administered only once per week and was reduced by half after 7 weeks, forcing the use of a time-weighted average approximation to a daily dose. The sample size (19) was also small. Edwards et al. (1942) exposed the mice for only 4 months and observed them

TABLE 1

Data for Cancer Studies Used in Unit Risk Calculations

Animal	Average Daily Dose	Responders/ Tested	Other Data	Reference
Hamster	0	0/80	Average bw: 0.108 kg	Della Porta et al., 1961
	0.95 mg	10/19	Exposure: 30 weeks	
			Experiment: 55 weeks	
			Assumed lifespan: 55 weeks	
Mouse	0	2/52	Average bw: 0.03 kg (assumed)	Edwards et al., 1942
	15 mg	34/73	Exposure: 17 weeks	
			Experiment: 31 weeks	
			Assumed lifespan: 78 weeks	
Mouse	0	6/157	Average bw: 0.028 kg	NCI, 1976a,b, 1977
	21 mg	89/89	Exposure: 78 weeks	
	42 mg	90/93	Experiment: 92 weeks	
			Assumed lifespan: 92 weeks	
Rat (M,F)	0	0/37	Average bw: 0.45 kg	NCI, 1976a,b, 1977
(M)	11 mg	2/45	Exposure: 78 weeks	
(F)	18 mg	4/46	Experiment: 110 weeks	
(M)	21 mg	2/47	Assumed lifespan: 110 weeks	
(F)	36 mg	1/30		

M = male, F = female

for ~8 months, much less than the desired lifetime experiment (1.5-2 yrs). The ages varied; the animals initially ranged from 2.5-7.5 months of age. In the NCI (1976a,b, 1977) study on mice, both low and high dose groups showed virtually 100% response (89/89 and 90/93, respectively), so that no information was available on the slope of the dose-response curve. As a consequence, risk projections for doses lower than those used in the study will be underestimated by an unknown amount. In the NCI (1976a,b, 1977) study on rats, survival to the end of exposure was poor, the dose was changed forcing use of a TWA dose estimate, and when segregated by sex, the sample sizes were small so that only the low-dose females were statistically significantly different from controls. The combining of the male and female rats when different, though similar, doses were used (see Table 1) may add further uncertainty.

Insufficient metabolic and pharmacokinetic data precluded the selection of the most appropriate species for use in estimating human risk. Because no study could be selected as "best" and "most appropriate", all four data sets are used in separate estimates of unit risk. In addition, an average unit risk estimate is also calculated which is the geometric mean of the four separate estimates.

DESCRIPTION OF THE PREFERRED LOW-DOSE ANIMAL EXTRAPOLATION MODEL

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where all coefficients (q_0, q_1 ...q_k) are non-negative. The unit risk estimates are based on excess or extra risk over the background rate at dose d, i.e. the effect of treatment:

$$P_t(d) = \frac{P(d) - P(o)}{1 - P(o)}$$

It follows that

$$P_t(d) = 1 - \exp\left[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)\right].$$

The point estimate of the coefficients q_i, $i = 0, 1, 2, \ldots, k$, and consequently the extra risk function $P_t(d)$ at any given dose d, is calculated by maximzing the likelihood function of the data. The point estimate and the 95% upper confidence limit of the extra risk $P_t(d)$ are calculated by using the computer program GLOBAL 79 developed by Crump and Watson (1979). The upper confidence limit for the extra risk calculated at low doses is always linear with dose. This is conceptually consistent with the linear non-threshold concept discussed earlier. The slope parameter q_1^* is taken as an upper bound (at low doses) of the potency of the chemical in inducing cancer.

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment including the control group.

Whenever the multistage model does not fit the data sufficiently well, the data point at the highest dose is deleted and the model is refitted to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1-P_i)}$$

is calculated where N_i is the number of animals in the ith dose group, X_i is the number of animals in the ith dose group with a tumor response, P_i is the probability of a response in the ith dose group estimated by fitting the multistage model to the data, and h is the number of dose groups. The fit is determined to be unacceptable whenever X^2 is larger

than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

CONSIDERATIONS IN SELECTING INCIDENCE DATA

The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. Usually, the conservative approach adopted by the Carcinogen Assessment Group selects the data set which gives the highest estimate of the unit risk for humans. Because of the difficulties with each CCl_4 study described earlier, no selection was deemed appropriate. Instead, the separate estimates and their geometric mean are presented.

If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

DESCRIPTION OF THE PREFERRED METHOD FOR CALCULATING HUMAN EQUIVALENT UNIT RISK

The method adopted by the Carcinogen Assessment Group for calculating a human equivalent estimate of unit risk from animal data employs two adjustments (Federal Register, 1980b) reflecting species differences and the influence of exposure duration on lifetime cancer risk. First, the animal doses are expressed as the time-weighted-average (TWA) daily dose over the duration of the experiment, and the low-dose extrapolation model is fitted to the resulting dose-incidence data. The risk is then estimated for a daily dose of 2 μg/day, which is the oral daily exposure corresponding to

a water concentration of 1 μg/ℓ and human intake of 2 ℓ/day. This risk is then multiplied by each of the above adjustment factors to obtain the human equivalent oral unit risk.

The models used to develop the species and duration adjustment factors represent the best scientific judgment based on available data. Other approaches have been suggested and are discussed in a later section.

The preferred model for equitoxic dose across species, or equivalently for risk at a constant dose across species, is based on an adjustment for metabolic diffferences. Metabolic rate has been suggested to be roughly proportional to body surface area (Mantel and Schneiderman, 1975; Calabrese, 1982), thus the equitoxic model is dose/surface area = constant. Equating the animal and human ratios and solving for the human dose gives:

$$d_h = d_a \ (S_h/S_a)$$

where d is daily dose (mg/day), S is surface area, and a and h refer to animal and human, respectively. The surface area is roughly proportional to the 2/3 power of body weight, and the proportionality constant is approximately the same (~10) for a variety of species. The human dose is then approximated by

$$d_h = d_a \ (W_h/W_a)^{2/3}$$

The unit risk estimate represents the lifetime risk for lifetime exposure to the carcinogen. When the animal experiment is partial lifetime, an adjustment is necessary to allow for positive responses that would have occurred had sufficient time been allowed for the tumors to develop. The risk is then adjusted upward (or equivalently the dose downward) to reflect the missing responders in the short experiment. The adjustment coefficient is $(L/L_e)^3$, where L is the animal lifespan and L_e is the duration of the experiment. The exponent 3 is supported in part by Doll (1971), who

showed that age-specific rates for humans increase by at least the second power of age, thus the cumulative tumor rate should increase by at least the third power of age. The choice of 3 for the exponent is also supported by Druckrey (1967) who showed that for a constant incidence rate, the dose-duration relationship was represented by dt^n = constant with n ranging from 2-4 in his experiments. With n=3, Druckrey's results suggest that the dose used for half-lifetime exposure (and observation) can be reduced to one-eighth its value for lifetime exposure and the incidence rate will be the same. Druckrey's results then reflect the influence of both exposure duration and observation period on the resulting incidence rate.

This adjustment factor is consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Crump (1979, 1982) where the probability of cancer by age t at dose d is

$$P(d,t) = 1 - \exp[-f(t)*g(d)].$$

For comparison, Crump's (1982) time-to-tumor model is also used to estimate unit risk for the NCI rat and mice studies (NCI, 1976a,b, 1977) which had time-to-tumor data. In the above model, g(d) is the multistage polynomial, and f(t) is $(t-t_o)^k$, where t_o may be interpreted as minimum induction time.

Interpretation of Quantitative Estimates

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface

area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors. The exposure levels used in the unit risk calculations (1 μg/ℓ, 1 μg/m³) correspond to estimated intake of 2 μg/day via ingestion and 20 μg/day via inhalation. The expected human intake rates for CCl_4 are in the same range: 4 μg/day from food, 9 μg/day from fluids and 13 μg/day from air (see Chapter 4). The assumed dose-response curve is quite linear in this dose range so that the risk is proportional to exposure level, i.e., the upper limit estimate of risk is the unit risk multiplied by the exposure concentration.

The unit risk estimate can give a rough indication of the relative potency of a given agent compared with other carcinogens. The comparative potency of different agents is more reliable when the comparison is based on studies in the same test species, strain and sex, and by the same route of exposure. For unit risk estimates for air, the preferable studies would use exposure by inhalation.

The quantitative aspect of the carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process (e.g., setting regulatory priorities, evaluating the adequacy of technology-based controls, etc.). However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the low-dose linear extrapolation model used here provides a rough, but plausible estimate of the upper-limit of risk, i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower. The risk estimates presented in subsequent sections should not be regarded as accurate representations of the expected

cancer risks even when the exposures are accurately defined. The estimates presented may be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

Unit Risk Estimates for Ingestion Exposure

The unit risk estimates based on human equivalent doses as discussed above are given in Table 2. Since the NCI studies (1976a,b, 1977) on rats and mice were the only ones to present time-to-tumor data, they are the only data sets evaluated using the time-to-tumor model. Both the maximum likelihood estimates (MLE) and upper 95% confidence limits are presented, as well as their geometric means. For the NCI (1976a,b) mouse data, the goodness-of-fit criterion was not satisfied ($\chi^2 = 14.4$) for the multistage (and one-hit) model. The risk estimates are presented anyway since the model cannot be fitted to the data if the high dose group is deleted, due to the 100% response at the low dose. Because of the protective approach discussed earlier which led (in part) to the adoption of the multistage model, and because the MLE does not account for estimation errors due to small sample sizes, the 95% upper limit on risk is preferred. Furthermore, since no study was entirely adequate for risk assessment purposes, the geometric mean of the upper confidence limits is preferred as the most plausible upper limit estimate of unit risk. For lifetime ingestion of 2 ℓ/day of water, the recommended (based upon present information and current understanding of carcinogenesis) estimate of unit risk (concentration of 1 μg/ℓ) is 3.7×10^{-6}.

ALTERNATIVE METHODOLOGICAL APPROACHES

The methods described above, which have been adopted by the Carcinogen Assessment Group, are consistently conservative, i.e., tending toward high estimates of cancer risk. The aspect which contributes most to this conservatism is the choice of the linearized multistage model for low-dose

TABLE 2

Human Equivalent Unit Risk Estimates for Ingestion Exposure with Specific Adjustments[a]

Data Set	Extrapolation Model			
	Multistage[b]		Time-to-Tumor[b]	
	MLE	UL	MLE	UL
Della Porta et al. (1961)	2.1E-5	3.4E-5	c/	
Edwards et al. (1942)	7.1E-6	9.4E-6	c/	
NCI (1976) mouse	1.4E-6	1.8E-6	1.8E-6	2.2E-6
NCI (1976) rat	1.9E-7	3.1E-7	3.1E-7	5.3E-7
All (geometric mean)	2.5E-6	3.7E-6	7.5E-7	1.1E-6

[a]For ingestion of 1 μg CCl_4 per ℓ water daily for life. Species conversion uses dose/body surface area. Duration adjustment for partial lifetime experiment used for Edwards et al. (1942) study is (fraction life-span)$^{-3}$.

[b]MLE = Maximum likelihood estimate; UL = upper 95% confidence limit.

[c]No time-to-tumor data were available for these studies.

extrapolation. Other extrapolation models have been suggested, and are included below for comparison. These other models generally give lower estimates of risk than does the multistage model.

The various adjustment factors can also be calculated in different ways. The uncertainties related to the several models and adjustment factors and their influences on the risk estimates are discussed below. Generally, most of the uncertainty in estimating cancer risk from animal data is due to the limited data available in the bioassays, especially due to the high dose levels used, so that almost nothing is known about the shape of the dose-response curve at low doses or about the differences in low-dose incidence rates across species.

Low-Dose Extrapolation Models

Four models are used to extrapolate from the region of the experimental ingestion data to the levels corresponding to 1 μg/ℓ (Albert, 1983). All of these models relate exposure level to the incidence of tumor-bearing animals (Table 3). The "linearized" multistage model is constrained to have non-negative parameter values, and has the same number of parameters as the number of dose groups (including the control group). The one-hit model has two parameters. These two models are linear at sufficiently low doses. The Weibull model has three parameters. When only two dose groups exist, the Weibull exponent is set at 1, and then the Weibull model is also linear at low doses. The log probit model is used to represent a class of models which are not linear at low doses. The multistage reduces to the one-hit if only two dose groups exist. With only two dose groups, the Weibull parameter k is set to 1 and the Weibull model also reduces to the one-hit model. Currently, as discussed previously, there is insufficient evidence to provide strong support for any low-dose extrapolation model, although there is some justification for low-dose linearity.

usually $n_d - 1$ parameters

true if $n_d - 1$

TABLE 3

Low-dose Extrapolation Models Used in Unit Risk Calculation

Model	Functional Form*	Comments
Multistage	$P(d) = 1-\exp(-q_0 - q_1 d^2 - \ldots - q_k d^k)$	$q_i \geq 0$, all i
One-hit	$P(d) = 1-\exp(-q_0 - q_1 d)$	$q_0, q_1 \geq 0$
Weibull	$P(d) = 1-\exp(-q_0 - q_1 d^k)$	$q_0, q_1 \geq 0$
Log-probit	$P(d) = C + (1-C)\,\phi\,(A + B \log d)$	$\phi(x)$ = cumulative normal distribution ($\mu = 0$, $\sigma^2 = 1$)
Time-to-Tumor	$P(d) = 1-\exp[(-q_0 - q_1 d - q_2 d^2)(t-t_0)^k]$,	$t \geq t_0$, $q_i \geq 0$, all i, $k \geq 0$
	$= 0$	$t < t_0$, t_0 = minimal induction time

*d = animal dose (mg/day). The parameters q_0, q_1, q_2 etc., A, B, C, t_0, k are all determined by statistically fitting each model to the animal dose-response data. P(d) = cancer risk at dose d. Note that unit risk is based on excess risk = $(P(d)-P(0))/(1-P(0))$, where P(0) is background incidence.

In addition, since the NCI (1976a,b, 1977) data provide information pertaining to early mortality and time-to-tumor estimates, a multistage Weibull model with five parameters (Crump, 1982) is also used (see Table 3). The time-to-tumor estimates are based largely on time-to-mortality with subsequent discovery of tumors. Since the NCI (1976a,b, 1977) studies are the only ones involving more than two dose groups, they are also the only data sets to which all four previous models can be applied.

Unit Risk Calculation Approach

Each low-dose extrapolation model is applied to the original unadjusted animal data. The resulting risk estimate is then converted into equivalent human unit risk by multiplication by several factors to adjust for experiment duration (if partial lifetime), species differences and, if necessary, route conversion. Uncertainties in each adjustment factor are investigated by changing the choice of each adjustment model and/or the assumed parameter values in the model. There is insufficient information to allow the alternatives to be characterized by likelihood or error distributions; hence, all decisions are based on scientific judgment. The adjustment categories and their decision alternatives are given in Table 4.

Each animal risk estimate obtained by fitting a low-dose extrapolation model to the animal data is presented as the maximum likelihood estimate (MLE) and, when possible, as the upper 95% confidence limit. The confidence limit is statistically more stable; the MLE may show substantial sensitivity to small changes in the original data. Some data errors are expected due to diagnostic uncertainties generally leading to underdetection, i.e., missed tumors. The confidence limit on risk, however, reflects sample size and random variability, and may be much higher than the MLE. Both estimates are investigated for their sensitivities to such data errors.

TABLE 4

Alternatives for Judgmental Decisions in Cancer Unit Risk Estimation

Decision Category	Alternatives
Low-dose extrapolation	Model: Multistage, one-hit, Weibull, log probit
	Estimator: Maximum likelihood estimate, upper 95% confidence limit
Equitoxic dose across species	Model: Dose/bw, dose/body surface area
Adjustment for partial lifetime experiment	Model: $(L/L_e)^k$, k = 1-4

The risk estimate from the low-dose extrapolation is based on average daily intake level. Gavage studies add uncertainty since gastrointestinal effects may be due to the repeated high local concentrations and may not occur if the same daily dose were given continuously, hence at a lower local concentration. Since insufficient pharmacokinetic information exists to adjust for intermittent exposure, the TWA daily intake rate is used.

The extrapolation from risk based on partial lifetime experiments to risk from lifetime exposure uses the factor: $(L/L_e)^k$, where L is life-span and L_e is the duration of the experiment. As discussed previously, there is some evidence from human and animal studies to support an exponent of 3. Druckrey (1967) found that, at constant risk, fitting the model dt^n = constant to a series of data on nitrosamines gave values of n of 2-4. Studies of age-specific cancer rates in humans give estimates of k at 3 or higher. The concept of total dose (dose rate x duration) or similarly time-weighted-average dose for the experiment has been used as an indication of toxic severity, but has not been verified for cancer risk. It is included here for completeness and is represented by the case k=1 in the adjustment factor. There is insufficient information at present to allow precise determination of k for most chemicals. In the absence of such information, the sensitivity of the risk estimate to k is demonstrated by varying k between 1 and 4, and displaying the resulting range of risk estimates.

The conversion factor for species differences is presently based on models for equitoxic dose. The two general models currently used are based on body burden, dose/bw = constant (Stara and Kello, 1974); and metabolic rate, dose/body surface area = constant (Mantel and Schneiderman, 1975; Calabrese, 1982). In the absence of pharmacokinetic data related to

toxicity on the test chemical for the experimental species and for humans, both models are used.

The conversion of administered dose from one route to another (e.g., ingestion to inhalation) is not well understood. The approach by Stockinger and Woodward (1958) uses approximate net absorption fractions and daily intake rate to convert from one route to an equitoxic exposure level via another route. This approach, discussed below, is used to give approximate estimates of exposure levels when insufficient data exist for the desired route, although the estimates are acknowledged as being highly uncertain and probably inaccurate.

Unit Risk Estimates for Ingestion Exposure

The unit risk estimates based on human equivalent doses consistent with previous guidelines (Federal Register, 1980b) are given in Table 5 for the four data sets and the applicable models. Note that for the NCI mouse and rat data, the unconstrained Weibull and unconstrained log probit models could not be used to estimate risk. The failure of the computer algorithm to yield meaningful results is attributed to the virtually flat slope at the low and high dose data. This caused the extrapolated risk to be essentially dose-independent, i.e., the same as the risk in the dosed groups regardless of the level of dose. The successfully applied models were fitted to the original animal data using average daily intake (mg/day); their parameter estimates are given in Table 6. The human risk was then calculated by multiplying the animal unit risk by the adjustment coefficients reflecting partial lifetime exposure and species conversion. The low-dose extrapolation of the NCI rat data is shown in Figure 1 as an example of the difference in unit risk estimation (risk at 1 μg/ℓ) due only to selection of extrapolation model. The risk projections have not been adjusted for species

TABLE 5

Unit Risk Estimates for Ingestion[a]

Study	Model (type of estimate)[b]					
	Multistage[c]		Time-to-Tumor		Weibull	Log Probit
	(MLE)	(UL)	(MLE)	(UL)		
Della Porta et al. (1961)	2.1E-5	3.4E-5	d/		e/	e/
Edwards et al. (1942)	7.1E-6	9.4E-6	d/		e/	e/
NCI (1976) mouse	1.4E-6	1.8E-6	1.8E-6	2.2E-6	f/	f/
NCI (1976) rat	1.9E-7	3.1E-7	3.1E-7	5.3E-7	f/	f/

[a]For ingestion of 1 μg CCl_4 per ℓ water daily for life. Species conversion uses dose/body surface area.

[b]MLE = Maximum likelihood estimate; UL = upper 95% confidence limit.

[c]The one-hit model results agreed with the multistage model results to three significant figures.

[d]No time-to-tumor data were available for these studies.

[e]These models have three parameters which could not be fit by the two dose groups in these studies.

[f]The unconstrained Weibull and unconstrained log probit models could not be used to estimate unit risk for these studies. See text.

TABLE 6

Parameter Estimates for the Low Dose Extrapolation Models Fitted to Animal Data[a]

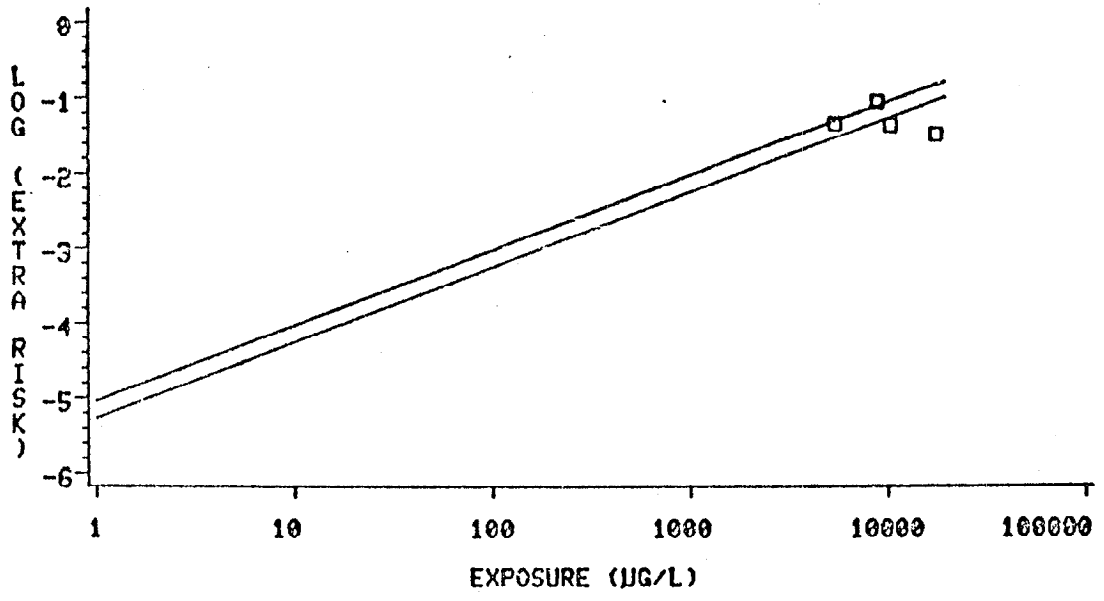
Study	Multistage				Time-to-tumor				
	q_0	q_1	q_1^*	q_2	q_0	q_1	q_1^*	t_0	k
Della Porta et al., 1961	0	0.784	1.28	--	--	--	--	--	--
Edwards et al., 1942	0.0133	0.0415	0.0549	--	--	--	--	--	--
NCI, 1976 mouse	0.0397	0.133	0.167	0	0.13E-12	4.96E-13	5.90E-13	0	5.87
NCI, 1976 rat	0	2.71E-3	4.47E-3	0[b]	0	2.47E-13	4.15E-13	0	5.03

[a]See Table 3 for model definitions. q_0 is dimensionless. q_1 and q_1^* are in $(mg/day)^{-1}$. q_2 is in $(mg/day)^{-2}$. t_0 is in (wk). All values are maximum likelihood estimates except q_1^*, which is the upper 95% confidence limit for q_1. E denotes powers of 10, i.e., $0.16E-13 = 0.16 \times 10^{-13}$.

[b]Estimates of q_3 and q_4 were also zero.

RISK ESTIMATES FOR CARBON TETRACHLORIDE

COMPARISON OF EXTRAPOLATION MODELS
DATA FROM NCI(1976) RAT STUDY



UPPER CURVE IS MLE TIME-TO-TUMOR MODEL
LOWER CURVE IS MLE MULTISTAGE MODEL

FIGURE 1

Comparison of low-dose extrapolation models. The models are applied to the NCI (1976) rat data: upper curve is MLE for time-to-tumor model, lower curve is MLE for multistage model. Risks are for animals. The curves are spline fits to the data; one data point not pictured is at the origin (0, 0). At 1 μg/ℓ the risk estimates from the curves differ by a factor of 17.

differences so that the actual rat response rates (the 4 data points) can be plotted. The logarithmic plot precluded the display of the control group response (0%).

The possibility of errors in the incidence data increase the uncertainty in the unit risk estimates. Such errors are usually under-detection of tumors (Anonymous, 1983), causing positively responding animals to be classified as nonresponders, and leading to underestimates of the unit risk. Furthermore, previous studies have suggested that the multistage maximum likelihood estimate, q_1, is more sensitive to such data errors than is the upper confidence limit, q_1*. The sensitivities of q_1 and q_1* to data changes are investigated for each of the three oral studies under consideration.

Discussion of possible detection errors in incidence data at the "ED_{01}" conference* suggested the following: that misclassification is more likely to underestimate the incidence of tumor-bearing animals than overestimate the incidence, and that having one animal misclassified in a study of 50 animals is not rare. The sensitivity of the parameter estimates to data errors was determined here by increasing the number of responders by 1 for every 50 animals tested (e.g., 1 for up to 50 animals, 2 for 51-100 animals, etc.), and then recalculating the parameters. The results are presented in Table 7. For each of these studies, the MLE (q_1) seems to be approximately as sensitive as the upper bound (q_1*) to the data changes. Note that the parameter estimates are obtained from the raw data, are unadjusted and, thus, are not comparable across studies.

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*"Workshop on Biological and Statistical Implications of the ED_{01} Study and Related Data Bases," Deer Creek State Park, Ohio, September 13-16, 1981.

TABLE 7

Sensitivity of Multistage Parameter Estimates to Changes in the Incidence Data

Study	Range of Parameter Values[a]			
	q_1 (MLE)	Relative Range[b]	q_1* (upper limit)	Relative Range[b]
Della Porta et al., 1961	0.758-0.907	16%	1.26-1.46	14%
Edwards et al., 1942	0.0402-0.0452	11%	0.0537-0.0592	9%
NCI, 1976 (mouse)	0.151-0.152	0.6%	0.227-0.228	0.4%
NCI, 1976 (rat	1.45E-4, 1.23E-3	89%	1.02E-3, 1.95E-3	48%

[a]These estimates are unadjusted for species or duration and are not comparable across studies. Relative ranges are comparable across studies.

[b]Relative range = (high-low)/high. The original data do not necessarily give the lower estimate, so the relative range does not necessarily represent the change from the original parameter estimates.

In Table 5, in line with previous guidelines (Federal Register, 1980b), the species conversion model was dose per body surface area and partial lifetime risk was adjusted to lifetime risk by the ratio $(L/L_e)^3$. The effects of using dose per body weight instead for species conversion, as well as exponents of 1 (total dose), 2 or 4 for the partial lifetime to lifetime adjustment are shown by the coefficients in Table 8 and the range of unit risk estimates in Table 9. Note that the adjustment coefficients in Table 8 are comparable only within a study, not across studies. The unit risk estimates in Table 9 are comparable across studies.

UNIT RISK ESTIMATES FOR INHALATION EXPOSURE

The unit risk for inhalation exposure is the excess cancer risk for lifetime exposure to 1 μg CCl_4/m^3 air. No inhalation cancer studies have been located which contain adequate dose-response information. However, the unit risk can be estimated from ingestion studies by assuming that the same daily intake rate results in the same lifetime risk. This assumption has not been thoroughly tested with other chemicals. In addition, each of the studies used for estimating oral unit risk has deficiencies. Therefore, the unit risk estimate for inhalation exposure should be considered approximate based on assumptions that have yet to be proven.

To estimate the risk corresponding to the concentration of 1 μg CCl_4/m^3 air, the effective dose in terms of mg/kg/day corresponding to 1 μg/m³ must first be estimated. Assuming an air intake of 20 m³/day (ICRP, 1975) and a 40% absorption rate by inhalation for humans (as recommended in this document), this effective dose can be estimated for a 70 kg human:

$$d_{air} = [20\ m^3/day \times 0.40 \times 1/(70\ kg)] \times 10^{-3}\ mg/m^3$$

$$= 1.14 \times 10^{-4}\ mg/kg/day = 7.98 \times 10^{-3}\ mg/day$$

TABLE 8

Adjustment Coefficients for Estimating Human Unit Risk
(duration adjustment) X (species adjustment)

Species Conversion: duration exponent k		Study[a]			
		Della Porta et al. (1961)	Edwards et al. (1942)	NCI (1976a,b, 1977) (mouse)	NCI (1976a,b, 1977) (rat)
Surface area:	1	0.0134	0.0140	0.00543	0.0346
	2	0.0134	0.0345	0.00543	0.0346
	3[b]	0.0134	0.0852	0.00543	0.0346
	4	0.0134	0.210	0.00543	0.0346
Body weight:	1	0.00154	0.00105	0.00040	0.00643
	2	0.00154	0.00259	0.00040	0.00643
	3	0.00154	0.00640	0.00040	0.00643
	4	0.00154	0.0158	0.00040	0.00643

[a]Only the Edwards et al. (1942) study had partial lifetime experiment duration requiring the duration adjustment factor: $(\text{fraction lifespan})^{-k}$.

[b]The animal unit risk estimates were multiplied by the coefficients in this row (k = 3 in duration factor, dose/surface area species conversion) to obtain the human unit risk estimates in Table 4.

TABLE 9

Range of Unit Risk Estimates for Oral Exposure[a]

Study	Multistage Model		Time-to-Tumor Model	
	MLE	Upper Limit	MLE	Upper Limit
Della Porta et al. (1961)	2.4E-6, 2.1E-5	3.9E-6, 3.4E-5	NA[b]	
Edwards et al. (1942)	8.7E-8, 1.7E-5	1.2E-7, 2.3E-5	NA	
NCI (1976) mouse	1.0E-7, 1.4E-6	1.3E-7, 1.8E-6	1.3E-7, 1.8E-6	1.6E-7, 2.2E-6
NCI (1976) rat	3.5E-8, 1.9E-7	5.8E-8, 3.1E-7	5.8E-8, 3.1E-7	9.8E-8, 5.3E-7

[a]Obtained by changing the adjustment coefficients for species differences and partial lifetime experiment duration. See text.

[b]NA = Not applicable. Time-to-tumor data not available.

which is 4.0 times the unit intake for oral exposure (1 μg/ℓ = $2x10^{-3}$ mg/day). The unit risk for inhalation is then estimated from the oral studies by multiplying the oral unit risk by 4.0. Based on the range of recommended risks (based upon present information and current understanding of carcinogenesis) derived from the four oral data sets, and using the linearized multistage model with the dose per body surface area conversion across species, and with the exponent k=3 in the adjustment for partial lifetime study, the upper limit estimate of unit risk for inhalation exposure ranges from $1.2x10^{-6}$ to $1.4x10^{-4}$ with a geometric mean of $1.5x10^{-5}$. As a measure of uncertainty, all models and adjustments were considered (see Table 9). The resulting upper limit unit risk estimate for inhalation exposure ranged from $2.3x10^{-7}$ to $1.4x10^{-4}$.

Because of the uncertainties in both the qualitative and quantitative aspects of risk assessment, the actual cancer risks may be lower than the best unit risks presented above, which should be regarded only as plausible upper-limits. The unit risk estimates are calculated using a dose-response extrapolation model which is linear at low doses. This low-dose linearity is based on mutagenicity studies and on some similarities between mutagenesis and carcinogenesis. Since the results on the mutagenicity of CCl_4 are inconclusive, the selected extrapolation model may be inappropriate, and hence the unit risk estimates are uncertain.

MULTIPLE EXPOSURE SITUATIONS

The above information provides recommended route-specific cancer risk estimates associated with exposure to given units of CCl_4. These estimates may be conservative due to the choice of the multistage model for dose extrapolation and the various adjustment factors. Nevertheless, unit

risks for cancer presented above are defined for independent water and air exposures in that their computation assumes 100% of the insult is via the stated route.

When exposure is by both oral and inhalation routes, an additivity assumption can be used to calculate the risk associated with the concurrent exposures. It is a general recommendation to use the additivity assumption which is made since the available data on CCl_4 are limited and do not allow the presentation of a defensible alternative. As new information becomes available, other alternatives should be considered. Here the additivity assumption is that the risk associated with exposure to a given chemical via two routes concurrently is roughly the sum of the risks associated with each independent route-specific exposure. Since interactions between the concurrent routes of intake cannot be quantified, uncertainty surrounds the resulting risk estimate that is derived from the concurrent risks.

In applying the assumption of additivity, the risks rather than the doses associated with each route are added, but the mere summation of these risks is presently justifiable only when doses are low enough that no interaction occurs between the two routes. Furthermore, the amounts of 1 μg/ℓ and 1 μg/m³ are concentrations in water and air, respectively, not doses. The dose can be estimated by assuming consumption of 2 ℓ water/day over the lifetime. Thus, the daily dose corresponding to a concentration of 1 μg/ℓ water would be 2 ℓ/day x 1 μg/ℓ = 2 μg/day.

COMPARISON OF RISK ESTIMATES FOR VARIOUS CARCINOGENS

The carcinogenic risk from exposure to CCl_4 is compared to the risk from exposure to other potential carcinogens in Table 10. For comparison

TABLE 10

Relative Carcinogenic Potencies Among 53 Chemicals Evaluated by the Carcinogen Assessment Group as Suspect Human Carcinogens[a,b,c]

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log_{10} index)
Acrylonitrile	0.24 (W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	2924	312.3	$9x10^{+5}$	6
Aldrin	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	15 (H)	149.8	$2x10^{+3}$	+3
B[a]P	11.5	252.3	$3x10^{+3}$	+3
Benzene	$5.2x10^{-2}$ (W)	78	$4x10^{0}$	+1
Benzidine	234 (W)	184.2	$4x10^{+4}$	+5
Beryllium	1.40 (W)	9	$1x10^{+1}$	+2
Cadmium	6.65 (W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	0.13	153.8	$2x10^{+1}$	+1
Chlordane	1.61	409.8	$7x10^{+2}$	+3
Chlorinated Ethanes				
1,2-dichloroethane	$6.9x10^{-2}$	98.9	$7x10^{0}$	+1
1,1,2-trichloroethane	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1
1,1,2,2-tetrachloroethane	0.20	167.9	$3x10^{+1}$	+1
Hexachloroethane	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,1-trichloroethane	$1.6x10^{-3}$	133.4	$2x10^{-1}$	-1
Chloroform	$7x10^{-2}$	119.4	$8x10^{0}$	+1

TABLE 10 (cont.)

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log_{10} index)
Chromium	41 (W)	104	$4x10^{+3}$	+4
DDT	8.42	354.5	$3x10^{+3}$	+3
Dichlorobenzidine	1.69	253.1	$4x10^{+2}$	+3
1,1-Dichloroethylene	0.147 (I)	97	$1x10^{+1}$	+1
Dieldrin	30.4	380.9	$1x10^{+4}$	+4
Dinitrotoluene	0.31	182	$6x10^{+1}$	+2
Diphenylhydrazine	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	1.14	143	$2x10^{+2}$	+2
Bis(chloromethyl)ether	9300 (I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	8.51	187.9	$2x10^{+3}$	+3
Ethylene oxide	1.26 (I)	44.1	$6x10^{+1}$	+2
Heptachlor	3.37	373.3	$1x10^{+3}$	+3
Hexachlorobenzene	1.67	284.4	$5x10^{+2}$	+3
Hexachlorobutadiene	$7.75x10^{-2}$	261	$2x10^{+1}$	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	$1x10^{+3}$	+3
alpha isomer	11.12	290.9	$3x10^{+3}$	+3
beta isomer	1.84	290.9	$5x10^{+2}$	+3
gamma isomer	1.33	290.9	$4x10^{+2}$	+3

TABLE 10 (cont.)

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log_{10} index)
Methylene chloride	$6.3x10^{-4}$	84.9	$5x10^{-2}$	-1
Nickel	1.15 (W)	58.7	$7x10^{+1}$	+2
Nitrosamines				
Dimethylnitrosamine	25.9 (not by q_1*)	74.1	$2x10^{+3}$	+3
Diethylnitrosamine	43.5 (not by q_1*)	102.1	$4x10^{+3}$	+4
Dibutylnitrosamine	5.43	158.2	$9x10^{+2}$	+3
N-nitrosopyrrolidine	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-N-methylurea	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	$4.92x10^{-3}$	198	$1x10^{0}$	0
PCBs	4.34	324	$1x10^{+3}$	+3
Phenols				
2,4,6-trichlorophenol	$1.99x10^{-2}$	197.4	$4x10^{0}$	+1

TABLE 10 (cont.)

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log_{10} index)
Tetrachlorodibenzo-p-dioxin (TCDD)	1.56×10^{5}	322	$5 \times 10^{+7}$	+8
Tetrachloroethylene	3.5×10^{-2}	165.8	6×10^{0}	+1
Toxaphene	1.13	414	$5 \times 10^{+2}$	+3
Trichloroethylene	1.9×10^{-2}	131.4	2.5×10^{0}	0
Vinyl chloride	1.75×10^{-2} (I)	62.5	1×10^{0}	0
Vinylidene chloride	0.13 (I)	97	$1 \times 10^{+1}$	+1

[a]Animal slopes are 95% upper-limit slopes based on the linear multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure, and H (human drinking water exposure). Human slopes are point estimates, based on linear non-threshold model.

[b]The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

[c]Not all the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

purposes, the risks are based on lifetime esposure to 1 mg/kg/day. These estimates are derived from various studies on humans and animals, for oral and inhalation exposure. These estimates are derived with the linearized multistage model with species adjustment using dose/body surface area and adjustment for partial lifetime study by using the exponent k=3. Carbon tetrachloride has a relatively low potency compared to the others in the group.

A relative potency index, proposed by the Carcinogen Assessment Group, is also presented in Table 10 for each chemical. This index represents the risk posed by daily exposure to 1 mMol of carcinogen per kg body weight, and thus allows comparison of risks from exposure to the same number of molecules. The frequency distribution of the relative potency indices, rounded to the nearest order of magnitude, is shown in Figure 2.

SUMMARY/CONCLUSIONS

No single study was entirely adequate for risk estimation. Thus, the unit risk estimate is based on the geometric mean of the individual unit risk estimates from the four studies considered. The studies contained data on three animal species: rats, mice and hamsters. From these data, the recommended upper limit unit risk estimates (based upon present information and current understanding of carcinogenesis) for ingestion are in the range of 3.1×10^{-7} to 3.4×10^{-5} with a geometric mean of 3.7×10^{-6}. Using these same oral data, unit risk estimates for inhalation are in the range of 1.2×10^{-6} to 1.4×10^{-4} with a geometric mean of 1.5×10^{-5}. Since no study was entirely adequate for risk assessment purposes, the geometric mean of the upper confidence limits is preferred as the most plausible upper limit estimate of unit risk.

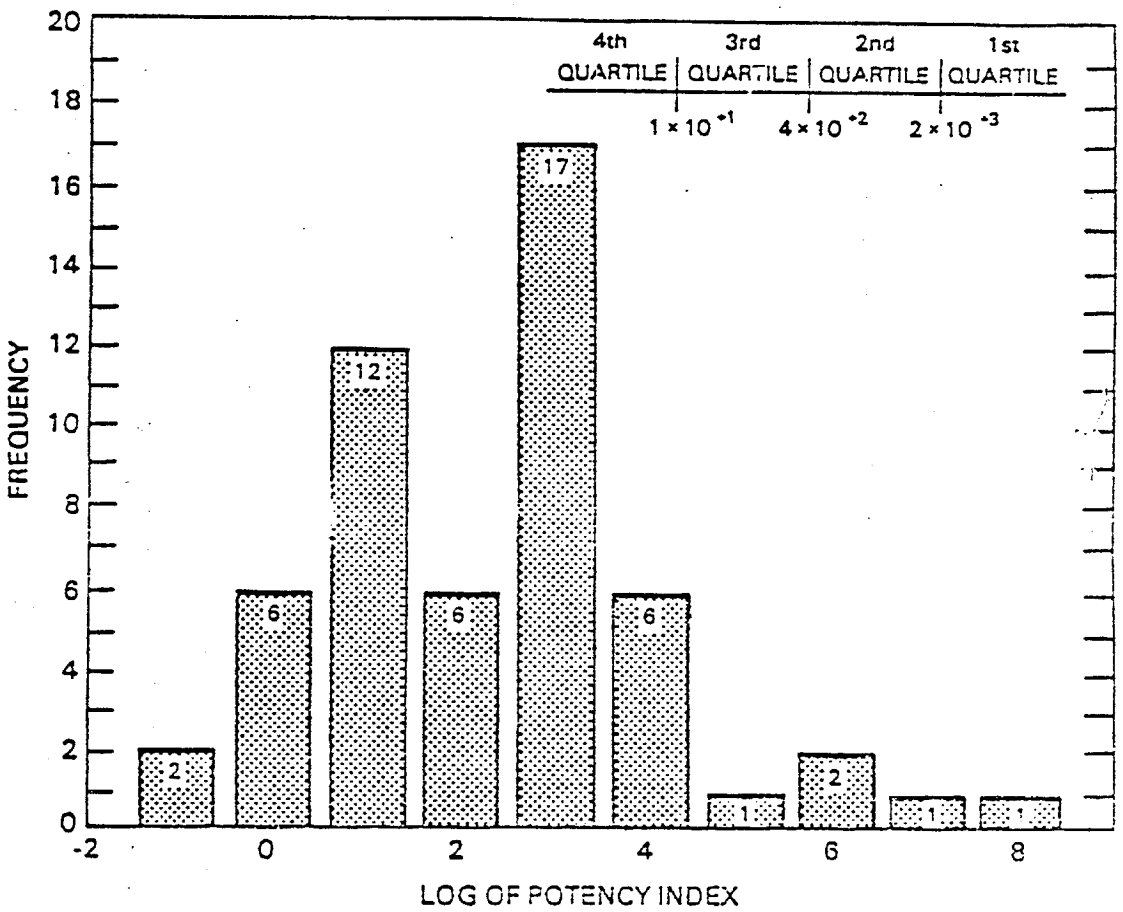

FIGURE 2

Histogram Representing the Frequency Distribution of the Potency Indices of 54 Suspect Carcinogens Evaluated by the Carcinogen Assessment Group

TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CARBON TETRACHLORIDE

PART C - PUBLIC COMMENTS AND RESPONSES

April 1987

PART C - PUBLIC COMMENTS AND RESPONSES TO THE DRAFT AND FINAL PART A AND PART B CARBON TETRACHLORIDE REPORT

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I. Chevron Environmental Health Center, Inc.

Chevron

Chevron Environmental Health Center, Inc.
A Chevron Research Company Subsidiary
15299 San Pablo Avenue, Richmond, California
Mail Address: P.O. Box 4054, Richmond, CA 94804-0054

R. D. Cavalli
Manager
Product Evaluation and Community Health

September 18, 1986

Carbon Tetrachloride Risk Assessment

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

Dear Mr. Loscutoff:

The draft risk assessment on carbon tetrachloride prepared for the Air Resources Board by the Department of Health Services (DHS) raises a significant question not directly encountered to date in the air toxics program, namely, "what constitutes sufficient valid data upon which to base a quantitative risk assessment?". While the studies presented by the DHS may be sufficient to qualitatively characterize the carcinogenic potential of carbon tetrachloride, the serious limitations that exist in the data, which are recognized by the DHS, prevent their application in quantitative risk estimation. While a range of risk can be derived from these data, we believe the very low nonstatistical confidence in such values severely limits their utility for the risk manager. Risk assessment, even when it is based on adequate reliable data, is uncertain due to the many assumptions that must be made and which may not be applicable to all of the individuals in the potentially exposed human population. We urge the Board to use more traditional approaches in assessing the potential adverse effects from this compound rather than developing and applying these highly uncertain and potentially misleading quantitative risk estimates (our reasons are set forth below). Should this be unacceptable, we suggest that the Board acquire additional data to better define the dose-response nature of carbon tetrachloride's potential carcinogenicity as its first step in the risk management of this compound. Such data would enable the Board to more confidently predict the excess risk which might be incurred by a population living in the vicinity of a specific source, and more accurately assess the benefits and attendant costs of any control options that might be considered.

The DHS has properly pointed out the serious limitations in the data upon which it has based a quantitative risk assessment. The flaws include improper or inadequate controls, small exposure groups, inadequate or inconsistent dosing regimens, incomplete histopathological examinations, premature sacrifice of experimental animals, high noncancer mortality rates, and questionable relevance of the dose route (oral gavage) to the

human exposure situation under evaluation. In addition, there is considerable debate over the human relevance of rodent liver tumors. It is unclear why flaws similar to these, and of equal severity, led the DHS to exclude several studies from further consideration, but not all. Given the serious limitations of the studies selected, their use in quantitative risk assessment is inconsistent with the principles discussed in both the State and Federal cancer risk assessment guidelines.

Recent data presented by Condie, et al. (Fundamental & Appl. Tox. 7:199-206, 1986) raises additional concerns over the appropriateness of using the results of animal gavage studies which utilize an oil vehicle to predict the carcinogenic risk encountered by humans from the inhalation of ambient concentrations of carbon tetrachloride. The use of oil as a vehicle was found to significantly increase both the incidence and severity of carbon tetrachloride's hepatotoxicity over that encountered when the agent is administered in water. This effect may be due to alteration of either the distribution and metabolism of carbon tetrachloride, or the nutritional status of the animal by the oil vehicle. Thus, it appears that the use of an oil vehicle further limits the utility of the studies selected by DHS for quantitatively estimating the risks to humans from inhalation exposure.

Finally, it is not clear why the study by Kotin, et al. (1962), in which carbon tetrachloride administered by gavage to mice failed to produce tumors, was excluded from the DHS's discussion of the carcinogenicity studies performed in mice.

Thank you for your continued interest in the public's comments concerning the toxic air contaminants program. Questions concerning our comments should be directed to R. M. Wilkenfeld of my staff at (415) 231-6018.

Sincerely,

R. D. Cavalli
Manager, Product Evaluation
and Community Health

RMW:dcc-C/0986-123

STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

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

January 23, 1987

Mr. R. D. Cavalli
Manager, Products Evaluation
and Community Health
Chevron Environmental Health Center, Inc.
P. O. Box 4054
Richmond, California 94804

Dear Mr. Cavalli:

Comments on the Draft Carbon Tetrachloride Report

Thank you for your comments on the Draft Carbon Tetrachloride Report. We referred your comments on "Part B - Health Effects of Carbon Tetrachloride" to the Department of Health Services (DHS). Their response to your comments are attached to this letter. Your comments and the DHS response will be included in Part C of the Final Draft Report on Carbon Tetrachloride.

We will have the Final Draft Report on Carbon Tetrachloride (Part A with the Overview, Part B, and the Part C) available for review within the next month. A copy of this report will be sent to you when it becomes available.

If you have any further questions on this matter, please contact Gary Murchison, Manager of the Compound Evaluation Section, at (916) 322-8521.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Peter D. Venturini
Michael Lipsett, DHS

II. DOW Chemical U.S.A.

DOW CHEMICAL U.S.A.

September 22, 1986

WILLARD H. DOW CENTER
MIDLAND, MICHIGAN 48674

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

ATTENTION: CARBON TETRACHLORIDE

INTRODUCTION

In his letter of August 15, 1986, Peter Venturini, Chief of the Secondary Source Division of the California Air Resources Board (CARB), announced the availability of a two part draft report designed for the consideration of carbon tetrachloride as a toxic air contaminant in the State of California. Part A discusses the uses, emissions and exposure to ambient concentrations of carbon tetrachloride in California, while Part B discusses the effects of that compound on health and the risk from exposure to ambient concentrations.

As Part A states, the Dow Chemical Company manufactures carbon tetrachloride at Pittsburg, California. Dow, therefore, appreciates the opportunity to comment on this carbon tetrachloride draft report.

Mr. Venturini indicated, starting with carbon tetrachloride, CARB was initiating a new process for public review of such reports on alleged toxic air contaminants. The new process is intended to improve the ability of interested parties to have input into the process of identifying toxic air contaminants before the report is reviewed by the SRP. We applaud that intent. However, we are concerned that the rigid 30 day period from the time when draft reports are mailed to when written comments must be received may not always be long enough. This is important, because the initial comment period is the only opportunity for comments on Parts A & B in entirety. The later, even shorter, rigid 20 day comment period for the final draft will only allow comments on the report overview and revision made to the preliminary draft report. That is the last opportunity for any public comment.

These issues are very important to all sectors of the public...from industry to environmental groups. Thus we strongly urge slight extensions of these comment periods (perhaps by 2 weeks each) or some provision for case-by-case extension. The time period allowed for this initial carbon tetrachloride review is a good example of the possible need for additional review time. In mid-August, industry's environmental personnel were engaged in answering several Clean Air Act

AN OPERATING UNIT OF THE DOW CHEMICAL COMPANY

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Section 114 data requests as well as numerous other state requests associated with their air toxics programs. Then, almost simultaneous to Mr. Venturini's letter, we received for comment, the federal EPA overview and 12 inch thick, technical reports on their proposed hazardous organics national emissions standards for hazardous air pollutants (HON) project. Comments on that massive project were required by the September 17th National Air Pollution Control Techniques Advisory Committee (NAPTAC) meeting. Industry has been very hard pressed to physically examine its facilities and records for accuracy and currency of cited data and to assimilate its comments into response documents. An additional two weeks to review CARB's carbon tetrachloride drafts and to cross-check references to carbon tetrachloride in the federal EPA HON technical reports and the EPA/UNEP stratospheric ozone studies would have been greatly appreciated and would have led to a more thorough review.

TECHNICAL COMMENTS

As to uses of carbon tetrachloride in California, Dow Chemical restricts sales of this product and has not knowingly sold it into fumigant or pesticide production usage for more than ten years. Our California customers use it to manufacture chlorofluorocarbons (CFC's). We believe current control on emissions from carbon tetrachloride production and its further usage in fluorocarbon manufacture do thoroughly protect the health of people.

The draft report reviews possible exposure to carbon tetrachloride from drinking water, based on an examination of 2,500 California wells sampled. The California Department of Health Services indicated less than 2% of these wells, which included 753 large public water systems, have CCl_4 concentrations above the 0.5 ug/liter. DOHS concluded California results to be consistent with federal EPA findings where EPA estimated over 86% of the U.S. population is exposed to levels below 0.5mg/liter and 12.5% is exposed to 0.5 to 5 ug/liter. Recent EPA proposals to set the Maximum Contaminant Level (MCL) for carbon tetrachloride at 5ppb or 5 ug/liter will lead to continued protection of the California and entire U.S. population.

Part A of the draft report correctly references our <u>previous</u> producer projections for a 1 to 2% growth in carbon tetrachloride through 1990, due to increased chlorofluorocarbon demand for automotive refrigerants and foaming agents for the housing industry. However, evolving environmental concern for the possibility of chlorofluorocarbons causing depletion of stratospheric ozone has led to manufacturers to be a no-growth industry.

With regard to carbon tetrachloride's stratospheric ozone depletion potential, a couple points should be noted. First, even the Rand Report prepared under contract for the federal EPA on "Projected Use, Emissions, and Banks of Potential Ozone Depleting Substances" notes that greater than 90% of carbon tetrachloride is totally consumed in its manufacturing usage. Thus only a limited percentage of CCl_4 manufactured could ever be available for stratospheric interaction.

The federal EPA, in conjunction with the United Nation's Environmental Programme (UNEP), is currently conducting research for use in future agency decisions on whether or not to regulate CFC's or other chemicals that may affect the ozone layer. Again, only a very small percentage of the CCl_4 produced could ever be available for stratospheric interaction. The EPA clearly stated in 51 Fed. Reg. 1257-1260, January 10, 1987, that any further decision on regulation in this area must be based on further research and analysis, and should be evaluated in the context of international actions. The EPA, again through the Rand Corporation, is also investigating the implications of immediate adoptions of regulations versus waiting for improved scientific understanding of this matter. We would ask CARB to remember these uncertainties in its consideration of carbon tetrachloride as a toxic air contaminant.

Due to time constraints, we have been unable to conduct a detailed review of Park B of the draft report on the health effects of carbon tetrachloride. We are, however, enclosing a section of a report explaining our position on the tumorigenicity of carbon tetrachloride in experimental animals.

Carbon tetrachloride has exhibited carcinogenic response in certain test animals. However, it has not demonstrated carcinogenicity in humans at low levels.

The usage of carbon tetrachloride is declining. As indicated, the federal EPA has proposed canceling registrations of fumigants products containing carbon tetrachloride. This is likely to lead to prohibition of such fumigants in California and even further reduction of carbon tetrachloride exposures to Californians. The remaining exposures from production and subsequent CFC manufacture are controlled as to protect the health of people. Current levels of regulation and federal EPA proposals to regulate fugitive emissions, process vents, and storage tanks in carbon tetrachloride manufacturing processes via a hazardous organics national emission standard will serve to effectively protect human health. It is not necessary for regulation to be so stringent as to eliminate the carbon tetrachloride industry and its beneficial end products.

Carol Niemi

Carol Niemi
Chemicals & Metals Department
Environmental Affairs
Phone: 517/636-1636

/slg

Note: On September 18, 1986, Mr. Todd Wong speaking in Gary Murchison's absence, granted The Dow Chemical Company an extention until September 23, 1986, for receipt of these comments.

2. Tumorigenicity of Carbon Tetrachloride in Experimental Animals

A number of studies in experimental animals have shown that carbon tetrachloride can induce liver tumors in various species. (Edwards, 1941; Edwards *et al.*, 1942; Eschenbrenner and Miller, 1946; Della Porta *et al.*, 1961; Reuber and Glover, 1967; Reuber and Glover, 1970; NCI, 1976). The dose levels administered in the studies on mice and rats which resulted in a tumorigenic response were in excess of 1000 mg/kg/day. A tumorigenic response in hamsters occurred at a level approximately 1/10 of that which was needed to produce a tumorigenic response in rats. A summary of the dose levels resulting in a tumorigenic response in the various studies are presented in Table 5.

TABLE 5

Dose Level Resulting in Tumorigenic Response in Animals Administered Carbon Tetrachloride

Species (Strain)	Dose Level mg/kg/day	Reference
Rat (Buffalo)	approx. 1000[a] (1.3 mg/kg of a 50% soln.)	Reuber and Glover, 1967
Rat (Japanese, Osborne-Mendel, Wistar)	2080	Reuber and Glover, 1970
Mice (C_3H)	approx. 1200[a] (0.1 ml of a 40% soln.; 50 g mouse)	Edwards, *et al.*, 1942
Mice (Inbred strain L)	approx. 1200[a] (0.1 ml of a 40% soln.; 50 g mouse)	Edwards, 1942
Mice (Strain A)	2400, 4800, and 9600	Eschenbrenner & Miller, 1946
Mice ($B_6C_3F_1$)	1250, 2500	NCI, 1976
Hamster (Golden Syrian)	198 reduced to 99 (after 7 weeks)	Della Porta, 1961

[a]Calculated dose

a. Association with cirrhosis

The preponderance of the data in the literature indicates that the tumorigenic response to carbon tetrachloride occurred as a consequence of the induction of post-necrotic cirrhosis.

Carbon tetrachloride induced cirrhotic changes in experimental animals were observed as low as 47 mg/kg in rats, 159 mg/kg in mice and 199 mg/kg reduced to 99 mg/kg after 7 weeks in hamsters. The data from various studies are summarized in Table 6.

TABLE 6

Levels of Carbon Tetrachloride Producing Cirrhotic Changes in Experimental Animals

Species (Strain)	Route	Exposure Level-mg/kg	Exposure Reference
Rat (not identified)	Sub-cutaneous injection	2000	Cameron and Karunaratne, 1936
Rat (Buffalo)	Sub-cutaneous injection	approx. 1000	Rueber and Glover, 1967
Rat (Japanese, Osborne-Mendel, Wistar, Black & Sprague-Dawley)	Sub-cutaneous injection	2080	Reuber and Glover, 1970
Rat (Osborne-Mendel)	P.O.	94 & 47	NCI, 1976
Mice ($B_6C_3F_1$)	P.O.	1250 & 2500	NCI, 1976
Mice (C_3H,A,C,Y)	P.O.	159	Edwards and Dalton, 1942
Hamster (Golden Syrian)	P.O.	198 reduced to 99 (after 7 weeks)	Della Porta, 1961

b. Mechanism of Action

The occurrence of hepatomas (in mice) as a result of the induction of post-necrotic cirrhosis suggests that carbon tetrachloride is not a direct acting carcinogen (Louria and Bogden, 1980). This observation is not contraindicated by the results of various short-term mutagenicity tests nor by the preponderance of the evidence indicating little or no covalent binding to liver DNA. The short-term mutagenicity test results using Salmonella typhinurium TA100, TA1535, TA1538, and E. Coli K12 have been consistently negative (McCann et al., 1975; McCann and Ames, 1976; Uehleke et al., 1976; Uehleke et al., 1977, and Simmon and Tardiff, 1978). Rocchi et al., 1973, reported no evidence of covalent binding in vivo to nuclear DNA in the liver of mice and rats. Whereas, Diaz Gomez et al., 1975, reported small but significant in vivo binding of ^{14}C from ^{14}carbon tetrachloride to liver nuclear DNA of mice and rats; however, these investigators, and also Uehleke et al., 1977, concluded that it was possible that a non-genetic mechanism was relevant for carbon tetrachloride. Callen et al., 1980 reported increases in gene mutation and mitotic recombination on D7 strain of Saccharomyces cerevisiae at high toxic levels. Dean and Hodson-Walker, 1979, reported negative results in an in vitro chromosome assay using cultured rat liver epithelial cells. Craddock and Henderson, 1978, and Mirsalis and Butterworth, 1980, reported no induction of unscheduled DNA synthesis in hepatocytes of rats exposed in vivo.

B. Implications of Scientific Data in the Assessment of Risk/Safety for Man

The implications of the results of the various studies on carbon tetrachloride in the assessment of risk for man are two-fold: (1) because of the differences in the capacity to metabolize carbon tetrachloride to the toxic intermediate between the rodents and the rhesus monkey, the animal selected for use in the assessment of risk for man must be based on sound scientific rationale and/or data and (2) a tumorigenic response to carbon tetrachloride occurs as a consequence of the induction of post necrotic cirrhosis and levels and durations of exposure which do not cause significant tissue damage would not be expected to produce tumors.

Since the toxicity of carbon tetrachloride is associated with the metabolism of the chemical, the animal species that are capable of metabolizing the chemical most efficiently and rapidly will be most sensitive to its adverse effects. Mice and rats metabolize carbon tetrachloride more efficiently than the rhesus monkey; a finding which correlates with the level of the metabolizing enzyme cytochrome P-450 in the liver of these species. The rhesus monkey, the species and strain most like man in regard to the level of liver cytochrome P-450, has been reported to have a no-observed-effect-level in the range of 25 to <50 ppm in a chronic study.

The results of studies on all species have established the existence of species specific thresholds for the toxic effects of carbon tetrachloride. Adams et al., 1952 reported thresholds for the rat, guinea pig, rabbit and rhesus monkey in chronic inhalation studies, Prendergast et al., 1967 for the rat, guinea pig, rabbit and squirrel monkey in subchronic inhalation studies, and Alumot et al., 1976 for the rat in a chronic dietary feeding study. Furthermore, the lack of

significant toxicity in the rhesus monkey chronically exposed to carbon tetrachloride and the lack of reported evidence of the carcinogenicity in humans exposed to the chemical must be considered supportive of an alternate approach to the assessment of risk. In regard to the preliminary screening study on occupationally exposed cohorts in the dry cleaning industry (Blair et al., 1979), the study suffers from such environmental confounders as undefined exposure levels, concomitant exposure to other solvents, possibility of abuses in handling the solvent, high turnover rate among the dry cleaning employees potentially exposed to the highest levels, and the lack of an appropriate control group. Regarding the latter point, data from the U.K. on the risk of development of various forms of cancer between six different social classes indicate that there is a distinct social class trend for some forms of cancer with the higher levels being associated with the lower social (-economic) classes. These findings and the significance for the workers employed in dry-cleaning establishments must be considered in the evaluation of the study results. The types of cancer showing an increased incidence among the workers at the lower social (-economic) scale in the U.K. were cancer of lung, bladder, uterine cervix and rectum (Registrar General, 1971, 1978). Furthermore, the social class gradient in the incidence in lung cancer among the various social classes in the U.K. has been attributed to the increased indulgence in the cigarette-smoking habits among those at the lower end of the social (-economic) scale (Todd, 1976).

In conclusion, on the basis that there are thresholds for the toxic effects of carbon tetrachloride and the mechanism of tumor formation is nongenetic and all the supportive evidence that indicates man metabolizes carbon tetrachloride more like the monkey than the rodent, the assessment of risk/safety for man should be based on the adequacy of that margin which exists between man's exposure to carbon tetrachloride in the ambient environment and the no-observed-effect level

in the study on the most appropriate animal model, the rhesus monkey, with a safety factor to compensate for the lack of lifetime data. Since, however, risk assessment on the basis of the monkey data may be subject to criticism since the monkeys were not exposed for their lifetimes, the no-observed-effect level in the rat dietary feeding study may be used. In this case, it must be recognized that the differences in metabolism between the rat and man affords another safety margin.

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STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

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

January 23, 1987

Ms. Carol Niemi
Environmental Affairs
Dow Chemical U.S.A.
The Willard H. Dow Center
Midland, MI 48674

Dear Ms. Niemi:

Comment on the Draft Carbon Tetrachloride Report

Your letter of September 18, 1986 concerning the Draft Report to the Scientific Review Panel (SRP) on Carbon Tetrachloride has been reviewed. The comments that pertains to Part A will be responded to by the Air Resources Board (ARB) staff. Comments pertaining to Part B were forwarded to the Department of Health Services (DHS). The DHS and ARB responses to your comments are attached to this letter. Your letter, the DHS response, and the ARB response will be included in Part C of the Final Draft Report to the SRP.

If you have any questions or comments, please feel free to contact Gary Murchison, Manager of the Compound Evaluation Section at (916) 322-8521.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Peter D. Venturini
Michael Lipsett, DHS

Air Resource Board Staff Responses to Public Comments on the Draft Part A Report on Carbon Tetrachloride

Comment: The rigid 30 and 20 day comment periods may not always be long enough to review the draft and final draft reports.

Response: In order for the toxic air contaminant (TAC) identification process to proceed in a timely manner, it is necessary for the ARB to have the rigid comment periods. The ARB staff believes that the 30 day and 20 day comment periods allow sufficient time to review the report and identify major issues of concern. However, to ensure the maximum time possible is available for the review of the reports, the previous review process was modified in two ways. First, an announcement letter is sent out in advance of the draft report so that interested parties can be identified. This letter requests the name and address of the person reviewing the report so they can receive it in the most direct way. Second, extra time is allowed for the report to reach the reviewer before the comment period starts.

Comment: Part A correctly references previous projections of a 1 to 2 percent growth in carbon tetrachloride demand through 1990. However, Dow Chemical feels that because of environmental concerns, carbon tetrachloride demand will probably not increase as previously expected.

Response: The 1 to 2 percent growth for carbon tetrachloride demand was reported in the "Chemical Marketing Reporter", 1986. In the absence of more detailed information on why this estimate is no longer correct, the ARB staff believes the 1 to 2 percent growth is still the best estimate.

Comment: As stated in EPA research studies and the Federal Register, there are uncertainties involved in the decision to regulate chlorofluorocarbons and other chemicals that may affect the ozone layer. Dow Chemical requested that the uncertainties in this area be considered by the CARB during its consideration of carbon tetrachloride as a TAC.

Response: Stratospheric interaction of carbon tetrachloride and other chlorofluorocarbons with ozone is an important issue. However, carbon tetrachloride is being considered for identification as a TAC because of its potential danger to human health from inhalation and not because of its affect on the ozone layer.

Comment: The current level of regulation and federal EPA proposals to regulate carbon tetrachloride manufacturing processes are sufficient to protect human health. It is not necessary for regulations to be so stringent as to eliminate the carbon tetrachloride industry and its beneficial end products.

Response: The identification of carbon tetrachloride as a TAC will not in and of itself eliminate the use of this compound. If carbon tetrachloride is identified as a TAC, the ARB staff will then proceed to assess the need and appropriate degree of controls that would be required for carbon tetrachloride sources. Some of the factors which will be considered during this assessment are availability and feasibility of control, cost, availability of substitutes, exposure to the public, and risk to public health. It is only after this assessment that a decision will be made by the Air Resources Board as to the need for control measures. The ARB staff will continue to work closely with the public and the affected industries throughout the development of the carbon tetrachloride needs report.

III. E.I. du Pont de Nemours and Company

FORM LG-4878

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

September 24, 1986

VIA EXPRESS MAIL

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
Attn: Carbon Tetrachloride
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

We have reviewed the document entitled "Health Effects of Carbon Tetrachloride", dated May 6, 1986 prepared by the Epidemiological Studies and Surveillance Section of the California Department of Health Services (DHS). The primary source document for the DHS risk assessment is the United States Environmental Protection Agency (EPA) Health Assessment Document for Carbon Tetrachloride (1984). The approach and conclusions of DHS are not substantially different from those of EPA. Consequently, the concerns we expressed in our comments on EPA's approach and conclusions are also relevant to DHS's.

We agree with DHS that at current ambient levels "there is a reasonable margin of safety to expect that noncarcinogenic, chronic intoxication would not result." We disagree with DHS that carbon tetrachloride may contribute to an increase in cancer-related mortality at ambient levels. This is because the most likely mechanism for carbon tetrachloride carcinogenesis requires a toxic response prior to initiation of the carcinogenic response and no toxic response is expected at ambient levels.

Both DHS's and EPA's conclusions of carcinogenic risk are based on a series of conservative biological assumptions and mathematical procedures which most likely lead to overestimates of the true risk. We do not think these assumptions and procedures are appropriate for reasons which are given in our comments on EPA's risk assessment (copy attached).

I recognize that these comments are a few days late but I contacted Mr. Todd Wang of your office and he suggested that this timing would be acceptable. If you have any questions concerning the report, please feel free to contact me at 302/774-8720.

Very truly yours,

Pamela Meitner

Pamela Meitner

PM:cde
Attachment
CARBONTET

COMMENTS OF

E. I. DU PONT DE NEMOURS AND COMPANY

TO THE

ENVIRONMENTAL PROTECTION AGENCY

NOTICE OF INTENT TO LIST CARBON TETRACHLORIDE
AS A HAZARDOUS AIR POLLUTANT

DOCKET NO. A-84-04

February 17, 1986

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APPENDIX A

Du Pont comments to the EPA filed July 1, 1982 on the Health Assessment Document for Carbon Tetrachloride (EPA-600/8-82-001, March 1982).

APPENDIX B

Biochemical and Peripheral Vision Evaluation of Carbon Tetrachloride - Exposed Workers, Gooch, James J., October 1981.

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EXECUTIVE SUMMARY

E. I. du Pont de Nemours and Company (Du Pont) offers the following comments on the EPA's Notice of Intent to List Carbon Tetrachloride as a hazardous air pollutant under Clean Air Act Section 112, 50 Fed. Reg. 32621 (August 13, 1985).

Du Pont manufactures carbon tetrachloride in an enclosed process as an intermediate in the production of chlorofluorocarbons in which it is totally consumed, and uses carbon tetrachloride as a process solvent in an enclosed process with minimal emission. As both a manufacturer and consumer of carbon tetrachloride, Du Pont is vitally concerned that an intention to list and establish emission standards be based on accurate, up-to-date scientific information. To this end, Du Pont has reviewed EPA's announcement in the Federal Register and the documents referenced therein, and offers detailed comments on the following subjects:

- Health Effects - Health Assessment Document and quantitative risk assessment.
- Exposure Assessment - Comparison of Human Exposure Model (HEM) with Industrial Source Complex (ISC) model.

Based on our review of the information available on carbon tetrachloride and our own analysis, we find that there is insufficient evidence to support the premise that carbon tetrachloride is a human carcinogen. No adverse health effects

are expected to occur at carbon tetrachloride concentrations to which the U.S. population is currently exposed. Thus, carbon tetrachloride does not qualify as a hazardous air pollutant. If EPA persists in their intent to list carbon tetrachloride, then even conservative estimates indicate that the exposure from Du Pont plants does not warrant additional emission controls.

CARBON TETRACHLORIDE

The EPA's reasoning for intending to list CCl_4 as a hazardous air pollutant is primarily based upon results of potential cancer risk calculations performed by the Carcinogen Assessment Group of the EPA. These cancer risk estimates state that at the current ambient air levels of CCl_4 there is a possibility of a maximum of 69 excess cases of cancer in the United States per year attributable to this chemical. The health effects data base leading to this conclusion are four long-term rodent studies. EPA also used the conclusions of these animal studies to state that <u>if</u> they (EPA) used the classification scheme set forth by IARC, CCl_4 would be classified as a group 2B material "Sufficient animal data exists to classify as a probable human carcinogen." It is important to note that in the FR notice, the EPA found that "noncarcinogenic effects are unlikely to occur at concentrations that are expected in the ambient air", p. 32624.

The health effects of CCl_4 that the EPA reviewed are contained in the document entitled Health Assessment Document for Carbon Tetrachloride - Final Report PB85 - 124196, dated September 1984. It contains an assessment of the health effects literature available up to March, 1983.

In July of 1982, Du Pont submitted comments to the EPA on the Health Assessment Document for Carbon Tetrachloride

(EPA-600/8) 82-001 March, 1982. Detailed comments addressing toxicology, carcinogenicity in man, and cancer risk assessment were made. A copy of those comments is attached. The major points identified in that response are highlighted below.

- Rodents are more sensitive than primates to the toxic effects of carbon tetrachloride. In particular, hamsters seem to be the most sensitive to carcinogenic effects, followed by mice and then rats.
- The monkey may be the appropriate animal model for extrapolation to man.
- Mouse liver tumors are seriously questioned as useful estimators of potential tumorigenicity for man.

Since that time there have been over one thousand citations in the toxicology literature related to CCl_4, based upon our review of the National Library of Medicine toxicity data bases. A review of these citations shows that there are several articles relevant to cancer risk assessment of CCl_4 and we believe that the EPA should have reviewed these papers so that the most current findings are incorporated into their risk assessment. Where appropriate our comments will include such recent studies.

We are also including a copy of a recent Du Pont study on workers chronically exposed to carbon tetrachloride. In that study (J. Gooch, 1981) results of clinical biochemical and vision tests were evaluated from workers exposed to carbon

tetrachloride. Several of these biochemical tests are useful in evaluating target organ toxicity from CCl_4 exposure i.e., BUN, creatinine and electrolytes for kidney damage and SGPT, SGOT, alkaline phosphatase, total bilirubin and albumin for liver damage. Exposed worker values for these tests were no different than unexposed workers. In that study personal CCl_4 exposure data collected during the time period under examination showed that exposures were less than 5 ppm (30 mg/m3) and averaged 2 ppm (12 mg/m3) as an 8 hr time-weighted average. These results show that at long-term exposures at about 1/2 of the TLV, no toxicity effects were seen. This further supports the findings in the clinical studies by Stewart, 1961, which were short-term exposures at 63 mg/m3 (10 ppm), that the NOEL for target organ effects in man is at least at the PEL of 10 ppm and is probably higher. Stewart did see some elevation of SGOT at exposures of 309 mg/m3.

Du Pont has developed internal guidance on a community air level for carbon tetrachloride and that is discussed at the end of this document.

Since cancer risk is the primary reason EPA decided to list CCl_4, our comment will focus on this issue and will address the following key items.

- Cancer studies - lack of dose response
- Route of exposure - absorption
- Metabolism
- Mechanisms of cancer
- Mutagenicity
- EPA's Quantitative Risk Assessment - Extrapolation models, Data quality, Animal to Man dose conversions, Linearity of dose-response, Use of unit risk estimate to compare relative potency.

Cancer Studies

Human Studies

Human case reports and studies have not shown that excess liver tumors are caused by CCl_4 exposure. For example in a recently published epidemiology study on cancer mortality in the rubber industry by Wilcosky et al., 1984, the authors state "the observed positive findings for lymphosarcoma and lymphatic leukemia require cautious interpretation. The modest number of cases of these cancers, and the possible biases discussed above further accentuate the need for guarded conclusions." The study is useful for the generation of future hypotheses, but it is not useful for making definitive statements about the relationship between exposure to given solvents, i.e., CCl_4, and cancer mortality. The five primary reasons for this caution are the nature of the exposure data, the limited number of cases, the exploratory nature of the study design, that the cancers observed here have not been observed in animal studies, and animal studies do not indicate blood forming organs as target tissue for CCl_4 toxicity.

The only exposure information which is actually used in this study is whether or not a given solvent was authorized for a given stage of production during a given period of time. Nothing is known about whether the solvent was actually used and if so, how much. The length of exposure for a given case is an important variable which is not well-accounted for in this study. (Any exposure for at least one year is included, therefore one year exposure is treated equivalently to a 20 year exposure.) The solvents were also used simultaneously and therefore each case was likely exposed to a variety of solvents. It is therefore impossible to provide a direct link between a single solvent and a particular cancer.

The limited number of cases and the exploratory nature of this study also make it difficult to determine which observed associations are real and which are spurious. Because the study is exploratory numerous hypotheses are tested, consequently false positives are not unlikely.

The studies of Capuno (1979) and Blair (1979) do not show proof that excess human cancer is linked to CCl_4 exposure. Detailed comments are found in our initial critique submitted in 1982 (see attachment).

Animal Studies - There is no disagreement that under certain conditions of exposure in certain species of animals, CCl_4 produced tumors. However, the studies are extremely limited for risk assessment calculation. The major problems with each study are discussed below. It is obvious that the lack of a chronic inhalation study makes it difficult to make an adequate risk assessment. We note that EPA does recommend such a study.

Rat Studies

Rats developed occasional hepatocellular carcinomas after being given a subcutaneous injection of CCl_4 in corn oil. The incidence was very low - 1/14 in 52-week-old males and 1/10 in 24-week-old and 1/11 in 52-week-old female Buffalo rats at a dose level of about 1,300 mg/kg (Reuben & Glover (1967a). No control animals were used and rats in the other age groups, 4 and 12 weeks, did not develop any liver tumors. In another study by Reuber & Glover, 1970, five different rats strain were given subcutaneous injections of CCl_4 in corn oil at a dose of 2080 mg/kg. The incidence of liver cancer ranged from 0/17 to 12/15. Both of these studies are not suitable for making a cancer risk assessment for man. They lack control groups, the route of exposure is not relevant, there was only a single dose level used and the material was given all at once. These dose levels caused significant toxicity and early

mortality. The doses were massive in comparison to what a person might encounter by the inhalation route. For example, a dose of 2080 mg/kg is 145,600 mg per person or 14,560 mg/M3 (2427 ppm) or 485 times the TLV of 5 ppm.

In studies conducted by NCI (1976a, 1976b, 1977), CCl_4 was used as a positive control and was given by oral gavage, a route which to humans are not exposed. Two dose levels were used, and the tumor incidence was low; just slightly over background for males, but higher for females. There was no dose response for liver tumor incidence for males and an inverse dose response for females. The only increase which was statistically significant was that for low dose females. These studies indicate CCl_4 may not be carcinogenic under these conditions.

Mouse Studies

Several studies have been conducted which show the induction of liver tumors in mice.

In a gavage study by Andervont (1958) C3H mice developed hepatomas with varying incidence rates at a dose level of 213 and 320 mg/kg. Edwards (1941) conducted two studies on C3H or mice with CCl_4 given by gavage with olive oil. The incidence of tumors was 88% in treated C3H mice vs.

4.3% for the olive oil controls. For strain L mice, males had a range of 47 to 54% and females of 27 to 38% for these liver tumors (Edwards, 1942).

In a study by Eschenbrenner and Miller (1948) Strain A mice developed hepatomas after receiving CCl_4 in olive oil by gavage under different dosing regimens, but the dose-response was not linear.

In an NCI study (1976a, 1976b, 1977) CCl_4 was used as a positive control. B6C3F1 mice were given CCl_4 by oral gavage at 1250 or 2500 mg/kg. There was no dose response, but nearly all treated animals (96-100%) developed hepatocellular carcinomas.

Other studies in other strains (A, Y and C) of mice given CCl_4 by gavage showed an increased incidence of hepatomas, Edwards and Dalton, 1942.

Hamster Studies

In a study with Syrian Golden hamsters, CCl_4 was administered as a 5% solution in corn oil by gavage, Della Porta et al. (1961). This was a single dose level study, but the dose was changed after the first seven weeks of treatment. Liver-cell carcinomas were seen in all of the animals, 5 males

and 5 females, that died or were sacrificed 13-25 weeks after each treatment. The authors considered the results to be significant because the historical control incidence of hepatic tumors was zero.

From the above animal studies it is important to note that liver damage was associated with tumor formation and dose-response for tumors was limited.

Route of Exposure

It is clear that by different routes of exposure subcutaneous injection, oral gavage and rectal instillation, CCl_4 produced liver tumors in several different animal species. Furthermore in these instances, the CCl_4 was dissolved in either corn oil or olive oil.

It is also clear that these routes of exposure are distinctively different from the way people would commonly be exposed to CCl_4 in their daily life. The CCl_4 was not given as a pure compound but given with large amounts of vegetable oils.

When chemicals are given by these routes, they arrive at the site of contact almost immediately in amounts that are many orders of magnitude greater than a person might ingest.

In an urban scenario, a person encounters less than one ppb (1.0 ug/M3) in the air (ambient air measurements) during a day. Compared to the amount given to animals to cause cancer (1250 mg/kg bw in mice) the amount inhaled is about one billion times smaller. This factor of one billion plus the fact a person does not receive a daily exposure of CCl_4 all at once, suggest that these data are not useful for assessing the hazard of CCl_4 as an air pollutant.

Metabolism

Carbon tetrachloride has been shown to readily absorb through lungs, the gastrointestinal tract and the skin. It has also been shown that the metabolism of CCl_4 produces toxic intermediates, i.e. free radicals, which are considered responsible for the adverse health effects of CCl_4. Thus reduced metabolism would be beneficial for the organism which has been exposed to CCl_4. Since it has also been shown that the mixed function oxidase system, specifically cytochrome P-450 of the liver, is the key component in CCl_4 metabolism, the amount and distribution of this enzyme in various species would help determine the relative species sensitivity to CCl_4 intoxication. The mouse, followed by the rat, and then the monkey, seems to be the order of species sensitivity to CCl_4 toxicity. The limited data on cancer induction shows that the hamster may be the most sensitive followed by the mouse and

rat. As EPA points out species sensitivities vary depending upon the toxic lesion produced (see 8-46). However, it is also observed that the rodent is more susceptable to the toxic effects of CCl_4 than the primate. This has been discussed in more detail in our 1982 submission (see attached). We believe this is an important distinction and should be incorporated into risk assessment calculations.

Mechanism of Cancer

Although the exact mechanism whereby CCl_4 produces cancer in experimental animals is not known, several important findings have been made which help shape our perspective on the potency of this chemical.

Carbon tetrachloride has been classified as a carcinogen which acts by an epigenetic mechanism, according to Shank and Barrows (1985). They indicate it satisfies several of the criteria for this classification which are:

- it appears to induce cancer only at exposure levels which are near lethal doses (maximum tolerated dose which depresses growth rate 10 to 20%)
- it increases the incidence of spontaneous tumors but does not induce formation of tumors which are rarely seen in control populations of the test species
- cancers arise only after a long exposure relative to the life span of the test animal
- it does not form detectable levels of DNA adducts in *in vivo* tests

They have reviewed the animal carcinogenicity studies, the same ones the EPA relied upon, and concluded that the animals only developed liver tumors after receiving doses of CCl_4 which produced liver necrosis, but not when exposed to nonnecrotizing doses. They state that a single low-level exposure to an epigenetic agent would be less likely to induce cancer than a genetically active carcinogen because animal studies suggest greater difficulty in inducing cancer with an agent which appears to require repeated exposures to high doses.

Related to the above assessment are the studies on mutagenicity.

Mutagenicity

Mutagenicity studies for the most part have failed to give positive results with CCl_4. In the Ames test with and without activation, E. coli and in in vitro chromosome assay results were uniformly negative. In one study which used yeast cells, CCl_4 produced increased frequencies of gene conversion and mitotic recombination; but only at concentrations which were lethal to the cells. These results support the concept that only under conditions of exposure where lethal effects occur, does mutagenic alteration happen. Thus weak genotoxic or no genotoxic activity is present. These results favor a weak carcinogen classification.

Since the end of the EPA update on toxicity studies in March 1983 several studies have pursued the question of genotoxic activity for CCl_4. The major ones are described below.

Carbon tetrachloride did not induce unscheduled DNA synthesis in cultured mouse hepatocytes (Mirsalis, 1985) or rat hepatocytes (Mirsalis, 1982) but did increase DNA replication and hepatic cell proliferation. Furthermore a significantly larger increase in the level of hepatic cell proliferation was found in mice vs. the rat at the same in vivo dose level (Mirsalis, 1985).

In genotoxicity assay system where CCl_4 was considered positive, the positive results were weak. For example, in an assay measuring morphological transformation of Syrian Hamster embryo cells, only one of 2003 colonies was transformed by CCl_4, (Amacher, 1983); in an alkaline elution/rat hepatocyte assay positive effects were seen only at CCl_4 doses which produced significant (>30%) cell toxicity (Sina, 1983) and in a study examining mouse liver nuclear DNA syntheses, adaptive changes occurred following long-term CCl_4 oral gavage administration (Gans, 1984).

These recent findings provide additional support for the weak potency (if any) of CCl_4 as a carcinogen at low doses.

EPA's Quantitative Risk Assessment

Our primary concern with the risk assessment of carbon tetrachloride is the "consistently conservative, i.e., tending toward high estimates of cancer risk" (Page A-11 of Health Assessment Document) approach taken by EPA. When a choice between two equally plausible assumptions is made EPA has consistently chosen the most conservative. This is contrary to the ideas of W. Ruckelshaus, who stated, while EPA Administrator that:

> This [piling up of conservative assumptions] is fine when the risks projected are vanishingly small; it's always nice to hear that some chemical is not a national crisis. But when the risks estimated through such assessments are substantial, so that some action may be in the offing, the stacking of conservative assumptions one on top of the other becomes a problem for the policy maker. If I am going to propose controls that may have serious economic and social effects, I need to have some idea how much confidence should be placed in the estimates. "Managing Risk in a Free Society." Princeton Alumni Weekly, 3/8/84, pp. 18-23.

EPA should present the risk manager with the range of possible estimates, including the most likely estimates, not just the most conservative estimates. Only with this information, can the risk manager make well-informed decisions.

Some specific areas of concern with the risk assessment of carbon tetrachloride include:

- the choice and implementation of extrapolation models
- the quality of the carcinogenicity data
- the conversion of doses within and across species
- the use of the unit risk to compare relative potency among various presumed carcinogens.

In the following discussion, we specifically address each of these areas.

Extrapolation Models

EPA states "There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at extremely low concentrations, including the unit concentration given above." (page A-1) We agree and this indicates to us that risk assessors should not rely heavily on the unit risk derived from the linearized-multistage model or any other single model. EPA has stated "The risk estimates presented in subsequent sections should not be regarded as accurate representations of the expected cancer risks ..." (Page A-10). Despite, EPA's recognition of the uncertainty and the lack of a solid scientific basis for the model, EPA has relied primarily on the unit risk derived from the linearized-multistage model. Given

this situation, the reduction of the estimate of risk to a single number is too simplistic.

The unit risk estimate as presented may serve to misinform. This is because the linearized multistage model is the only model used by EPA to estimate risk when in fact other models have been proposed for estimating risk. These alternative models are no less plausible since the underlying biological mechanisms for cancer are not known. Although they do not differ in plausibility they will provide different estimates of risk which will generally be lower. For example, if we assume all of EPA assumptions are true but use the best estimate rather than the upper limit, 14.2 extra cancers are expected rather than 69. The linearized multistage model is also the most conservative model since it is not actually a model, but rather an upper bound or confidence limit.

The unit risk, as calculated by EPA, represents "the most plausible upper-limit for the risk, i.e., the true risk is not likely to be higher than the estimate..." (Page A-2) It represents the worst case scenario, a scenario <u>not</u> likely to occur, thus it is not the type of number which is useful for well-informed decisions. Worst case scenarios have their place but so do <u>most likely</u> case scenarios.

As implemented by EPA, the multistage model has a numerical difficulty. "It [the linearized multistage model] is constrained to ensure linearity in the low dose region .." (Page A-2) That is, even if the data indicate non-linearity or sub-linearity the model does not allow for this possibility. This is an artificial constraint which requires that risk increases with increasing dose over the entire dose-range, regardless of what the data may suggest. The multistage model would be more useful if these constraints were removed, so that risk assessors could more accurately describe the known data.

Data Quality

By EPA's own admission the four studies used to estimate risk are "less than ideal for risk estimation for continuous daily exposure over a lifetime." (Page A-3) In fact, they are very poor for estimating risk at low doses. EPA recognizes the problems with these studies but nonetheless conducts a risk assessment using them; the consequence is that a good risk assessment is not likely from such poor data. Because of the limitations of each of the studies EPA has chosen to estimate unit risk by the geometric mean of the estimates from each of the studies. This does not solve the problem, the geometric mean of four poor estimates is still a poor estimate.

Animal to Man Dose Conversions

In determining human equivalent estimates of risk from animal data, EPA make adjustments for exposure duration and metabolic differences. Comments on these two items follow.

Exposure Duration

Calculating time-weighted average doses to convert from one dosing schedule to another has limited usefulness. Time-weighted conversions can be made when it is believed the biological effect is equivalent for the time-weighted average dose of two different dosing schedules. In three recent inhalation studies on carbon tetrachloride it has been demonstrated that this is not true. (Uemitsu, et al., 1985, David, et al., 1981 and Van Stee, et al. 1982). All three studies indicate that the severity of various toxic responses to carbon tetrachloride is more influenced by concentration than by time. The results of these studies suggest that at ambient exposure levels, where concentrations are low but exposures are long term, toxic responses will be less than predicted by the hypotheses of equivalence of time-weighted average doses. Even without information from these studies it is not reasonable to expect that the time-weighted conversions for two of the studies used by EPA to estimate risk are likely to be accurate because the actual dosing schedules used in the studies are not similar to ambient exposure schedules. In the

Della Porta et al. study (1961) the doses were administered once per week for only 30 weeks; the doses were converted to a daily dose for a lifetime (55 weeks). In the Edwards et al. (1942) study the doses were administered for 17 weeks and the study lasted 31 weeks; the doses were converted to a daily dose for a lifetime (78 weeks).

Metabolic Differences

EPA converts doses across species by assuming biologically equivalent doses can be obtained by correcting for the surface area differences among species. Two other methods are often used to make interspecies comparisons; correcting for body weight differences and doing no conversion. EPA has stated "the concept of equivalent dose for humans compared to animals on a mg/surface area basis is virtually without experimental verification." (page A-9) Given this uncertainty, EPA should provide estimates based on all three unless there is prior information which suggests that one method is most appropriate. In the case of CCl_4, EPA has not provided evidence for the appropriateness of the surface area conversion.

The risk calculation is very dependent on these assumptions. If we assume that mg/kg is a more appropriate inter-species adjustment (there is no scientific reason to

discount this assumption) the most likely estimate of the number of extra cancer cases is 19 times less than would be estimated by the surface area conversion.

Linearity of Dose Response

The unit risk approach assumes that the dose response for carcinogenesis is linear from zero dose up through the observed dose range of the studies used to estimate that risk. This is not likely to be true for carbon tetrachloride which is likely to have an epigenetic mechanism as discussed earlier.

Use of Unit Risk Estimate to Compare Relative Potency

Comparison of potency of presumed carcinogens by using the unit risk estimates is an entirely unvalidated procedure. That is, it is not known how well, if at all, these estimates of relative potency actually reflect the true differences in potency among carcinogens at 1 ug/m3, the arbitrary standard. Even if the relative potencies are accurate at this standard, they are not likely to be accurate over the exposure ranges where risk is estimated, since the dose response curves for each carcinogen will have different shapes over the exposure range.

Du Pont's Internal Guidance on a Community Air Leval for Carbon Tetrachloride

At Du Pont's Haskell Laboratory, health scientists have reviewed the available toxicological data base on carbon tetrachloride and recommended that Du Pont operations be controlled so as to limit surrounding community air levels to at or below 100 parts per billion (0.63 mg/m^3) averaged for a 24-hour period, a level at which no adverse human health effects are expected to occur.

It is recognized that 100 ppb is a conservative number and that it is based upon a limited amount of animal data which is pertinent to risk assessment. Furthermore, this value is not a demarkation between safe and unsafe but it is an exposure value that we believe presents no significant health risk for humans. This value is subject to revision when new data becomes available.

There are certain research gaps in the toxicity picture of carbon tetrachloride which preclude the establishment of a more precise value. Research is needed to explore the dose response relationship for tumor production in animals by the inhalation exposure route, the mechanism of action of carbon tetrachloride's carcinogenicity, pharmacokinetic differences in animals and man at low exposure

levels of carbon tetrachloride, the appropriate conversion for extrapolating from the oral to the inhalation route of exposure, and the role corn oil plays in liver toxicity.

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APPENDIX A

DRM LO-4878

DU PONT

ESTABLISHED 1802

I. DU PONT DE NEMOURS & COMPANY
INCORPORATED

WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

July 1, 1982

Solvents Project Officer
Environmental Criteria and Assessment
Office (MD-52)
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Dear Sir:

Health Assessment Document for Carbon Tetrachloride
EPA-600/8-82-001 MARCH 1982

On behalf of E. I. du Pont de Nemours and Company (Du Pont), I am pleased to submit these comments on the above-referenced document. We appreciate the Agency affording us this opportunity to comment.

Du Pont manufactures carbon tetrachloride in an enclosed process as an intermediate in the production of chlorofluorocarbons in which it is totally consumed, and uses carbon tetrachloride as a process solvent in an enclosed process with minimal emission. As both a manufacturer and a consumer of carbon tetrachloride, Du Pont is vitally concerned that any Health Assessment Document (HAD) issued by the EPA on carbon tetrachloride be an accurate, up-to-date and objective presentation of the known information on the material. To this end, we have reviewed the HAD for carbon tetrachloride and offer detailed comments on the following subjects as they are presented in the HAD.

- PART 1 - EFFECT OF STRATOSPHERIC OZONE
- PART 2 - TOXICOLOGY
- PART 3 - CARCINOGENICITY-HUMANS
- PART 4 - APPENDIX: UNIT RISK ESTIMATE FOR CANCER

While our specific comments are directed to the above subjects, our lack of comments on other aspects of the HAD should not be interpreted as acceptance of the remainder as an unflawed presentation.

Based on our close review of the subjects as presented in the HAD, we find that the document does not include all available and extremely pertinent data, particularly recently published information, on the subjects. In some cases the review of the data has been sufficiently superficial to lead to questionable conclusions regarding its meaning. An especially obvious deficiency is the appearance of selective use of data to direct the reader toward the conclusion that there is need for stricter control of carbon tetrachloride. These concerns are amplified in more detail in the attached comments.

We trust the EPA will take note of our comments and review and revise the HAD so that a timely, technically accurate HAD with sound and practical policy implication is produced.

Very truly yours,

David T. Modi
Environment Division

DTM:scl
Attachments

PART 1

EFFECT ON STRATOSPHERIC OZONE

Although carbon tetrachloride has been associated with chlorofluorocarbons (CFCs) in concerns over calculated future depletion of stratospheric ozone since the theory was published in 1974, it should be recognized that most carbon tetrachloride is utilized as a chemical intermediate, and not released to the environment. Manufacturing emissions and emissions from non-intermediate uses where evaporation and release may be more significant constitute the major input to the atmosphere.

CALCULATED DEPLETION OF STRATOSPHERIC OZONE

Revisions in Calculations of Potential Future Depletion of Stratospheric Ozone

Since 1979, major revisions have occurred in modeling calculations of potential future depletion of stratospheric ozone and in our appreciation of the significance of analyses of actual ozone measurements.

- Reaction rates and other basic data in the computer models have been revised, with the result that calculated future depletion when CFCs are considered alone has been sharply reduced from 16.5 percent to 5-7 percent for most model calculations, or to about one-third the earlier values. A similar proportional decrease occurs for emission scenarios involving carbon tetrachloride.

- Modelers have recently recognized the importance of performing simultaneous calculation of the effect on stratospheric ozone

of the estimated future emissions of all the compounds presently thought to affect ozone. One "multiple perturbation" calculation included CFCs, other chlorinated compounds specifically including carbon tetrachloride, nitrogen oxides from aircraft exhaust, nitrous oxide from fertilizer denitrification, and carbon dioxide from fossil fuel combustion (Wuebbles et al. 1982).

On an individual basis, some of these compounds are calculated to decrease ozone, while others are calculated to increase it. When the compounds are considered together, important interactions and offsets occur. The simultaneous multiple perturbation scenario referred to above calculates no depletion of total stratospheric ozone during the period 1911-2100*. Similar results were reported recently by the World Meterological Organization (WMO 1982).

- It is now acknowledged (WMO, 1982; NAD, 1982) that measurements do not detect any depletion of total ozone and that analyses of these measurements (ozone trend analyses) can provide a measure of the upper limit of any ozone change (increase or decrease) that may be occurring.

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*In Wuebbles et al. (1982), it should be noted that carbon tetrachloride was specifically included in the multiple perturbation calculation, and is a part of the "CFC" scenario. Carbon tetrachloride is not a CFC and the CFC label for the group of chlorinated compounds could be misleading if not clearly and specifically explained. Note that the year 1911 was selected as representative of the stratosphere prior to anthropogenic chlorocarbon emissions.

Uncertainty

In 1979 The National Academy of Sciences (NAS, 1979 a,b) expressed confidence that model calculations of future ozone depletion reflected the real world effects of CFC and chlorocarbon emissions, thereby implying that regulatory action could be confidently based on the calculations. In fact, confidence limits were precisely stated for the calculated ozone depletion from CFCs.

In contrast, following the large revisions in model calculations since 1979, NAS cautions in 1982 as follows:

> "These results should be interpreted in light of the uncertainties and insufficiencies of the models and observations." (NAS, 1982, p.3)

and uncertainty ranges are not stated.

Revisions in the Potential Effects of Ozone Depletion

The NAS in 1979 (NAS, 1979b) listed four categories of effects anticipated from increased UV-B, which, in turn, would result from depletion of total ozone. They were:

(1) Increased incidence of nonmelanoma skin cancer in humans.
(2) Increased incidence of malignant melanoma skin cancer in humans.
(3) Significant crop yield reductions.
(4) Appreciable killing of marine organisms.

The assessment for three of these categories has changed substantially.

The current assessment on malignant melanoma is that the "association between sunlight and melanoma is not strong enough to make a prediction of increased incidence due to increased exposure to UV based on epidemiological data." (NAS, 1982, p.9).

The semiquantitative estimates of increased melanoma incidence and mortality which were made in 1979 have been dropped.

For crops, NAS finds "The potential for further adaptation [by food crops] to predicted increases in ambient UV-B is not known." (NAS, 1982, p.7)

The predictions of significant crop yield reductions which were made in 1979 have been dropped.

For marine organisms, NAS finds "Currently there is no information from which to predict the magnitude of adverse effects of enhanced UV-B on aquatic organisms." (NAS, 1982, p.7)

The prediction of appreciable killing of marine organisms at the base of the marine food chain, which was made in 1979, has been dropped.

Skin Cancer Trends

With recent revisions of calculated future ozone depletion, it is incorrect to allude that carbon tetrachloride may increase the incidence of certain forms of skin cancer. While epidemiological evidence indicates that the incidence of skin cancer is increasing, this increase has occurred in a period when there is no indication from actual measurements that total ozone

is being depleted, nor is there any indication of an increase in UV-B (Berger and Urbach, 1982). Thus there is no evidence or rational basis to connect current epidemiological trends in skin cancer incidence with ozone depletion or carbon tetrachloride emissions.

Climate Effects

NAS (1979b, p.116) discussed the likelihood of adverse changes in climate due to calculated depletion of ozone by CFC, should it occur. The report concluded that important changes in surface climate were not expected as a result of this effect. Similar arguments apply to carbon tetrachloride emissions if NAS had discussed them.

SIGNIFICANCE OF THE SCIENTIFIC REVISIONS FOR THE CARBON TETRACHLORIDE HEALTH ASSESSMENT DOCUMENT

Although the 1982 NAS report is cited, the draft review discusses the concepts of 1978 and then, as a second thought, mentions the sharply revised estimates and conclusions of 1982. Technical accuracy and the sound technical perspective necessary for the appropriate policy implications require the principal emphasis and stress to be on the 1982 data and the conclusions, and the considerable uncertainty associated with them, supplemented where appropriate with references to the recent history of the issue.

MISLEADING COMMENTS ON ENVIRONMENTAL EFFECTS OF CARBON TETRACHLORIDE

Examples of ways in which the HAD perspective misleads:

- The calculated effects of carbon tetrachloride alone are discussed ignoring the latest combined perturbation calculations. The combined perturbation calculations consider all the chemicals suspected of affecting stratospheric ozone simultaneously. Thus discussion of the effect of carbon tetrachloride alone, or even of atmospherically-stable chlorine compounds alone, presents a distorted picture of current scientific understanding of the stratospheric ozone question. The important issue is to determine the net effect of all human activities on ozone, not just a single group of chemical compounds.
- The HAD makes essentially no mention that analyses of actual measurements of total ozone do not detect any ozone depletion.
- Current scientific reports suggest that large uncertainties exist but there is time to reduce the uncertainties without significant risk. This situation has major policy implications, yet is not discussed.
- The estimated effects of ozone depletion, should it occur, have also been sharply revised in 1982. For instance, estimates of the effects of ozone depletion on the incidence of malignant melanoma, on crop yields, and marine organism survivability, specifically, have been significantly modified. Yet, again the most recent estimates are appended to earlier assessments rather than being given the principal emphasis

Collectively, these recent revisions not only greatly reduce or even essentially eliminate calculated future ozone depletion, but also lessen potential adverse effects from ozone depletion should it occur from any cause.

The HAD requires editing to reflect these technical developments. Without such editing the HAD does not provide either a technically accurate picture of environmental questions on carbon tetrachloride, nor does it provide appropriate policy implications.

Specific Locations of Misleading Comments on Environmental Effects on Carbon Tetrachloride Emissions

A. Carbon tetrachloride considered as the only emission affecting total ozone, and absence of discussion of multiple perturbation calculations.

   HAD pages 2-2, 5-2, 6-5.

B. Failure to distinguish adequately between the real atmosphere and model calculation or attribution of predictive value to model calculations.

   HAD pages 2-2, 6-5, 6-6, 6-7.

C. Use of early reports on effects of ozone depletion with inadequate mention of subsequent technical revision.

   HAD pages 2-2, 4-3, 6-6, 6-7.

D. Misleading discussion on skin cancer.

HAD pages 2-2, 4-3, 11-36.

E. Lack of perspective on potential climate effects.

HAD page 4-3.

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PART 2

TOXICOLOGY

The toxicology, metabolism, and carcinogenicity portions of the HAD document for Carbon Tetrachloride (EPA-600/8-82-001, March, 1982) have been reviewed to assess the general usefulness of the document to allow evaluation of relative risk to man. The document frequently emphasizes certain exposure results over others without any objective reasons being given. The overall effect of this selection is to present carbon tetrachloride (CCl_4) in a light so as to make more strict control mandatory. This is unfortunate because in controlling for human exposures (setting exposure limits), a good portion of the data needs to be de-emphasized (rodent studies) while another part (monkey studies) needs more careful analysis. Here is a good example of the tenet that toxicological evaluations are most relevant when the information obtained from animal surrogates is in a species which handles the compound in a manner most like man. In this case we have the data (granted the information in monkey and man is considerably less complete than that in rodents) and should be willing to use it.

The literature has been collected and is presented for review in a not-altogether non-biased fashion. As an example, the long-term toxicity of carbon tetrachloride has been studied by a number of investigators whose work is cited. Paquet and

Kamphausen (1975) treated rats for 8 weeks with CCl_4 - their study is described in 2 pages (8-17 and 8-18). Similarly, Alumot (1976) fed rats CCl_4 for 5 or 6 weeks and described a number of effects - cited here in detail on pages 8-18 and 8-19. A chronic inhalation study conducted by Adams (1952) which looked at the subchronic effects of 7 concentrations ranging from 5 to 400 ppm in 4 species including the monkey is given in 1 paragraph on page 8-23. The HAD has not given the appropriate balance in this and any number of other specific cases. The instance cited here is highlighted by the fact that, although conducted in 1952, the Adams study is sound and stands today as a good reference point in assessing the subchronic toxicity of CCl_4.

The same oversight in terms of data presentation appears in the mutagenicity section (10) where at least 2 prominent studies, both showing that CCl_4 is inactive in genetic test systems, are omitted. Both Craddock and Henderson (Cancer Res., 38:2135:1978) and Mirsalis and Butterworth (Carcinogenesis, 1:621:1980) have shown that CCl_4 does not induce unscheduled DNA synthesis in in hepatocytes of rats exposed in vivo.

However, the greatest oversight in the toxicology/carcinogenicity portion is the presented point of view which relies almost exclusively on rodent data to predict the effects of CCl_4 in man. This clearly is not indicated when the available information is reviewed properly.

Prendergast (1967), Adams (1952), and Smyth (1936) have clearly shown that species-related susceptibility to CCl_4 toxicity exists. Prendergast ranked 5 species, each exposed to 82 ppm, 8 hours/day, for 6 weeks, according to the fatty changes seen in the liver - the guinea pig was the most sensitive (adversely affected) followed by the rat, rabbit, dog, and monkey (least affected). Similarly, Smyth showed the guinea pig to be more sensitive than the rat which, in turn , was far more sensitive than the Rhesus monkey. Adams also found a similar ranking - under his experimental conditions the no-observed-effect-level in the guinea pig and rat was 5 ppm, that in the rabbit was 10 ppm, and the monkey showed no effects at 25 ppm. If the endpoint in the Adams study is fatty changes in the liver observed microscopically, the quantitative differences are even more pronounced with the quinea pig and rat responding at 10 ppm, the rabbit at 25 ppm, and the monkey at 100 ppm.

Animal experiments have also demonstrated that the effects produced by CCl_4 are related both to the magnitude of the dose and the length of time the chemical is given. Other than the studies of Adams, Prendergast, and Smyth which demonstrate this nicely, Alumot (1976) showed that no liver changes, particularly elevations in lipid and triglyceride levels, were seen when CCl_4 was fed to rats at 22 mg/kg/day whereas the feeding of either 40 or 76 mg/kg/day produced increases (more pronounced at the higher

level). The same author determined that feeding equivalent doses of 10 to 18 mg/kg/day in rats did not lead to liver damage when rats were fed CCl_4 for approximately 2 years.

The time relationship with dose is best illustrated in the liver of rats in the experiment by Smyth. Rats exposed to either 100, 200, or 400 ppm developed cirrhosis of the liver following repeated cellular degeneration/regeneration. As the exposure level doubled, the time of observed cirrhosis essentially halved with cirrhosis developing in 173 exposures at 100 ppm, 115 exposures at 200 ppm, and 54 exposures at 400 ppm.

The reason for the difference in CCl_4 toxicity among species is related to its metabolism. Unmetabolized CCl_4 does not appear to be very toxic (Recknagel and Glende, 1973 and Sagai and Tappel, 1979 both cited in the HAD, Slater, Nature 209:36: 1977, Recknagel and Ghoshal, Lab. Invest. 15:132:1966, Cignoli and Castro, Exp. Mol. Pathol. 14:43:1971 not cited in the HAD). Studies have demonstrated that the toxic effects are mediated through reactive metabolite(s) generated by cytochrome P-450. The mechanism for toxicity can be either a direct attack on cell protein by the highly-reactive free radical products of homolytic cleavage of the CCl_3-Cl bond or, more likely, an indirect mechanism of lipid peroxidation. Since cytochrome P-450 is central to this metabolism, the relative amount of this enzyme among the various species is important. The literature contains several

references showing that activity in both man and monkey is between 0.30-0.40 nM cytochrome P-450/mg microsomal protein while that of the rat and mouse is 0.70 to 0.85. The quantity of CCl_4 metabolized at the cytochrome P-450 site is reflected in the toxic response of the liver, the mouse most damaged, followed closely by the rat, followed by the monkey (and man). This strongly suggests that the monkey may be the appropriate animal for extrapolation to man.

The carcinogenicity section points out that liver tumors can be induced in various species (rat, mouse, hamster) by CCl_4. The relative sensitivity appears to be: hamsters, most sensitive, followed by mouse, then rat. In contrast to the presentation in the HAD, the preponderance of the data in the literature indicates that the tumorgenic response occurs as a consequency of post-necrotic cirrhosis (Cameron and Karunaratne, 1936; Rueber and Glover, 1967 and 1970; NCI 1976; Della Porta, 1961; Edwards and Dalton, 1942).

In mice, the occurrence of hepatomas following necrosis suggests that CCl_4 is not a direct-acting carcinogen (Louria and Bogden, Crit. Rev. in Toxicology, CRC Press 7:177:1980). This is supported by consistent negative results from short-term mutagenicity tests (McCann, 1975; McCann and Ames, Proc. Natl. Acad. Sci. USA 73:950:1976, Simmon and Tardiff, 1978; Uehleke et al. 1976 and 1977). No evidence of covalent binding to nuclear DNA in mouse and rat liver tissue was found by Rocci (1973). Although

small but significant ^{14}C binding following exposure of rats and mice to ^{14}C-CCl_4 was reported by Diaz Gomez et al. (1975), the authors felt it possible that a non-genetic mechanism of action was relevant for carbon tetrachloride. This is also the conclusion reached by Uehleke (1977) following the study of CCl_4 and nucleic acid binding. The HAD document correctly states that all point mutation studies are negative. However, on the hypothetical base that the "mutagenic reactive intermediate of carbon tetrachloride" is so short-lived that it cannot interact in the test system studied, HAD suggests that "evidence is inadequate to conclude that CCl_4 is not genotoxic." Asking for additional tests here ignores the data already in hand (p. 10-6).

The teratogenicity and other reproductive effects section does a good job of reviewing the pertinent data. The review does not properly point out that when reproductive changes (testicular histology, aspermatogenesis) have been produced in experimental animals, the dose used was extremely high and the route of treatment sometimes not relevant (i.e. intraperitoneal). Changes seen regarding teratogenic, embryotoxic, or reproductive effects have been seen only following higher doses. Schwetz (1974) concludes that CCl_4 is not teratogenic nor is it highly embryotoxic. Indeed, in that study the authors point out that "CCl_4 at concentrations up to 100 times its TLV of 10 ppm was not teratogenic, and in fact, caused very little evidence of embryotoxicity." (Note: Current TLV is 5 ppm.)

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PART 3

CARCINOGENICITY - HUMAN

There are two types of human data that are presented in Section 11.4 on human carcinogenicity. Case reports are one type of evidence. EPA recognizes that "although interesting, these type of data are not suitable to quantitative analysis," and "furthermore, there usually are a number of uncontrolled variables (alcohol intake, age, simultaneous exposures) or unknown variables (exposure amount) making it difficult to attribute the outcome to CCl_4 exposure." Case reports are extremely weak evidence on which to base a judgment.

The second type of evidence comes from epidemiologic studies. The first study by Capurro (1979) reports on a series of cancer cases in a rural valley polluted by vapors from a solvent recovery plant. It was described only for the purpose of being "complete." According to EPA, "due to its lack of specificity and questionable statistical methods, the study is of limited value." Furthermore, "it should not be used as evidence of the carcinogenicity of CCl_4 due to the concomitant exposure and poor techniques."

A second study by Blair (1979) looked at causes of death in 330 laundry and dry cleaning workers. This study reported excess deaths due to cancer of the lung, cervix, and liver

and to leukemia. The study had several limitations that weaken its results and make it difficult to interpret.

- It was a PMR (proportionate mortality rate) study. PMR studies are recognized as being weak methodologically by the scientific community. They cannot measure mortality rates, or estimate relative risks and standardized mortality ratios. An excess of cancer deaths based on the PMR approach is consistent with a true deficit of cancer deaths based on other methods that are methodologically stronger and that have greater scientific validity. Results from PMR studies should be reviewed as preliminary evidence and should be confirmed by other prospective or retrospective studies.

- The dry cleaning workers were exposed to a variety of chlorinated solvents in addition to CCl_4.

- The expected number of cancer deaths in the dry cleaning workers was based on proportionate mortality rates for the entire U.S. population. Thus, the study did not take into account possible geographic or socioeconomic differences in mortality rates.

- There was no statistically significant excess of liver cancer deaths in the study (4 observed deaths vs. 1.7 expected).

- In only one of 4 liver cancer deaths was it possible to distinguish primary liver cancer from secondary (metastatic) liver cancer; that is, 3 of 4 "liver" cancers may in fact have originated in sites other than the liver.

- Due to questionable methods of case ascertainment, there were potential biases in the set of decedents studied. The decedents "do not represent a complete listing of deaths among individuals ever belonging to these two (dry cleaning workers) locals."

- The authors stated that "the small number of deaths, possible biases in the set of decedents obtained, and the general limitations of the PMR methodology necessitate cautious interpretation of the study results."

- The authors drew no conclusions concerning CCl_4's carcinogenic potential in humans. They concluded only that there was a "need for additional epidemiologic studies of this occupational group."

Thus, based on a closer look at the original article, support for the statement on p. 11-37 that "Human data as reported by Blair et. al. (1979), also are consistent with this conclusion" ["that CCl_4 is a potential human carcinogen"] is weak.

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PART 4

APPENDIX: UNIT RISK ESTIMATE FOR CANCER

This appendix is a good start on the development of a quantitative risk assessment for carbon tetrachloride (CCl_4); however, much more work must be done if this risk assessment is to be complete and useful in determining the risk to humans from CCl_4 exposure. In particular, the strengths and limitations of the data base and low-dose extrapolation model used must be better documented and the results of the quantitative risk assessment must be interpreted in light of available data on the mutagenicity, metabolism, and epidemiology of the substance.

The EPA should also consider whether to present any information at all on the quantitative risk assessment. On page A-6 of the appendix the authors conclude with respect to the estimates of potential risk

> "..., each upper bound of risk is presently regarded as having limited plausibility due to the inconclusive nature of the available evidence for the mutagenicity of CCl_4. Furthermore, because of the uncertainties in both the qualitative and quantitative aspects of risk assessment, the actual cancer risks may be lower than those indicated above and may approach zero."

Such low confidence in the results suggests that it may be better not to present any quantitative results stating the reasons given in the document. If the risk estimates are included, it is almost certain that they will be accepted as fact

with all the caveats ignored. In this situation, the presentation of a highly imprecise and inaccurate estimate may serve only as a source of misinformation.

Other suggestions on how this appendix might be improved are detailed below.

1. The linearized multistage model is only one of eight possible risk extrapolation models (i.e., probit, Mantel-Bryan, logit, Weibull, one-hit, multi-hit, linear, multistage) that could have been used in this analysis. This narrow approach should be pointed out to the reader, and it should be stated that the other models were not considered because of prior policy decisions. The reader should also be informed that the use of models, in general, and the linearized multistage model, in particular, is not widely accepted by the scientific community. For example, Squire (1981) points out that "no models can actually be based on biological events, since these are not known for any carcinogens."

2. The reasons for the unit risk estimates being "presently regarded as having limited plausibility" should be more fully documented. First, it should be pointed out that the data base is of poor quality for risk assessment because the doses were very high and produced essentially 100% response.

Exposures of 1 ug/l of water and 1 ug/m^3 of air are, by the document's calculations, equivalent to doses of 2.86 X 10^{-5} mg/kg/day and 1.14 X 10^{-4} mg/ky/day, respectively. These doses are more than 10^7 times less than the lowest tested dose of 1250 mg/kg/day. This, of course, results because the study was not designed for risk assessment but as a positive control in another study. We also emphasize that in the estimation of risk the relevant dose is that seen by the target tissue rather than the administered dose. This relevant dose is necessarily smaller than the administered dose.

It should also be pointed out that the linearized multistage model is the most conservative risk assessment model and that the estimates of potential risk are actually the upper 95% confidence limits on potential risk. This approach, in effect, uses mathematical sophistication to cover up two layers of conservatism. EPA has the right to use such overly conservative procedures; however, EPA also has an obligation to clearly describe their methodology to decision makers.

3. The unit risk estimate is meaningless without relating it to exposure. A potential hazard isn't a risk until there is exposure. The quantitative risk assessment is incomplete and of little value until exposure is quantified and evaluated in the risk assessment.

4. Quantitative risk assessment involves more than the dose-response modeling of tumor incidence data collected in animal studies. To be useful and have scientific meaning, the results of the animal studies must be related to the findings of mutagenicity, metabolism, and epidemiologic studies and the presence of no-observed-effect-levels (NOEL). This information is discussed in the health assessment document but is not considered in the risk assessment. The risk assessment is of very little value until such an overall evaluation is made. The following considerations should be added to the appendix to complete the risk assessment.

At the end of the appendix (page A-6) the authors conclude that "the actual cancer risks may be lower than those indicated above and may approach zero." Such a low risk is consistent with the mutagenicity and metabolism data reported to date. This will be discussed further in the following paragraphs. It is unfortunately impossible to reach any firm conclusions from the epidemiologic data because of inadequate study design and data analysis techniques. These limitations were also noted in the document.

The data reported in the document indicate that CCl_4 is not mutagenic. CCl_4 has been found not to interact with nucleic acids. The results of mutation studies with indicator

microorganisms are also negative, supporting this conclusion. Negative mutagenic studies are consistent with a nongenotoxic mechanism for tumor incidence and its associated no-effect threshold. The existence of a threshold is supported by the liver weight and liver damage no-observed-effect-levels (NOEL) reported for the rat, rabbit, guinea pig, and monkey by Adams, et. al., (1952) and the very low unit risk estimates reported in the document.

The metabolism data also support the low potential risk due to CCl_4 exposure. Adams, et. al., (1952) found that the monkey, which is most like man, had a NOEL of 50 ppm which is considerably higher (by a factor of 2 to 50 depending on species and response) than the NOEL of the rat, guinea pig, and rabbit.

The species that are able to metabolize CCl_4 most efficiently and rapidly will be most sensitive to its adverse effects because CCl_4 must be metabolized to exhibit its adverse effects. Data in the document show that mice and rats metabolize CCl_4 more efficiently than the monkey. The levels of the liver enzyme cytochrome T-450 responsible for CCl_4 metabolism are similar in man and monkey. This indicates that the toxicity of CCl_4 in man and monkey which metabolize CCl_4 slowly will be considerably different from that of mice and rats. The unit risk estimates quoted in the document were developed from a study of liver cancer incidence in male mice.

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APPENDIX E

BIOCHEMICAL AND PERIPHERAL VISION EVALUATION OF CARBON TETRACHLORIDE-EXPOSED WORKERS

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ABSTRACT

Carbon tetrachloride is used at the Du Pont Company's Beaumont Plant in the manufacture of "Hypalon" synthetic rubber. In the "Hypalon" process, carbon tetrachloride is used as a solvent for the chlorosulfonation of polyethylene. Hepatic and renal toxicity and abnormal peripheral vision have been reported in the medical literature as a consequence of acute and chronic exposure to high concentrations of carbon tetrachloride. To assure that the health of "Hypalon" workers is being safeguarded, their biochemical profiles were analyzed and peripheral vision was assessed.

The mean biochemical test values of 123 exposed workers were compared to those of 104 workers never exposed to carbon tetrachloride. The data were analyzed by job classification and duration of exposure. In a paired analysis of 46 workers, their before carbon tetrachloride exposure biochemical test results were compared to their after exposure test results.

Except for some slight variations and differences, the biochemical test values observed for the exposed workers were statistically comparable to those observed for the workers never exposed to carbon tetrachloride. It was concluded that the health of workers in the "Hypalon" manufacturing area is being safeguarded with respect to conditions that can be detected by the biochemical tests.

Additionally, it was concluded from the visual field screening data that the peripheral vision of the carbon tetrachloride exposed workers was normal.

INTRODUCTION

Carbon tetrachloride (CCl_4), also known as tetrachloromethane, is a clear colorless liquid with a characteristic strong ethereal odor. It is widely used as a chemical intermediate in the manufacturing of a great many products. Its most serious toxicological problems have been introduced by its use as a solvent. The primary toxic effects occur through inhalation of carbon tetrachloride fumes.

Hepatic and renal toxicity resulting from acute and chronic exposures to carbon tetrachloride has been reported by many investigators (1-11). In their reports, mortality associated with carbon tetrachloride exposure was most often the result of pathologic effects on the liver and kidneys and subsequent organ failure. The concurrent intake of significant amounts of alcohol with exposure to carbon tetrachloride was reported to have increased the probability of liver or kidney injury.

Cases of visual disturbance among carbon tetrachloride exposed individuals have been reported in the medical literature (14-19). In those case reports, bilateral peripheral constriction was the eye defect most often reported.

The Occupational Safety and Health Administration's (OSHA) standard for employee exposure to carbon tetrachloride is 10 parts of carbon tetrachloride per million parts of air (ppm) averaged over an eight-hour shift, with an acceptable ceiling exposure concentration of 25 ppm, and maximum allowable peak of 200 ppm for no more than five minutes in any four hours

period. This standard is intended to prevent any adverse health effects known to occur from overexposure to carbon tetrachloride.

In the Du Pont Company, carbon tetrachloride is used at the Beaumont Plant in the manufacture of Hypalon® synthetic rubber. In the Hypalon® process, carbon tetrachloride is used as a solvent for the chlorosulfonation of polyethylene. Manufacturing practices at the Beaumont Plant have been established to maintain employee exposure to carbon tetrachloride vapors below the threshold limit value of 10 ppm and to avoid any exposures to liquid. In the Hypalon® area, protective equipment must be worn when airborne concentration of carbon tetrachloride are above 10 ppm.

To assure that the health of Hypalon® workers is being safeguarded, their biochemical profiles were analyzed and their peripheral vision was assessed. This report presents and discusses the findings of that investigation.

METHODS

Biochemical Evaluation

The study groups included male and female employees that were on the wage roll as of September 30, 1979. On the basis of their work histories, the workers were assigned to one of three defined study groups:

- Currently Exposed.* Workers assigned to the Hypalon® manufacturing area of the plant on September 30, 1979.

*See Supplement, attached.

- Not Currently Exposed Workers with a past work history of assignment to the Hypalon® manufcturing area of the plant.
- Never Exposed Workers with no work history of assignment to the Hypalon® manufacturing area of the plant.

Occupational exposure to carbon tetrachloride, for purposes of this study, was defined as having been assigned to the Hypalon® manufacturing area of the plant.

Three job classifications were associated with the Hypalon® process: operators, auxiliary workers, and mechanics. Operators were responsible for manufacturing Hypalon® . Their primary exposure to carbon tetrachloride occurred in the Hypalon® drum-drying operation. The auxiliary workers were responsible for packaging Hypalon®, disposal of waste, and the cleaning of the rollers in the drum-dryer operations. The mechanics were responsible for the general maintenance of equipment in the Hypalon® area. In general, equipment was cleaned before it was serviced. Therefore, mechanical workers had very low exposure to carbon tetrachloride.

All Hypalon® area workers were given a battery of biochemical tests in conjunction with their annual physical examinations. Biochemistry determinations resulting from testing done between 1977 and September 30, 1979 were analyzed in this study. During the study period, the majority of the workers were tested on at least two or more occasions.

From each worker, two 10 ml. fasting blood samples were collected using routine venipuncture procedures. The blood samples were allowed to clot at room temperature. Within 1-2 hours of collection, the blood samples were sent to a private contract clinical laboratory (Wilcox Pathology Laboratories, Inc.) where they were centrifuged and the serum removed.

The following battery of biochemical determinations were made from the serum: glucose, blood-urea-nitrogen (BUN), creatinine, sodium, potassium, chloride, uric acid, calcium, inorganic phosphate, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and globulin. The biochemical measurements were made on a multichannel analyzer.

The biochemical test results were reported to the plant physician on standard report forms. These forms were placed in the worker's medical record. For this study, the biochemical test results were abstracted from the medical record and keypunched for computer tabulations.

Biochemical test results obtained prior to employment and exposure to carbon tetrachloride, with the unique exception of 46 currently exposed workers, were not included in this study. In the course of normal events, 46 of the 56 currently exposed workers were tested <u>before</u> and <u>after</u> being assigned to the Hypalon® manufacturing area. These laboratory data were included in a paired analysis.

The test data were analyzed according to a one-way analysis of variance (ANOVA). The F-statistic resulting from the ANOVA and its probability value were used to compare the test parameters. If the ANOVA probability value was less than 0.05, a two-tailed student t-test for groups of unequal size was used to determine which test parameters in the exposed group were significantly different from those of the never exposed groups. For the t-test, a p-value of less than 0.05 was considered to be statistically significant.

Lipid levels, especially cholesterol, tends to increase with age. Using covariance analysis, cholesterol and triglyceride levels were adjusted to take into account the age of the workers in the three study groups.

The biochemical test results obtained before exposure to carbon tetrachloride were compared to those obtained after exposure in the same currently exposed worker. This procedure of using a subject as his own control has the advantage of controlling many sources of variation in the data. The mean difference between the two measurements was tested by applying the t-test for paired comparisons calculated at the 0.05 significance level.

Peripheral Vision Assessment

Visual field assessments were made on 83 employees assigned to the Hypalon® area in November, 1980 with the potential for carbon tetrachloride exposure, and 90 employees who had never been assigned to the Hypalon® area and had no known exposure to carbon tetrachloride. The visual field was

measured using a tangent screen. The tangent screen was covered with black felt located 100 mm from the eyes of the employee. The tests were all administered by the plant nurse and interpreted by the plant physician. Employees found during the initial testing to have any visual field defects were referred to a consulting ophthalmologist. The peripheral isopter, the blind spot, and various scotomas can be demonstrated testing with the tangent screen. Standard criteria were used to define the above central or peripheral defects of the visual field.

RESULTS

The exposed group consisted of 123 wage roll workers, 117 (95%) males and 6 (5%) females. By time of exposure, 56 (46%) of the 123 workers were currently working in the "Hypalon" manufacturing area at the time of the study. The remaining 67 (54%) workers had previously worked in the "Hypalon" area for some period of time before the end of the study. The never-exposed group, the controls, consisted of 104 wage roll workers with 100 (96%) males and 4 (4%) females.

The mean age for the currently exposed workers was 33.0, for the not currently exposed 33.8, and for the never exposed groups 37.0 years. Overall, the three groups were comparable in ages.

The biochemical test results are summarized in Tables 1 through 4. In each table, the test values of the exposed workers are compared to those of the never exposed group.

Overall, the biochemical test values for the exposed workers did not differ significantly from the test values of the 104 never exposed workers (Table 1). On an individual test basis, the currently exposed workers have higher LDH and lower triglyceride levels than did the never exposed workers (Table 1). In Table 2 the test results among the currently exposed workers were analyzed by three job classifications. By job classification the test results among the currently exposed workers were very comparable overall to those of the never exposed workers in the study (Table 2). However, the operators had higher LDH values compared to the never exposed workers. The auxillary workers has higher alkaline phosphatase values but lower triglyceride levels than did the never exposed workers (Table 2).

Duration, defined as the time between first exposure to carbon tetrachloride and the end of the study in September 1979, was strafied into less than 25 months, 25 to 48 months, and greater than 48 months in Table 3. In the data analysis, duration of exposure was not associated overall with abnormal biochemical test results (Table 3). Thus, compared to never exposed workers, the test values among the currently exposed workers did not overall show significant deviations with increased duration of exposure to carbon tetrachloride.

Blood-Urea-Nitrogen (BUN). Each study group had a mean BUN value of around 16 mg/dl (Tables 1-3). The frequency

of deviant values for the not currently exposed workers did not differ significantly from the never exposed (Table 1).

Creatinine. The creatinine determinations averaged 1.2 mg/dl for each study group (Tables 1-3). No significant differences were noted. The total exposed group had significantly more deviant values when compared to the controls (Table 1).

Sodium. The sodium determinations averaged 141 meq/L for each study group (Tables 1-3). No significant differences were noted.

Potassium. The potassium levels for each study group averaged 4.4 meq/L (Tables 1-3). No significant differences were noted.

Chloride. The three study groups each had a chloride level which averaged approximately 104 meq/L (Tables 1-3). No significant differences were noted.

Uric Acid. Uric acid measurements averaged for each study group about 6 mg/dl (Tables 1-3). No significant differences were noted.

Calcium. For each study group, calcium averaged around 10 mg/dl (Tables 1-3). No significant differences were noted.

Inorganic Phosphorous. For each study group, inorganic phosphorous averaged around 3.0 mg/dl (Tables 1-3). Significant differences were not noted.

Cholesterol. When the cholesterol values were analyzed by exposure group, significant differences among the

unadjusted means were noted (Tables 1-3). After adjusting the cholesterol levels for age of the workers, the previous noted differences were no longer present (Tables 1-3). With the age adjustment, the never exposed groups had a mean cholesterol level of 186 mg/dl, the total exposed group a mean level of 191 mg/dl with those currently exposed at 187.3 mg/dl and not currently exposed at 194.7 mg/dl (Table 1).

Triglyceride. Triglyceride differed significantly among the three study groups (Tables 1-3). Age-adjusting the triclyceride levels did not change the noted differences. By exposure group, the currently exposed workers' triglyceride level of 119.6 mg/dl was significantly different from the 132.2 mg/dl found among the control group (Table 1). Among active workers, the auxiliary workers had a triglyceride level significantly less than that of the control group (Table 2). Workers with 48 months or less time in the Hypalon® area had significantly lower triglyceride values compared to the controls (Table 3). The frequencies of deviant values were comparable among the study groups.

Total Protein. Total protein measurements averaged about 7 g/dl, for each study group (Tables 1-3). No significant differences were noted.

Albumin. The albumin levels were 4.4 g/dl for each study group (Tables 1-3). No significant differences were noted.

Alkaline Phosphatase. The 87.1 U/L level of alkaline phosphatase among the auxiliary workers was significantly

greater than the 75.6 U/L level observed for the control group (Table 2). All other levels of alkaline phosphatase analyzed were comparable to that of the control group (Tables 1-3). The frequencies of deviant values were comparable among the study groups.

Serum Glutamic Oxaloacetic Transaminase (SGOT). The SGOT values averaged around 24 U/L for each study group (Tables 1-3). No significant differences were noted.

Serum Glutamic Pyruvic Transaminase (SGPT). The never exposed group had a mean value of 23.6 U/L while the exposed groups had SGOT values which were comparable.

Lactic Dehydrogenase (LDH). Among the actively exposed workers the LDH level of 176.0 U/L was significantly higher than the 165.2 U/L level seen among the controls. By job classification, the elevation in LDH was restricted to the operators (Table 2). When analyzed by duration, the significant elevation was found among the workers with less than 12 months in the Hypalon® area (Table 3). The total exposed group had significantly more deviant LDH values than did the control group (Tables 1-3).

Globulin. The three groups each had a globulin mean value of approximately 2.7 g/dl. Although the means were the same, the exposed workers had significantly more deviant globulin values compared to the control group.

Paired Analysis. When individual comparisons were made for the 46 workers before and again after their first assignment to the Hypalon® manufacturing area, no statistically

significant changes were noted among the battery of biochemical determinations (Table 4). The 46 workers spent an average of 16.4 months in the Hypalon® area.

Peripheral Vision Assessment

No peripheral vision field defects were found among the Hypalon® workers potentially exposed to carbon tetrachloride. Among the 90 employees in the control groups, two employees upon initial screening had visual fields which deviated slightly from the normal pattern. These two employees were referred to a consulting ophthalomologist for retesting and evaluation. The results were that both employees had normal visual fields, as assessed by the ophtholomologist. Thus, the control groups of employees were found to all have normal visual fields.

DISCUSSION

The biochemical test results presented in this report indicate that the health of Hypalon® area workers is being safeguarded with respect to conditions that can be detected by those tests. Overall, biochemical test values obtained in the exposed groups were statistically comparable to those values obtained from the never exposed workers. The test values for the exposed group tended to cluster about the mean values of the never exposed with no gross elevations or decreases. Further, job classification and or time since first assigned to the Hypalon® manufacturing area appeared to have had no adverse influence on the normality of test results. No relationship

between the frequency of deviant values and exposure to carbon tetrachloride was found.

The most significant finding in the study came from the paired analysis of 46 active Hypalon® area workers. In that analysis, the workers' biochemical test values obtained before exposure to carbon tetrachloride were compared to those taken following exposure. When comparisons were made, no statistically significant changes were noted between the before and after measurements. This finding is enhanced by the fact that each worker served as his own control.

Carbon tetrachloride has been recognized for many years as a very toxic solvent to man (12). Studies to date would indicate that physiological alterations occurred only at exposure to high concentrations of carbon tetrachloride (12). Furthermore, those individuals affected usually had skin contact with the liquid as well as the vapor. In the current study, potential exposure to carbon tetrachloride ranged from 0 to 10 ppm void of direct contact with liquid. Thus, the Hypalon® workers were not exposed to carbon tetrachloride levels which pose serious threats to health.

Functional and destructive injury of the liver and kidneys have most often been the reported result of overexposure to carbon tetrachloride (12). Liver function parameters analyzed in the present study included serum bilirubin, SGOT, SGPT, LDH, and alkaline phosphatase. Bilirubin, SGOT and SGPT levels observed among the exposed workers were very comparable to those of the controls. Slight,

but statistically significant mean differences were noted when the alkaline phosphatase and LDH levels when analyzed. These differences are not interpreted to be, however, medically significant. Moderate elevations, two to fourfold increases, are generally regarded as diagnostic (13). Elevations of such magnitude were not evident in the current study.

LDH and alkaline phosphatase levels alone do not provide a sensitive measure of hepatic disease (13). The diagnostic usefulness of LDH and alkaline phosphatase levels are detracted somewhat due to the large number of conditions which can elevate them. The diagnostic usefulness of LDH and alkaline phosphatase is enhanced by observing the patterns of abnormalities obtained by measuring SGOT and SGPT. No abnormal patterns occurred in the current study with SGOT and SGPT.

Renal function evaluations are generally made using creatinine and BUN tests. In this study, no abnormal creatinine or BUN levels were observed.

The current study, using a tangent screen to obtain precise measurement of the visual field, found no visual field defects among workers with potential exposure to carbon tetrachloride. The peripheral vision defects cited in the literature (14-19) appeared to have occurred among individuals exposed to carbon tetrachloride vapors many folds higher than the 10 ppm limit presently maintain in the Hypalon® area. It is concluded from visual field screening data that the peripheral vision of the Hypalon® workers is normal.

ACKNOWLEDGEMENT

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TABLE 1

BIOCHEMICAL TEST RESULTS BY STUDY GROUPS

Laboratory Test	Never Exposed (N=104)	Currently Exposed (N=56)	Currently Exposed (N=67)
Glucose (mg/dl)	93.7	91.8	93.8
BUN (mg/dl)	15.4	16.1	14.8
Creatinine (mg/dl	1.2	1.2	1.2
Sodium (meq/L)	141.4	141.6	141.4
Potassium (meq/L	4.4	4.4	4.3
Chloride (meq/L	103.9	103.9	103.6
Uric Acid (mg/dl)	6.2	5.9	6.2
Calcium (mg/dl)	9.8	9.7	10.2
Inorganic Phosphorous (mg/dl)	3.0	3.2	3.1
Total Protein (g/dl)	7.1	7.1	7.1
Albumin (g/dl)	4.4	4.4	4.4
Alkaline Phosphatase (U/L)	75.6	79.7	70.4
Total Bilirubin (mg/dl)	0.6	0.5	0.5
SGOT (U/L)	24.0	23.2	23.5
SGPT (U/L)	25.6	23.1	23.8
LDH (U/L)	165.2	176.0*	165.1
Globulin (g/dl)	2.7	2.7	2.7
Chloresterol (mg/dl)	186.0	187.3	194.7
Triglyceride (mg/dl)	132.2	119.6*	145.3

*$p < 0.05$

TABLE 2

BIOCHEMICAL TEST RESULTS FOR CURRENTLY EXPOSED WORKERS
BY JOB CLASSIFICATION

Laboratory Test	Never Exposed (N=104)	Currently Exposed Operators (N=32)	Currently Exposed Auxiliary (N=17)	Currently Exposed Mechanic (N=7)
Glucose (mg/dl)	93.7	90.3	91.9	97.1
BUN (mg/dl)	15.4	15.6	16.6	17.3
Creatinine (mg/dl	1.2	1.2	1.1	1.2
Sodium (meq/L)	141.4	141.7	140.7	143.1
Potassium (meq/L	4.4	4.5	4.3	4.4
Chloride (meq/L	103.9	103.7	103.9	104.6
Uric Acid (mg/dl)	6.2	6.0	5.8	5.6
Calcium (mg/dl)	9.8	9.7	9.7	9.8
Inorganic Phosphorous (mg/dl)	3.0	3.2	3.4	2.7
Total Protein (g/dl)	7.1	7.1	7.2	6.8
Albumin (g/dl)	4.4	4.4	4.5	4.2
Alkaline Phosphatase (U/L)	75.6	75.8	87.1*	79.1
Total Bilirubin (mg/dl)	0.6	0.5	0.6	0.5
SGOT (U/L)	24.0	21.9	24.7	25.8
SGPT (U/L)	25.6	34.4	19.9	25.3
LDH (U/L)	165.2	177.6*	171.1	180.0
Globulin (g/dl)	2.7	2.7	2.7	2.6
Chloresterol (mg/dl)	187.1	190.1	195.1	180.4
Triglyceride (mg/dl)	132.4	124.3	97.9*	152.9

*$p < 0.05$

TABLE 3
BIOCHEMICAL TEST RESULTS FOR CURRENTLY EXPOSED WORKERS
BY DURATION OF EXPOSURE

Laboratory Test	Never Exposed (N=104)	Currently Exposed 25 Months Duration	Currently Exposed 25 to 48 Months Duration	Currently Exposed 48 Months Duration
Glucose (mg/dl)	93.7	94.9	90.2	89.9
BUN (mg/dl)	15.4	16.4	16.0	16.0
Creatinine (mg/dl	1.2	1.2	1.2	1.2
Sodium (meq/L)	141.4	141.3	141.5	142.1
Potassium (meq/L	4.4	4.3	4.5	4.5
Chloride (meq/L	103.9	103.5	104.3	103.7
Uric Acid (mg/dl)	6.2	5.9	6.0	5.5
Calcium (mg/dl)	9.8	9.7	9.8	9.8
Inorganic Phosphorous (mg/dl)	3.0	3.2	3.3	3.2
Total Protein (g/dl)	7.2	7.2	7.1	6.9
Albumin (g/dl)	4.4	4.4	4.4	4.4
Alkaline Phosphatase (U/L)	75.6	79.6	81.4	76.7
Total Bilirubin (mg/dl)	0.6	0.5	0.5	0.5
SGOT (U/L)	24.0	24.8	23.0	21.1
SGPT (U/L)	25.6	21.6	24.0	23.8
LDH (U/L)	165.2	179.9*	171.3	178.4
Globulin (g/dl)	2.7	2.8	2.7	2.5
Chloresterol (mg/dl)	184.5	179.2	192.9	182.2
Triglyceride (mg/dl)	132.0	105.8*	120.3	139.2

*$p < 0.05$

TABLE 4
BIOCHEMICAL TEST RESULTS FOR WORKERS BEFORE AND AFTER ASSIGNMENT TO THE HYPALON® MANUFACTURING AREA (N=46)

Laboratory Test	Before	After
Glucose (mg/dl)	93.3	92.7
BUN (mg/dl)	14.2	15.0
Creatinine (mg/dl	1.2	1.2
Sodium (meq/L)	141.9	141.2
Potassium (meq/L	4.6	4.3
Chloride (meq/L	103.7	103.9
Uric Acid (mg/dl)	6.0	5.9
Calcium (mg/dl)	10.0	9.6
Inorganic Phosphorous (mg/dl)	3.1	3.1
Total Protein (g/dl)	7.1	7.1
Albumin (g/dl)	4.4	4.3
Alkaline Phosphatase (U/L)	78.2	78.4
Total Bilirubin (mg/dl)	0.6	0.5
SGOT (U/L)	24.0	24.2
SGPT (U/L)	28.4	23.1
LDH (U/L)	167.0	168.3
Globulin (g/dl)	2.8	2.7
Chloresterol (mg/dl)	193.6	189.3
Triglyceride (mg/dl)	139.8	133.8

SUPPLEMENT

"HYPALON" EXPOSURE ASSESSMENT
BEAUMONT PLANT

A review of the personal breathing zone samples collected for employees assigned to the Beaumont "Hypalon" Area during the period 1977-1979 showed that routine carbon tetrachloride exposures, excluding maintenance tasks and some filter change work where respiratory protection is worn, were less than 5 ppm and averaged 2 ppm as 8-hour time-weighted averages.

Patricia G. Gilby
Industrial Hygienist
CIH 1352

PGG:lrg
2/14/86

EXPOSURE ASSESSMENT

Three of the five Du Pont plants for which predicted carbon tetrachloride exposures were listed in EPA's August 1985 Exposure and Risk document were dispersion modeled using the most current plant specific data. The other two Du Pont plants were not modeled because sufficient meteorological data were not in our computer files. However, we believe conclusions drawn from the modeled plants will be generally applicable.

Using the Industrial Source Complex (ISC) short-term model, the highest off-plant annual and 24-hour average concentrations were predicted. Comparisons of these ISC model results with model results reported in EPA's Exposure and Risk document and with a pertinent health effect criterion are given in Tables 1 and 2. (Computer output sheets listing data and results for the ISC model are attached.)

Table 1 shows that, for the most exposed person off plant, the Human Exposure Model (HEM) model prediction is about a factor of 100 too high. Table 2 shows that all the off-plant exposures predicted by ISC are well below Haskell Lab's health effects criterion.

Two reasons for the large ISC and HEM differences in predicted concentration are apparent. First, the HEM model assumes the most exposed person lives about 200 yards from the emission points. In most cases, this would equate to someone living on the plant site. In contrast, the ISC model results

are based on locations where someone could live. In addition to excluding areas within the plant boundary, other terrain features likely to prevent housing were considered in the ISC results. For instance, all three plants are located on major waterways (i.e., the Gulf of Mexico) where it appears unlikely that houses will ever be built. Secondly, EPA apparently assumes that fugitive emission (i.e., leaks) are very high for these plants. It is our experience that EPA fugitive emission estimates frequently overestimate leaks from our plants by factors of 10 to 100. We have reviewed design and operating practices at our plants to determine a better way to predict fugitive emissions from Du Pont plants and have discussed our conclusions with EPA. We plan to collect additional supporting data through field testing. Briefly, our position on fugitive emission estimation is as follows:

EPA's fugitive emission estimates are based on data from a wide cross section of industry with greatly different design and operating characteristics (i.e., petroleum refineries and chemical plants, non-toxic and toxic materials) commodity chemicals and specialty products, etc.). Consequently, EPA s estimating factors may he reasonable for national estimates but are unlikely to be accurate for a specific plant or industry subgroup.

We believe Du Pont processes can be divided into four categories based on design specifications and two categories

based on operation and maintenance practices. Thus, there is a matrix of eight categories of Du Pont plants. It should be possible to quantify the fugitive emissions from each of these categories.

Field data collected so far show that processes with similar design and maintenance practices to those of carbon tetrachloride using plants have much lower fugitive emissions than predicted using EPA's factors. We believe future field tests will verify this. The results of these field tests will be shared with the agency when they are available.

In conclusion, maximum off-plant exposures predicted using the ISC model do not agree with predictions made by the HEM model. We believe the ISC results are more realistic predictions of maximum exposure. Furthermore, maximum off-plant exposures predicted using the ISC model are well below levels associated with possible health concerns.

TABLE 1

COMPARISON OF ISC AND HEM MODEL RESULTS FOR THE HIGHEST OFF-PLANT, ONE-YEAR AVERAGE EXPOSURE

	Maximum Off-Plant, One-year Average Exposure (μ grams/m^3)	
	HEM Model	ISC Model
Beaumont Plant		
Carbon Tetrachloride	120	1.4
Chambers Works		
Carbon Tetrachloride	11	0.3
Corpus Christi Plant		
Carbon Tetrachloride	110	1.3

TABLE 2

COMPARISON OF ISC MODEL PREDICTED OFF-PLANT, 24-HOUR EXPOSURES VERSUS HASKELL LAB COMMUNITY AIR LEVEL

	Maximum Off-Plant, 24-Hour Exposure (μ grams/m^3)	
	ISC Predicted Concentration	Haskell Lab Community Air Level
Beaumont Plant		
Carbon Tetrachloride	16	600
Chambers Works		
Carbon Tetrachloride	10	600
Corpus Christi Plant		
Carbon Tetrachloride	24	600

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

```
CALCULATE (CONCENTRATION=1,DEPOSITION=2)                          ISW(1) =  1
RECEPTOR GRID SYSTEM (RECTANGULAR=1 OR 3, POLAR=2 OR 4)           ISW(2) =  2
DISCRETE RECEPTOR SYSTEM (RECTANGULAR=1,POLAR=2)                  ISW(3) =  2
TERRAIN ELEVATIONS ARE READ (YES=1,NO=0)                          ISW(4) =  0
CALCULATIONS ARE WRITTEN TO TAPE (YES=1,NO=0)                     ISW(5) =  0
LIST ALL INPUT DATA (NO=0,YES=1,MET DATA ALSO=2)                  ISW(6) =  1

COMPUTE AVERAGE CONCENTRATION (OR TOTAL DEPOSITION)
WITH THE FOLLOWING TIME PERIODS:
  HOURLY (YES=1,NO=0)                                             ISW(7) =  0
  2-HOUR (YES=1,NO=0)                                             ISW(8) =  0
  3-HOUR (YES=1,NO=0)                                             ISW(9) =  0
  4-HOUR (YES=1,NO=0)                                             ISW(10) =  0
  6-HOUR (YES=1,NO=0)                                             ISW(11) =  0
  8-HOUR (YES=1,NO=0)                                             ISW(12) =  0
  12-HOUR (YES=1,NO=0)                                            ISW(13) =  0
  24-HOUR (YES=1,NO=0)                                            ISW(14) =  1
PRINT 'N'-DAY TABLE(S) (YES=1,NO=0)                               ISW(15) =  1

PRINT THE FOLLOWING TYPES OF TABLES WHOSE TIME PERIODS ARE
SPECIFIED BY ISW(7) THROUGH ISW(14):
  DAILY TABLES (YES=1,NO=0)                                       ISW(16) =  0
  HIGHEST & SECOND HIGHEST TABLES (YES=1,NO=0)                    ISW(17) =  1
  MAXIMUM 50 TABLES (YES=1,NO=0)                                  ISW(18) =  0
METEOROLOGICAL DATA INPUT METHOD (PRE-PROCESSED=1,CARD=2)         ISW(19) =  1
RURAL-URBAN OPTION (RURAL=0,URBAN MODE 1=1,URBAN MODE 2=2)        ISW(20) =  0
WIND PROFILE EXPONENT VALUES (DEFAULTS=1,USER ENTERS=2,3)         ISW(21) =  1
VERTICAL POT. TEMP. GRADIENT VALUES (DEFAULTS=1,USER ENTERS=2,3)  ISW(22) =  1
SCALE EMISSION RATES FOR ALL SOURCES (NO=0,YES>0)                 ISW(23) =  0
PROGRAM CALCULATES FINAL PLUME RISE ONLY (YES=1,NO=2)             ISW(24) =  1
PROGRAM ADJUSTS ALL STACK HEIGHTS FOR DOWNWASH (YES=2,NO=1)       ISW(25) = 20

NUMBER OF INPUT SOURCES                                           NSOURC =  12
NUMBER OF SOURCE GROUPS (=0,ALL SOURCES)                          NGROUP =   0
TIME PERIOD INTERVAL TO BE PRINTED (=0,ALL INTERVALS)              IPERD =   0
NUMBER OF X (RANGE) GRID VALUES                                   NXPNTS =   3
NUMBER OF Y (THETA) GRID VALUES                                   NYPNTS =  36
NUMBER OF DISCRETE RECEPTORS                                      NXWYPT =   0
SOURCE EMISSION RATE UNITS CONVERSION FACTOR                          TK = .10000*07
ENTRAINMENT COEFFICIENT FOR UNSTABLE ATMOSPHERE                    BETA1 = .600
ENTRAINMENT COEFFICIENT FOR STABLE ATMOSPHERE                      BETA2 = .600
HEIGHT ABOVE GROUND AT WHICH WIND SPEED WAS MEASURED                   ZR =  10.00  METERS
LOGICAL UNIT NUMBER OF METEOROLOGICAL DATA                          IMET =  12
DECAY COEFFICIENT FOR PHYSICAL OR CHEMICAL DEPLETION               DECAY = .000000
SURFACE STATION NO.                                                  ISS = 12918      Lake Charles
YEAR OF SURFACE DATA                                                 ISY = 84
UPPER AIR STATION NO.                                                IUS =  3937      Houston
YEAR OF UPPER AIR DATA                                               IUY = 84
ALLOCATED DATA STORAGE                                            LIMIT = 43500 WORDS
REQUIRED DATA STORAGE FOR THIS PROBLEM RUN                        MIMIT =  3483 WORDS
```

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

*** METEOROLOGICAL DAYS TO BE PROCESSED ***
(IF=1)

```
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1
```

*** UPPER BOUND OF FIRST THROUGH FIFTH WIND SPEED CATEGORIES ***
(METERS/SEC)

1.54, 3.09, 5.14, 8.23, 10.80,

*** WIND PROFILE EXPONENTS ***

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00
B	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00
C	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00
D	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00
E	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00
F	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00

*** VERTICAL POTENTIAL TEMPERATURE GRADIENTS ***
(DEGREES KELVIN PER METER)

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.00000	.00000	.00000	.00000	.00000	.00000
B	.00000	.00000	.00000	.00000	.00000	.00000
C	.00000	.00000	.00000	.00000	.00000	.00000
D	.00000	.00000	.00000	.00000	.00000	.00000
E	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01
F	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

*** RANGES OF POLAR GRID SYSTEM ***
(METERS)

550.0, 1000.0, 1500.0,

*** RADIAL ANGLES OF POLAR GRID SYSTEM ***

(DEGREES)

10.0,	20.0,	30.0,	40.0,	50.0,	60.0,	70.0,	80.0,	90.0,	100.0,
110.0,	120.0,	130.0,	140.0,	150.0,	160.0,	170.0,	180.0,	190.0,	200.0,
210.0,	220.0,	230.0,	240.0,	250.0,	260.0,	270.0,	280.0,	290.0,	300.0,
310.0,	320.0,	330.0,	340.0,	350.0,	360.0,				

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

*** SOURCE DATA ***

SOURCE NUMBER	TYPE	WALK	NUMBER PART. CATS.	EMISSION RATE TYPE=0,1 (GRAMS/SEC) TYPE=2 (GRAMS/SEC) *PER METER**2	X (METERS)	Y (METERS)	BASE ELEV. (METERS)	HEIGHT (METERS)	TEMP. TYPE=0 (DEG.K); VERT.DIM TYPE=1 (METERS)	EXIT VEL. TYPE=0 (M/SEC); HORZ.DIM TYPE=1,2 (METERS)	DIAMETER TYPE=0 (METERS)	BLDG. HEIGHT TYPE=0 (METERS)	BLDG. LENGTH TYPE=0 (METERS)	BLDG. WIDTH TYPE=0 (METERS)
176	2	0	0	.66000-05	-15.0	-390.0	.0	1.00	.00	175.00	.00	.00	.00	.00
114	2	0	0	.27200-03	83.0	-376.0	.0	1.00	.00	2.50	.00	.00	.00	.00
277	2	0	0	.53000-03	15.0	-266.0	.0	1.00	.00	1.50	.00	.00	.00	.00
112	0	0	0	.12900+01	23.0	-271.0	.0	34.10	316.00	8.50	3.05	.00	.00	.00
14	0	0	0	.17300+00	99.0	-423.0	.0	9.15	263.00	.10	.10	.00	.00	.00
151	0	0	0	.14700+00	23.0	-362.0	.0	18.90	302.00	20.90	.76	9.15	68.60	30.50
15234	0	0	0	.36300+00	.0	-339.0	.0	18.90	302.00	22.80	.67	9.15	68.60	30.50
15567	0	0	0	.21600+00	-11.0	-320.0	.0	18.90	302.00	9.90	.76	9.15	68.60	30.50
1589	0	0	0	.14600+00	-23.0	-317.0	.0	18.90	302.00	9.90	.76	9.15	68.60	30.50
234	2	0	0	.60000-06	143.0	-223.0	.0	1.00	.00	400.00	.00	.00	.00	.00
284	2	0	0	.12500-04	-200.0	-285.0	.0	3.00	.00	20.00	.00	.00	.00	.00
302	2	0	0	.36000-03	-190.0	-250.0	.0	3.00	.00	20.00	.00	.00	.00	.00

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

* SOURCE-RECEPTOR COMBINATIONS LESS THAN 100 METERS OR THREE BUILDING HEIGHTS IN DISTANCE. NO AVERAGE CONCENTRATION IS CALCULATED *

SOURCE NUMBER	- - RECEPTOR LOCATION - - X OR RANGE (METERS)	Y (METERS) OR DIRECTION (DEGREES)	DISTANCE BETWEEN (METERS)
234	550.0	70.0	47.79
234	550.0	80.0	5.63
234	550.0	90.0	-17.40
234	550.0	100.0	-14.21
234	550.0	110.0	14.07
234	550.0	120.0	59.41

N-DAY
366 DAYS
SGROUP# 1

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

* 366-DAY AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *

* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 8.83453 AND OCCURRED AT (550.0, 170.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 550.0	1000.0	1500.0
360.0 /	3.64363	2.19464	1.50627
350.0 /	3.81926	2.32463	1.51589
340.0 /	4.44845	2.53349	1.73496
330.0 /	4.35736	2.48059	1.51022
320.0 /	3.98257	2.03671	1.25420
310.0 /	4.19720	2.07422	1.37661
300.0 /	3.77150	2.21726	1.42091
290.0 /	4.22898	2.30518	1.32389
280.0 /	4.67497	2.09058	1.05805
270.0 /	4.91079	1.65266	.82539
260.0 /	4.48185	1.48070	.98212
250.0 /	4.00784	1.51413	.69220
240.0 /	4.16700	1.35041	.80669
230.0 /	5.13015	1.74732	1.00832
220.0 /	5.65246	1.92035	.99024
210.0 /	5.41567	1.68928	.76292
200.0 /	7.13174	1.40595	.64922
190.0 /	6.85216	1.87595	.96680
180.0 /	6.72860	2.56213	1.36612
170.0 /	8.83453	2.72197	1.37553
160.0 /	6.72412	2.16648	1.21280
150.0 /	4.43973	1.73336	.88717
140.0 /	3.95489	1.20212	.65895
130.0 /	3.66638	1.10092	.53847
120.0 /	2.34992	1.07810	.62894
110.0 /	1.90650	1.04349	.47655
100.0 /	1.72763	.96800	.61150
90.0 /	1.41025	.92605	.51160
80.0 /	1.32077	.91699	.47296
70.0 /	1.29738	.80449	.51046
60.0 /	2.39115	.76929	.43373
50.0 /	2.51045	.80167	.45197
40.0 /	2.62596	.88187	.47196
30.0 /	2.56221	1.23667	.69466
20.0 /	2.78910	1.31904	.81820
10.0 /	3.47700	1.76322	1.00803

could be developed

month

HIGH
24-HR
SGROUP# 1

*** BEAUMONT CARBONTLTRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

* HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 76.39106 AND OCCURRED AT (550.0, 200.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 550.0	1000.0	1500.0
360.0 /	17.05154 (93, 1)	11.81561 (54, 1)	11.98942 (54, 1)
350.0 /	29.66660 (316, 1)	18.69719 (316, 1)	13.39256 (316, 1)
340.0 /	33.76887 (316, 1)	22.28638 (316, 1)	17.23629 (316, 1)
330.0 /	32.71018 (316, 1)	21.31725 (316, 1)	10.36035 (316, 1)
320.0 /	30.04691 (316, 1)	13.42992 (197, 1)	8.32577 (215, 1)
310.0 /	32.35473 (242, 1)	14.46879 (197, 1)	8.61185 (130, 1)
300.0 /	24.55381 (215, 1)	12.46728 (307, 1)	12.12847 (76, 1)
290.0 /	24.02946 (214, 1)	17.55556 (76, 1)	13.12499 (266, 1)
280.0 /	27.78714 (76, 1)	21.09559 (137, 1)	11.81021 (210, 1)
270.0 /	46.15883 (266, 1)	20.25728 (210, 1)	7.62028 (210, 1)
260.0 /	40.02137 (306, 1)	16.08029 (265, 1)	16.18208 (325, 1)
250.0 /	30.20821 (71, 1)	14.61454 (178, 1)	9.24873 (178, 1)
240.0 /	43.09166 (51, 1)	11.84137 (49, 1)	10.02888 (48, 1)
230.0 /	57.59985 (343, 1)	18.05512 (343, 1)	14.66219 (343, 1)
220.0 /	63.67666 (343, 1)	25.00345 (343, 1)	8.95701 (336, 1)
210.0 /	52.13167 (303, 1)	17.81172 (286, 1)	11.22510 (286, 1)
200.0 /	76.39106 (343, 1)	19.33754 (33, 1)	8.64737 (342, 1)
190.0 /	59.46055 (342, 1)	16.40954 (120, 1)	13.68380 (33, 1)
180.0 /	41.96233 (326, 1)	20.91711 (280, 1)	10.64529 (297, 1)
170.0 /	47.24961 (341, 1)	20.87218 (280, 1)	11.65533 (348, 1)
160.0 /	43.86863 (6, 1)	16.36571 (65, 1)	10.03028 (59, 1)
150.0 /	51.18594 (312, 1)	15.63598 (6, 1)	9.48522 (350, 1)
140.0 /	37.72174 (53, 1)	20.72038 (154, 1)	7.99870 (157, 1)
130.0 /	45.19592 (190, 1)	15.22067 (312, 1)	9.58675 (312, 1)
120.0 /	25.00657 (60, 1)	15.67533 (190, 1)	10.57626 (312, 1)
110.0 /	22.81148 (60, 1)	11.67558 (218, 1)	9.36799 (190, 1)
100.0 /	32.41092 (60, 1)	14.85608 (60, 1)	13.20932 (255, 1)
90.0 /	13.70987 (330, 1)	20.60566 (60, 1)	15.21350 (60, 1)
80.0 /	12.00953 (79, 1)	14.99455 (25, 1)	10.59317 (25, 1)
70.0 /	12.75844 (79, 1)	8.53818 (39, 1)	8.29402 (25, 1)
60.0 /	13.89985 (222, 1)	9.14122 (79, 1)	6.31302 (79, 1)
50.0 /	28.23134 (315, 1)	6.72338 (194, 1)	5.35527 (62, 1)
40.0 /	30.13459 (315, 1)	9.17793 (222, 1)	5.01264 (357, 1)
30.0 /	18.34649 (360, 1)	22.71020 (315, 1)	16.70508 (315, 1)
20.0 /	19.60399 (54, 1)	11.51338 (360, 1)	9.18462 (360, 1)
10.0 /	25.89062 (54, 1)	16.47065 (54, 1)	8.93751 (54, 1)

could be looped

2ND HIGH
24-HR
SGROUP# 1

*** BEAUMONT CARBONTETRACHLORIDE CONCENTRATION 1984 EMISSIONS ***

* SECOND HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 54.58133 AND OCCURRED AT (550.0, 220.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 550.0	1000.0	1500.0
360.0 /	14.21198 (174, 1)	11.67631 (92, 1)	7.99798 (26, 1)
350.0 /	18.10803 (172, 1)	11.83400 (244, 1)	7.36438 (244, 1)
340.0 /	21.41244 (71, 1)	13.23522 (242, 1)	10.09985 (242, 1)
330.0 /	27.65481 (242, 1)	14.10980 (242, 1)	10.31332 (242, 1)
320.0 /	18.66661 (322, 1)	12.43265 (215, 1)	7.95368 (197, 1)
310.0 /	30.04987 (316, 1)	11.16241 (145, 1)	7.92268 (197, 1)
300.0 /	19.46966 (214, 1)	12.26207 (214, 1)	11.23387 (71, 1)
290.0 /	23.99640 (307, 1)	14.03501 (266, 1)	13.09227 (137, 1)
280.0 /	27.04095 (214, 1)	19.19456 (266, 1)	16.33736 (306, 1)
270.0 /	43.12777 (137, 1)	11.43706 (88, 1)	6.47112 (331, 1)
260.0 /	34.93087 (210, 1)	12.25619 (266, 1)	14.25625 (265, 1)
250.0 /	29.73413 (265, 1)	14.47346 (306, 1)	8.12502 (146, 1)
240.0 /	42.23664 (178, 1)	11.20069 (178, 1)	8.54895 (254, 1)
230.0 /	50.74813 (254, 1)	13.14961 (254, 1)	8.26148 (342, 1)
220.0 /	54.58133 (10, 1)	18.67173 (342, 1)	8.70744 (343, 1)
210.0 /	47.42510 (120, 1)	17.56975 (342, 1)	8.81549 (342, 1)
200.0 /	43.89002 (305, 1)	19.14667 (286, 1)	8.45687 (120, 1)
190.0 /	46.01748 (334, 1)	15.70487 (341, 1)	8.30906 (302, 1)
180.0 /	41.76697 (342, 1)	18.30979 (141, 1)	10.33135 (280, 1)
170.0 /	46.64656 (280, 1)	20.27820 (153, 1)	11.45363 (280, 1)
160.0 /	41.54346 (284, 1)	15.82624 (59, 1)	9.74012 (179, 1)
150.0 /	36.43504 (154, 1)	13.49168 (157, 1)	9.42332 (6, 1)
140.0 /	37.54560 (312, 1)	15.29948 (312, 1)	7.80342 (49, 1)
130.0 /	26.53009 (290, 1)	13.52759 (154, 1)	7.75442 (329, 1)
120.0 /	23.85152 (265, 1)	12.53188 (53, 1)	10.55554 (53, 1)
110.0 /	20.04432 (25, 1)	11.62878 (255, 1)	6.81050 (350, 1)
100.0 /	21.75927 (330, 1)	14.15656 (255, 1)	7.65935 (218, 1)
90.0 /	13.50069 (25, 1)	11.68586 (305, 1)	6.19317 (180, 1)
80.0 /	11.37269 (25, 1)	10.27737 (330, 1)	6.99598 (305, 1)
70.0 /	12.02232 (62, 1)	8.12747 (330, 1)	6.37646 (330, 1)
60.0 /	13.27685 (116, 1)	7.91822 (313, 1)	5.34091 (311, 1)
50.0 /	16.31564 (193, 1)	6.22583 (289, 1)	5.00122 (79, 1)
40.0 /	19.97545 (360, 1)	8.17589 (193, 1)	4.70127 (222, 1)
30.0 /	17.24207 (315, 1)	12.35543 (193, 1)	9.61161 (193, 1)
20.0 /	16.99561 (360, 1)	9.71310 (193, 1)	8.30733 (315, 1)
10.0 /	25.33868 (315, 1)	10.53833 (360, 1)	7.35354 (360, 1)

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1964 ***

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CALCULATE (CONCENTRATION=1,DEPOSITION=2)                          ISW(1) =   1
RECEPTOR GRID SYSTEM (RECTANGULAR=1 OR 3, POLAR=2 OR 4)           ISW(2) =   2
DISCRETE RECEPTOR SYSTEM (RECTANGULAR=1,POLAR=2)                  ISW(3) =   2
TERRAIN ELEVATIONS ARE READ (YES=1,NO=0)                          ISW(4) =   0
CALCULATIONS ARE WRITTEN TO TAPE (YES=1,NO=0)                     ISW(5) =   0
LIST ALL INPUT DATA (NO=0,YES=1,MET DATA ALSO=2)                  ISW(6) =   1

COMPUTE AVERAGE CONCENTRATION (OR TOTAL DEPOSITION)
WITH THE FOLLOWING TIME PERIODS:
  HOURLY (YES=1,NO=0)                                             ISW(7) =   0
  2-HOUR (YES=1,NO=0)                                             ISW(8) =   0
  3-HOUR (YES=1,NO=0)                                             ISW(9) =   0
  4-HOUR (YES=1,NO=0)                                             ISW(10) =  0
  6-HOUR (YES=1,NO=0)                                             ISW(11) =  0
  8-HOUR (YES=1,NO=0)                                             ISW(12) =  0
  12-HOUR (YES=1,NO=0)                                            ISW(13) =  0
  24-HOUR (YES=1,NO=0)                                            ISW(14) =  1
PRINT 'N'-DAY TABLE(S) (YES=1,NO=0)                               ISW(15) =  1

PRINT THE FOLLOWING TYPES OF TABLES WHOSE TIME PERIODS ARE
SPECIFIED BY ISW(7) THROUGH ISW(14):
  DAILY TABLES (YES=1,NO=0)                                       ISW(16) =  0
  HIGHEST & SECOND HIGHEST TABLES (YES=1,NO=0)                    ISW(17) =  1
  MAXIMUM 50 TABLES (YES=1,NO=0)                                  ISW(18) =  0
METEOROLOGICAL DATA INPUT METHOD (PRE-PROCESSED=1,CARD=2)         ISW(19) =  1
RURAL-URBAN OPTION (RURAL=0,URBAN MODE 1=1,URBAN MODE 2=2)        ISW(20) =  0
WIND PROFILE EXPONENT VALUES (DEFAULTS=1,USER ENTERS=2,3)         ISW(21) =  1
VERTICAL POT. TEMP. GRADIENT VALUES (DEFAULTS=1,USER ENTERS=2,3)  ISW(22) =  1
SCALE EMISSION RATES FOR ALL SOURCES (NO=0,YES>0)                 ISW(23) =  0
PROGRAM CALCULATES FINAL PLUME RISE ONLY (YES=1,NO=2)             ISW(24) =  2
PROGRAM ADJUSTS ALL STACK HEIGHTS FOR DOWNWASH (YES=2,NO=1)       ISW(25) =  1

NUMBER OF INPUT SOURCES                                           NSOURC =  11
NUMBER OF SOURCE GROUPS (=0,ALL SOURCES)                          NGROUP =   0
TIME PERIOD INTERVAL TO BE PRINTED (=0,ALL INTERVALS)             IPERD  =   0
NUMBER OF X (RANGE) GRID VALUES                                   NXPNTS =   5
NUMBER OF Y (THETA) GRID VALUES                                   NYPNTS =  36
NUMBER OF DISCRETE RECEPTORS                                      NXWYPT =   0
SOURCE EMISSION RATE UNITS CONVERSION FACTOR                      TK     = .10000+07
ENTRAINMENT COEFFICIENT FOR UNSTABLE ATMOSPHERE                   BETA1  = .600
ENTRAINMENT COEFFICIENT FOR STABLE ATMOSPHERE                     BETA2  = .600
HEIGHT ABOVE GROUND AT WHICH WIND SPEED WAS MEASURED              ZR     = 10.00  METERS
LOGICAL UNIT NUMBER OF METEOROLOGICAL DATA                        IMET   = 12
DECAY COEFFICIENT FOR PHYSICAL OR CHEMICAL DEPLETION              DECAY  = .000000
SURFACE STATION NO.                                               ISS    = 13739
YEAR OF SURFACE DATA                                              ISY    = 76
UPPER AIR STATION NO.                                             IUS    = 93734
YEAR OF UPPER AIR DATA                                            IUY    = 76
ALLOCATED DATA STORAGE                                            LTMIT  = 43500 WORDS
REQUIRED DATA STORAGE FOR THIS PROBLEM RUN                        MIMIT  =  3846 WORDS
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ph.l.

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*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1964 ***

*** METEOROLOGICAL DAYS TO BE PROCESSED ***
(IF=1)

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1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1
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*** UPPER BOUND OF FIRST THROUGH FIFTH WIND SPEED CATEGORIES ***
(METERS/SEC)

1.54, 3.09, 5.14, 8.23, 10.80,

*** WIND PROFILE EXPONENTS ***

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00
B	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00
C	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00
D	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00
E	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00
F	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00

*** VERTICAL POTENTIAL TEMPERATURE GRADIENTS ***
(DEGREES KELVIN PER METER)

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.00000	.00000	.00000	.00000	.00000	.00000
B	.00000	.00000	.00000	.00000	.00000	.00000
C	.00000	.00000	.00000	.00000	.00000	.00000
D	.00000	.00000	.00000	.00000	.00000	.00000
E	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01
F	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1964 ***

*** RANGES OF POLAR GRID SYSTEM ***
(METERS)

730.0, 1230.0, 1730.0, 2230.0, 2730.0,

*** RADIAL ANGLES OF POLAR GRID SYSTEM ***

(DEGREES)

10.0,	20.0,	30.0,	40.0,	50.0,	60.0,	70.0,	80.0,	90.0,	100.0,
110.0,	120.0,	130.0,	140.0,	150.0,	160.0,	170.0,	180.0,	190.0,	200.0,
210.0,	220.0,	230.0,	240.0,	250.0,	260.0,	270.0,	280.0,	290.0,	300.0,
310.0,	320.0,	330.0,	340.0,	350.0,	360.0,				

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1984 ***

*** SOURCE DATA ***

SOURCE NUMBER	TYPE	PK FL	NUMBER PART. CATS.	EMISSION RATE TYPE=0,1 (GRAMS/SEC) TYPE=2 (GRAMS/SEC) *PER METER**2	X (METERS)	Y (METERS)	BASE ELEV. (METERS)	HEIGHT (METERS)	TEMP. TYPE=0 (DEG.K); VERT.DIM TYPE=1 (METERS)	EXIT VEL. TYPE=0 (M/SEC); HORZ.DIM TYPE=1,2 (METERS)	DIAMETER TYPE=0 (METERS)	BLDG. HEIGHT TYPE=0 (METERS)	BLDG. LENGTH TYPE=0 (METERS)	BLDG. WIDTH TYPE=0 (METERS)
16431	0	0 0	0	.23000-04	-579.0	-244.0	.0	21.30	283.00	4.20	.60	15.20	122.00	15.20
16432	0	0 0	0	.76000-03	-579.0	-244.0	.0	21.30	283.00	10.20	.03	15.20	122.00	15.20
16433	0	0 0	0	.76000-03	-579.0	-244.0	.0	21.30	283.00	10.20	.03	15.20	122.00	15.20
16434	0	0 0	0	.53000-03	-579.0	-244.0	.0	20.10	283.00	13.60	.60	15.20	122.00	15.20
16435	0	0 0	0	.17600-01	-579.0	-244.0	.0	12.20	283.00	7.00	.51	15.20	122.00	15.20
16791	0	0 0	0	.55000-03	152.0	-37.0	.0	4.60	283.00	.60	.10	.00	.00	.00
16792	0	0 0	0	.72000-03	152.0	-37.0	.0	1.00	283.00	.60	.10	.00	.00	.00
351	0	0 0	0	.54000-01	-457.0	244.0	.0	8.20	283.00	2.20	.25	8.00	54.00	54.00
352	0	0 0	0	.54000-01	-457.0	244.0	.0	8.20	283.00	2.20	.25	8.00	54.00	54.00
353	0	0 0	0	.27000-01	-457.0	244.0	.0	6.10	283.00	.03	.25	8.00	54.00	54.00
1	2	0 0	0	.10000-05	-457.0	244.0	.0	1.00	.00	200.00	.00	.00	.00	.00

'N'-DAY
366 DAYS
SGROUP# 1

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1984 ***

* 366-DAY AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *

* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 1.54143 AND OCCURRED AT (730.0, 320.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 730.0	1230.0	1730.0	2230.0	2730.0
360.0 /	1.08168	.15983	.08259	.05225	.03439
350.0 /	.88803	.17224	.11619	.08974	.06814
340.0 /	.64624	.28732	.17118	.10707	.07900
330.0 /	.86265	.35516	.15123	.09115	.06467
320.0 /	1.54143	.30413	.12819	.08546	.05629
310.0 /	1.50706	.29535	.14143	.08256	.05374
300.0 /	1.16656	.21629	.10031	.06051	.04069
290.0 /	.98335	.22239	.10529	.06292	.04296
280.0 /	.61821	.20151	.09386	.05850	.04260
270.0 /	.46054	.16119	.11913	.07560	.04848
260.0 /	.21856	.12020	.07038	.04461	.03467
250.0 /	.24694	.10723	.05952	.03706	.02562
240.0 /	.19442	.05130	.04672	.03398	.02434
230.0 /	.32674	.04196	.02189	.01771	.01333
220.0 /	.35908	.06288	.02139	.01751	.01434
210.0 /	.38984	.11468	.04711	.02113	.01194
200.0 /	.36664	.17331	.07923	.04580	.03327
190.0 /	.28802	.18725	.12246	.07800	.05416
180.0 /	.27815	.15242	.11636	.08808	.06555
170.0 /	.30976	.15082	.09751	.06735	.05025
160.0 /	.28609	.18374	.11492	.07962	.06016
150.0 /	.29003	.17322	.11046	.08194	.06698
140.0 /	.27455	.15569	.10743	.08162	.06529
130.0 /	.25168	.15085	.10368	.07758	.06075
120.0 /	.25544	.15002	.10189	.07450	.05757
110.0 /	.25337	.15447	.10608	.07812	.06047
100.0 /	.29128	.17761	.12015	.08666	.06933
90.0 /	.30902	.19764	.13558	.09925	.07503
80.0 /	.34168	.18901	.11941	.08157	.06018
70.0 /	.33410	.15047	.09751	.07367	.05914
60.0 /	.28907	.16835	.10149	.07184	.05716
50.0 /	.31570	.16994	.12709	.10428	.08795
40.0 /	.32165	.24578	.21000	.17647	.13979
30.0 /	.41538	.40888	.26916	.15119	.10410
20.0 /	.63611	.40651	.18845	.09094	.05085
10.0 /	1.03914	.28279	.09974	.04838	.03107

121

HIGH
24-HR
SGROUP# 1

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1984 ***

* HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 25.16731 AND OCCURRED AT (730.0, 290.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 730.0	1230.0	1730.0	2230.0	2730.0
360.0 /	6.49288 (238, 1)	4.04068 (258, 1)	2.68214 (46, 1)	1.80649 (190, 1)	.70808 (298, 1)
350.0 /	12.50959 (332, 1)	4.59699 (190, 1)	3.10153 (248, 1)	2.53932 (248, 1)	1.48226 (126, 1)
340.0 /	11.08122 (258, 1)	6.90759 (246, 1)	2.51533 (87, 1)	2.81536 (87, 1)	1.91307 (338, 1)
330.0 /	13.60614 (190, 1)	6.70503 (338, 1)	2.90688 (35, 1)	1.67023 (35, 1)	1.24733 (259, 1)
320.0 /	15.25122 (126, 1)	4.81153 (248, 1)	2.69779 (247, 1)	2.73646 (51, 1)	1.61795 (51, 1)
310.0 /	17.15203 (259, 1)	5.25305 (52, 1)	3.41976 (107, 1)	2.36825 (107, 1)	1.60205 (107, 1)
300.0 /	15.81065 (269, 1)	5.15620 (269, 1)	2.73195 (269, 1)	1.74687 (269, 1)	1.25324 (269, 1)
290.0 /	25.16731 (331, 1)	6.26243 (282, 1)	2.47142 (282, 1)	1.61907 (44, 1)	1.37863 (44, 1)
280.0 /	9.15390 (276, 1)	4.12159 (331, 1)	3.43287 (331, 1)	2.05274 (282, 1)	2.22190 (282, 1)
270.0 /	7.04646 (363, 1)	2.68376 (116, 1)	2.17621 (341, 1)	2.33696 (282, 1)	2.29141 (282, 1)
260.0 /	7.09733 (34, 1)	2.08587 (363, 1)	1.36607 (116, 1)	1.18136 (116, 1)	.88787 (116, 1)
250.0 /	4.26918 (156, 1)	3.77223 (273, 1)	1.44920 (363, 1)	1.04432 (116, 1)	.68949 (116, 1)
240.0 /	2.99784 (25, 1)	2.56874 (34, 1)	3.82425 (273, 1)	.85049 (273, 1)	.58540 (363, 1)
230.0 /	4.75184 (180, 1)	1.47822 (156, 1)	.54206 (331, 1)	1.14829 (34, 1)	.88494 (274, 1)
220.0 /	5.08723 (286, 1)	1.34874 (25, 1)	.69252 (186, 1)	1.18829 (331, 1)	1.58338 (331, 1)
210.0 /	6.95936 (351, 1)	2.19335 (180, 1)	1.01672 (145, 1)	.47515 (25, 1)	.36903 (253, 1)
200.0 /	7.84296 (341, 1)	2.03021 (197, 1)	1.48208 (286, 1)	1.08467 (180, 1)	.90426 (215, 1)
190.0 /	4.64920 (251, 1)	4.08260 (341, 1)	2.12971 (351, 1)	1.03252 (197, 1)	.96789 (286, 1)
180.0 /	6.59223 (340, 1)	2.13283 (267, 1)	3.19336 (341, 1)	2.39705 (341, 1)	1.67600 (341, 1)
170.0 /	9.93707 (340, 1)	3.83811 (340, 1)	3.23306 (251, 1)	1.50838 (251, 1)	1.03480 (267, 1)
160.0 /	6.96384 (340, 1)	6.62073 (340, 1)	3.55336 (340, 1)	2.49870 (340, 1)	2.23213 (340, 1)
150.0 /	4.28089 (340, 1)	4.31986 (340, 1)	2.84763 (340, 1)	1.94478 (340, 1)	1.62292 (340, 1)
140.0 /	3.03807 (358, 1)	1.47382 (340, 1)	1.50419 (293, 1)	1.34643 (293, 1)	1.13554 (293, 1)
130.0 /	2.76502 (117, 1)	2.11849 (117, 1)	1.68341 (117, 1)	1.38883 (117, 1)	1.18133 (117, 1)
120.0 /	3.97722 (267, 1)	2.61543 (267, 1)	1.92484 (267, 1)	1.52900 (267, 1)	1.25100 (267, 1)
110.0 /	6.17880 (355, 1)	4.40144 (355, 1)	3.27260 (355, 1)	2.57884 (355, 1)	2.09718 (355, 1)
100.0 /	9.48636 (355, 1)	4.55991 (355, 1)	2.11683 (355, 1)	1.09661 (355, 1)	.69069 (338, 1)
90.0 /	2.76068 (355, 1)	2.05913 (238, 1)	1.29003 (149, 1)	.99659 (149, 1)	.79741 (57, 1)
80.0 /	2.72242 (149, 1)	1.91551 (143, 1)	1.60986 (332, 1)	1.58250 (332, 1)	1.07439 (332, 1)
70.0 /	3.14419 (57, 1)	2.58986 (105, 1)	2.19924 (333, 1)	1.69442 (333, 1)	1.09886 (333, 1)
60.0 /	4.09864 (105, 1)	2.74343 (333, 1)	1.89016 (287, 1)	1.27245 (287, 1)	.96666 (213, 1)
50.0 /	5.54088 (333, 1)	2.33490 (213, 1)	1.41257 (289, 1)	.89253 (107, 1)	.92328 (107, 1)
40.0 /	4.99689 (287, 1)	2.06247 (107, 1)	1.73921 (225, 1)	1.56408 (238, 1)	1.26106 (41, 1)
30.0 /	3.81979 (97, 1)	3.44131 (238, 1)	2.90899 (179, 1)	1.20851 (238, 1)	.97385 (121, 1)
20.0 /	5.22628 (304, 1)	2.66150 (56, 1)	3.38250 (107, 1)	2.18220 (332, 1)	.74180 (136, 1)
10.0 /	7.08215 (236, 1)	5.45254 (332, 1)	3.15961 (258, 1)	.74960 (308, 1)	.48515 (99, 1)

2ND HIGH
24-HR
SGROUP# 1

*** CHAMBERS WORKS CARBONTETRACHLORIDE CONCENTRATIONS USING 1964 ***

* SECOND HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 14.36824 AND OCCURRED AT (730.0, 300.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 730.0	1230.0	1730.0	2230.0	2730.0
360.0 /	6.09217 (56, 1)	3.62476 (274, 1)	1.66568 (274, 1)	1.01912 (298, 1)	.65624 (190, 1)
350.0 /	9.64635 (107, 1)	2.36809 (41, 1)	2.39541 (109, 1)	1.58838 (109, 1)	1.31014 (109, 1)
340.0 /	10.14335 (274, 1)	4.14262 (109, 1)	2.26484 (258, 1)	1.83286 (338, 1)	1.55870 (211, 1)
330.0 /	7.39100 (298, 1)	5.52988 (87, 1)	2.82729 (281, 1)	1.46918 (259, 1)	1.20572 (122, 1)
320.0 /	12.71863 (248, 1)	3.79824 (122, 1)	2.55326 (346, 1)	2.22527 (247, 1)	1.07482 (6, 1)
310.0 /	13.94041 (122, 1)	5.20740 (268, 1)	3.03397 (221, 1)	1.98849 (221, 1)	1.24688 (6, 1)
300.0 /	14.36824 (347, 1)	5.11136 (46, 1)	2.51182 (46, 1)	1.57292 (46, 1)	1.09631 (46, 1)
290.0 /	12.50139 (95, 1)	3.01799 (294, 1)	1.66705 (44, 1)	1.05642 (282, 1)	.73310 (330, 1)
280.0 /	7.83297 (151, 1)	3.68288 (309, 1)	1.86770 (95, 1)	1.62872 (331, 1)	.76734 (331, 1)
270.0 /	6.54882 (309, 1)	2.40030 (151, 1)	1.47127 (13, 1)	1.77100 (72, 1)	.92018 (72, 1)
260.0 /	3.43027 (274, 1)	1.91821 (116, 1)	1.03711 (269, 1)	.73696 (151, 1)	.53921 (151, 1)
250.0 /	3.42904 (331, 1)	2.03611 (32, 1)	1.16232 (116, 1)	.72464 (363, 1)	.42498 (276, 1)
240.0 /	2.95723 (277, 1)	1.22865 (274, 1)	1.44746 (274, 1)	.84641 (32, 1)	.49353 (348, 1)
230.0 /	4.14640 (277, 1)	1.18883 (331, 1)	.53237 (34, 1)	.78096 (274, 1)	.51323 (273, 1)
220.0 /	4.28167 (186, 1)	1.08638 (301, 1)	.51088 (156, 1)	.98949 (156, 1)	.80268 (156, 1)
210.0 /	4.00294 (341, 1)	1.74474 (277, 1)	.96589 (144, 1)	.44757 (286, 1)	.33184 (286, 1)
200.0 /	4.03720 (253, 1)	1.81771 (187, 1)	1.22094 (186, 1)	.76056 (277, 1)	.68229 (180, 1)
190.0 /	4.18054 (107, 1)	3.46051 (351, 1)	1.45583 (61, 1)	.90515 (187, 1)	.91578 (197, 1)
180.0 /	3.13604 (236, 1)	1.98774 (256, 1)	1.42208 (339, 1)	1.75264 (253, 1)	1.53611 (351, 1)
170.0 /	5.49976 (350, 1)	1.83242 (349, 1)	2.43209 (107, 1)	1.39372 (267, 1)	.89688 (120, 1)
160.0 /	3.00793 (320, 1)	3.31448 (350, 1)	2.69057 (350, 1)	1.64617 (350, 1)	.85161 (236, 1)
150.0 /	3.70938 (293, 1)	2.45365 (293, 1)	1.27434 (320, 1)	1.04989 (251, 1)	1.15954 (251, 1)
140.0 /	2.98500 (285, 1)	1.41304 (293, 1)	1.21277 (340, 1)	.98958 (340, 1)	.84252 (340, 1)
130.0 /	2.51802 (354, 1)	1.89331 (354, 1)	1.46844 (285, 1)	1.17978 (285, 1)	.96423 (285, 1)
120.0 /	3.59447 (344, 1)	2.42406 (344, 1)	1.76372 (344, 1)	1.37949 (344, 1)	1.11713 (344, 1)
110.0 /	2.98320 (266, 1)	1.70588 (266, 1)	1.09526 (266, 1)	.77207 (266, 1)	.60706 (325, 1)
100.0 /	3.18135 (108, 1)	1.76774 (83, 1)	1.15646 (258, 1)	.88349 (258, 1)	.65744 (258, 1)
90.0 /	2.27345 (338, 1)	1.71798 (316, 1)	1.13903 (238, 1)	.94488 (57, 1)	.68316 (149, 1)
80.0 /	2.25420 (57, 1)	1.88528 (57, 1)	1.35301 (105, 1)	1.20915 (256, 1)	.96710 (105, 1)
70.0 /	3.06245 (105, 1)	1.53423 (281, 1)	1.53342 (57, 1)	.94307 (57, 1)	.70223 (75, 1)
60.0 /	2.75113 (333, 1)	2.01154 (75, 1)	1.60790 (94, 1)	1.03426 (213, 1)	.65747 (326, 1)
50.0 /	2.81589 (307, 1)	1.74190 (326, 1)	1.41088 (97, 1)	.87928 (162, 1)	.92077 (304, 1)
40.0 /	2.93142 (354, 1)	1.95813 (336, 1)	1.49162 (238, 1)	1.42515 (106, 1)	1.21529 (235, 1)
30.0 /	3.48340 (354, 1)	2.98889 (106, 1)	1.84972 (75, 1)	1.12567 (121, 1)	.89233 (108, 1)
20.0 /	5.10160 (264, 1)	2.43088 (238, 1)	1.94018 (332, 1)	1.41414 (240, 1)	.61810 (240, 1)
10.0 /	6.40805 (41, 1)	3.96160 (107, 1)	3.07091 (274, 1)	.64009 (258, 1)	.45477 (46, 1)

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

CALCULATE (CONCENTRATION=1,DEPOSITION=2)	ISW(1) =	1
RECEPTOR GRID SYSTEM (RECTANGULAR=1 OR 3, POLAR=2 OR 4)	ISW(2) =	2
DISCRETE RECEPTOR SYSTEM (RECTANGULAR=1,POLAR=2)	ISW(3) =	2
TERRAIN ELEVATIONS ARE READ (YES=1,NO=0)	ISW(4) =	0
CALCULATIONS ARE WRITTEN TO TAPE (YES=1,NO=0)	ISW(5) =	0
LIST ALL INPUT DATA (NO=0,YES=1,MET DATA ALSO=2)	ISW(6) =	1
COMPUTE AVERAGE CONCENTRATION (OR TOTAL DEPOSITION)		
WITH THE FOLLOWING TIME PERIODS:		
HOURLY (YES=1,NO=0)	ISW(7) =	0
2-HOUR (YES=1,NO=0)	ISW(8) =	0
3-HOUR (YES=1,NO=0)	ISW(9) =	0
4-HOUR (YES=1,NO=0)	ISW(10) =	0
6-HOUR (YES=1,NO=0)	ISW(11) =	0
8-HOUR (YES=1,NO=0)	ISW(12) =	0
12-HOUR (YES=1,NO=0)	ISW(13) =	0
24-HOUR (YES=1,NO=0)	ISW(14) =	1
PRINT 'N'-DAY TABLE(S) (YES=1,NO=0)	ISW(15) =	1
PRINT THE FOLLOWING TYPES OF TABLES WHOSE TIME PERIODS ARE		
SPECIFIED BY ISW(7) THROUGH ISW(14):		
DAILY TABLES (YES=1,NO=0)	ISW(16) =	0
HIGHEST & SECOND HIGHEST TABLES (YES=1,NO=0)	ISW(17) =	1
MAXIMUM 50 TABLES (YES=1,NO=0)	ISW(18) =	0
METEOROLOGICAL DATA INPUT METHOD (PRE-PROCESSED=1,CARD=2)	ISW(19) =	1
RURAL-URBAN OPTION (RURAL=0,URBAN MODE 1=1,URBAN MODE 2=2)	ISW(20) =	0
WIND PROFILE EXPONENT VALUES (DEFAULTS=1,USER ENTERS=2,3)	ISW(21) =	1
VERTICAL POT. TEMP. GRADIENT VALUES (DEFAULTS=1,USER ENTERS=2,3)	ISW(22) =	1
SCALE EMISSION RATES FOR ALL SOURCES (NO=0,YES>0)	ISW(23) =	0
PROGRAM CALCULATES FINAL PLUME RISE ONLY (YES=1,NO=2)	ISW(24) =	1
PROGRAM ADJUSTS ALL STACK HEIGHTS FOR DOWNWASH (YES=2,NO=1)	ISW(25) =	20
NUMBER OF INPUT SOURCES	NSOURC =	14
NUMBER OF SOURCE GROUPS (=0,ALL SOURCES)	NGROUP =	0
TIME PERIOD INTERVAL TO BE PRINTED (=0,ALL INTERVALS)	IPERD =	0
NUMBER OF X (RANGE) GRID VALUES	NXPNTS =	3
NUMBER OF Y (THETA) GRID VALUES	NYPNTS =	36
NUMBER OF DISCRETE RECEPTORS	NXWYPT =	0
SOURCE EMISSION RATE UNITS CONVERSION FACTOR	TK =	.10000+07
ENTRAINMENT COEFFICIENT FOR UNSTABLE ATMOSPHERE	BETA1 =	.600
ENTRAINMENT COEFFICIENT FOR STABLE ATMOSPHERE	BETA2 =	.600
HEIGHT ABOVE GROUND AT WHICH WIND SPEED WAS MEASURED	ZR =	10.00 METERS
LOGICAL UNIT NUMBER OF METEOROLOGICAL DATA	IMET =	12
DECAY COEFFICIENT FOR PHYSICAL OR CHEMICAL DEPLETION	DECAY =	.000000
SURFACE STATION NO.	ISS =	12924 Corpus Christi
YEAR OF SURFACE DATA	ISY =	64
UPPER AIR STATION NO.	IUS =	12919 Brownsville
YEAR OF UPPER AIR DATA	IUY =	64
ALLOCATED DATA STORAGE	LIMIT =	43500 WORDS
REQUIRED DATA STORAGE FOR THIS PROBLEM RUN	MIMIT =	3913 WORDS

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

*** METEOROLOGICAL DAYS TO BE PROCESSED ***
(IF=1)

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1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1 1 1 1 1
1 1 1 1 1 1 1 1 1 1   1 1 1 1 1 1
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*** UPPER BOUND OF FIRST THROUGH FIFTH WIND SPEED CATEGORIES ***
(METERS/SEC)

1.54, 3.09, 5.14, 8.23, 10.80,

*** WIND PROFILE EXPONENTS ***

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00	.10000+00
B	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00	.15000+00
C	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00	.20000+00
D	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00	.25000+00
E	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00
F	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00	.30000+00

*** VERTICAL POTENTIAL TEMPERATURE GRADIENTS ***
(DEGREES KELVIN PER METER)

STABILITY CATEGORY	WIND SPEED CATEGORY 1	2	3	4	5	6
A	.00000	.00000	.00000	.00000	.00000	.00000
B	.00000	.00000	.00000	.00000	.00000	.00000
C	.00000	.00000	.00000	.00000	.00000	.00000
D	.00000	.00000	.00000	.00000	.00000	.00000
E	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01	.20000-01
F	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01	.35000-01

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

*** RANGES OF POLAR GRID SYSTEM ***
(METERS)

900.0, 1800.0, 2700.0,

*** RADIAL ANGLES OF POLAR GRID SYSTEM ***

(DEGREES)

10.0,	20.0,	30.0,	40.0,	50.0,	60.0,	70.0,	80.0,	90.0,	100.0,
110.0,	120.0,	130.0,	140.0,	150.0,	160.0,	170.0,	180.0,	190.0,	200.0,
210.0,	220.0,	230.0,	240.0,	250.0,	260.0,	270.0,	280.0,	290.0,	300.0,
310.0,	320.0,	330.0,	340.0,	350.0,	360.0,				

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

*** SOURCE DATA ***

SOURCE NUMBER	TYPE	WAKE	NUMBER PART. CATS.	EMISSION RATE TYPE=0,1 (GRAMS/SEC) TYPE=2 (GRAMS/SEC) *PER METER**2	X (METERS)	Y (METERS)	BASE ELEV. (METERS)	HEIGHT (METERS)	TEMP. TYPE=0 (DEG.K); VERT.DIM TYPE=1 (METERS)	EXIT VEL. TYPE=0 (M/SEC); HORZ.DIM TYPE=1,2 (METERS)	DIAMETER TYPE=0 (METERS)	BLDG. HEIGHT TYPE=0 (METERS)	BLDG. LENGTH TYPE=0 (METERS)	BLDG. WIDTH TYPE=0 (METERS)
30	2	0	0	.79000-03	193.0	-1583.0	.0	7.00	.00	10.00	.00	.00	.00	.00
96	2	0	0	.56000-04	231.0	-1020.0	.0	3.00	.00	25.00	.00	.00	.00	.00
97	0	0	0	.46000-02	244.0	-1085.0	.0	15.24	283.00	22.90	.15	.00	.00	.00
100	0	0	0	.10400+00	183.0	-1079.0	.0	14.60	283.00	.10	.25	.00	.00	.00
101	0	0	0	.10400+00	171.0	-1059.0	.0	14.60	283.00	.10	.25	.00	.00	.00
103	0	0	0	.10400+00	201.0	-1101.0	.0	14.60	283.00	.10	.25	.00	.00	.00
121	0	0	0	.18700+00	332.0	-927.0	.0	26.60	283.00	18.30	.20	.00	.00	.00
134	0	0	0	.19000-01	587.0	-846.0	.0	9.80	283.00	.10	.05	.00	.00	.00
135	0	0	0	.10400+01	480.0	-854.0	.0	6.10	300.00	16.20	.61	.00	.00	.00
140	2	0	0	.41000-04	462.0	-884.0	.0	5.00	.00	75.00	.00	.00	.00	.00
144	0	0	0	.61000-01	361.0	-841.0	.0	11.40	283.00	.10	.08	.00	.00	.00
145	0	0	0	.12800+00	434.0	-838.0	.0	7.60	297.00	.10	.25	.00	.00	.00
146	0	0	0	.12800+00	434.0	-848.0	.0	7.60	297.00	.10	.25	.00	.00	.00
147	0	0	0	.12800+00	450.0	-848.0	.0	7.60	297.00	.10	.25	.00	.00	.00

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

* SOURCE-RECEPTOR COMBINATIONS LESS THAN 100 METERS OR THREE BUILDING HEIGHTS IN DISTANCE. NO AVERAGE CONCENTRATION IS CALCULATED *

SOURCE NUMBER	- - RECEPTOR LOCATION - - X OR RANGE (METERS)	Y (METERS) OR DIRECTION (DEGREES)	DISTANCE BETWEEN (METERS)
121	900.0	160.0	84.80
135	900.0	150.0	80.38
140	900.0	150.0	41.05
144	900.0	150.0	92.48
144	900.0	160.0	73.33
145	900.0	150.0	60.72
146	900.0	150.0	70.42
147	900.0	150.0	68.58

N-DAY
366 DAYS
SGROUP# 1*

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

* 366-DAY AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *

* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 13.13320 AND OCCURRED AT (900.0, 160.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 900.0	1800.0	2700.0
360.0 /	1.90225	.83390	.54913
350.0 /	2.55366	1.17829	.67928
340.0 /	2.58880	1.49301	1.01292
330.0 /	2.75543	1.57515	1.04118
320.0 /	2.96775	1.63074	1.09180
310.0 /	3.02381	1.73476	1.08060
300.0 /	3.03256	1.40880	.88802
290.0 /	2.60003	1.27928	.85408
280.0 /	2.63521	1.22188	.50786
270.0 /	2.69854	.84672	.41570
260.0 /	2.52621	.71511	.47541
250.0 /	1.99149	.85524	.46607
240.0 /	2.10936	.83914	.27004
230.0 /	2.32097	.55041	.21537
220.0 /	2.79044	.49521	.20759
210.0 /	3.29559	.52797	.44580
200.0 /	3.89697	.99750	.57629
190.0 /	4.83522	1.49734	.77670
180.0 /	6.61164	2.68079	.92936
170.0 /	10.69942	2.71646	1.13124
160.0 /	13.13320	1.93491	.78006
150.0 /	.70007	1.27970	.46397
140.0 /	4.95661	.75105	.27212
130.0 /	2.55758	.62272	.36583
120.0 /	1.58068	.32162	.29854
110.0 /	1.12679	.31595	.14289
100.0 /	.89322	.43989	.12837
90.0 /	.78303	.42364	.23721
80.0 /	.73286	.36061	.23619
70.0 /	.74797	.25010	.18145
60.0 /	.74962	.24285	.13718
50.0 /	.78564	.24811	.13918
40.0 /	1.14935	.31542	.14695
30.0 /	1.45163	.33373	.20918
20.0 /	1.49946	.62314	.24910
10.0 /	1.53853	.84976	.50890

2ND HIGH
24-HR
SGROUP# 1

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

* SECOND HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 124.98201 AND OCCURRED AT (900.0, 160.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 900.0	1800.0	2700.0
360.0 /	9.85516 (196, 1)	9.37077 (222, 1)	6.84849 (222, 1)
350.0 /	16.49278 (31, 1)	6.70542 (252, 1)	4.18412 (196, 1)
340.0 /	11.07141 (31, 1)	8.57345 (31, 1)	6.91248 (157, 1)
330.0 /	13.63689 (291, 1)	8.27979 (291, 1)	5.90248 (291, 1)
320.0 /	13.99859 (286, 1)	12.19684 (245, 1)	8.85885 (245, 1)
310.0 /	22.47788 (245, 1)	13.50388 (245, 1)	12.54329 (247, 1)
300.0 /	25.60769 (247, 1)	18.30679 (282, 1)	9.47037 (282, 1)
290.0 /	34.54330 (282, 1)	9.22761 (282, 1)	9.63193 (305, 1)
280.0 /	18.49042 (181, 1)	15.73811 (154, 1)	3.46239 (135, 1)
270.0 /	22.17330 (251, 1)	7.34299 (135, 1)	5.11828 (28, 1)
260.0 /	24.45590 (154, 1)	9.67326 (286, 1)	5.65801 (298, 1)
250.0 /	12.87574 (147, 1)	11.57970 (284, 1)	8.69033 (65, 1)
240.0 /	20.18779 (267, 1)	13.14785 (65, 1)	5.34003 (71, 1)
230.0 /	27.53189 (143, 1)	9.46725 (71, 1)	4.54505 (199, 1)
220.0 /	23.23332 (284, 1)	9.16318 (199, 1)	4.33730 (87, 1)
210.0 /	28.66107 (258, 1)	5.63997 (101, 1)	7.60487 (210, 1)
200.0 /	39.64485 (257, 1)	15.96328 (8, 1)	8.23194 (246, 1)
190.0 /	33.10665 (286, 1)	15.96578 (335, 1)	6.82721 (298, 1)
180.0 /	44.16308 (121, 1)	20.05011 (341, 1)	10.71833 (276, 1)
170.0 /	74.13754 (121, 1)	23.71299 (276, 1)	11.29454 (13, 1)
160.0 /	124.98201 (248, 1)	21.05065 (350, 1)	19.16989 (5, 1)
150.0 /	9.86000 (254, 1)	19.15759 (345, 1)	9.25398 (176, 1)
140.0 /	56.82959 (356, 1)	18.70662 (133, 1)	6.56902 (346, 1)
130.0 /	54.96087 (254, 1)	17.86933 (315, 1)	8.78656 (345, 1)
120.0 /	29.87482 (37, 1)	9.08982 (17, 1)	13.56511 (330, 1)
110.0 /	28.19943 (250, 1)	12.56409 (16, 1)	4.80972 (17, 1)
100.0 /	20.93646 (250, 1)	18.86090 (216, 1)	6.15207 (16, 1)
90.0 /	14.90367 (360, 1)	11.51197 (333, 1)	12.98802 (216, 1)
80.0 /	13.78634 (223, 1)	8.99461 (295, 1)	7.57855 (17, 1)
70.0 /	9.64986 (80, 1)	5.69131 (2, 1)	5.09892 (295, 1)
60.0 /	23.13575 (206, 1)	7.38771 (37, 1)	3.55426 (2, 1)
50.0 /	12.16117 (206, 1)	4.78859 (191, 1)	4.14507 (37, 1)
40.0 /	19.39661 (314, 1)	4.66023 (148, 1)	3.12446 (223, 1)
30.0 /	21.00538 (263, 1)	8.20550 (206, 1)	6.94936 (206, 1)
20.0 /	14.83749 (11, 1)	9.35680 (270, 1)	3.97063 (207, 1)
10.0 /	14.39657 (222, 1)	10.53770 (154, 1)	9.20488 (270, 1)

HIGH
24-HR
SGROUP# 1

*** CORPUS CARBONTET CONCENTRATION 1984 EMISSIONS ***

* HIGHEST 24-HOUR AVERAGE CONCENTRATION (MICROGRAMS/CUBIC METER) *
* FROM ALL SOURCES *
* FOR THE RECEPTOR GRID *

* MAXIMUM VALUE EQUALS 132.78583 AND OCCURRED AT (900.0, 160.0) *

DIRECTION / (DEGREES) /	RANGE (METERS) 900.0	1800.0	2700.0
360.0 /	12.92289 (31, 1)	13.33096 (142, 1)	15.07054 (142, 1)
350.0 /	23.96689 (205, 1)	9.02282 (31, 1)	4.95263 (31, 1)
340.0 /	17.15593 (26, 1)	10.61453 (26, 1)	7.90474 (205, 1)
330.0 /	19.05630 (198, 1)	13.65413 (198, 1)	10.35887 (198, 1)
320.0 /	17.91101 (245, 1)	17.00735 (247, 1)	14.95548 (247, 1)
310.0 /	32.30156 (247, 1)	18.60923 (247, 1)	14.67592 (282, 1)
300.0 /	28.38977 (282, 1)	23.87755 (156, 1)	28.04258 (156, 1)
290.0 /	34.97801 (156, 1)	11.05661 (156, 1)	11.97179 (251, 1)
280.0 /	46.28261 (156, 1)	18.24469 (251, 1)	4.16140 (251, 1)
270.0 /	23.56467 (154, 1)	7.84673 (203, 1)	8.24930 (143, 1)
260.0 /	32.42746 (251, 1)	13.21889 (143, 1)	7.44318 (284, 1)
250.0 /	14.68864 (156, 1)	12.62766 (248, 1)	12.15901 (155, 1)
240.0 /	20.52443 (26, 1)	18.14066 (155, 1)	8.74410 (246, 1)
230.0 /	27.71280 (286, 1)	11.55299 (246, 1)	5.87227 (198, 1)
220.0 /	31.80392 (251, 1)	9.38512 (198, 1)	4.35158 (118, 1)
210.0 /	53.13469 (248, 1)	7.33743 (45, 1)	8.89268 (157, 1)
200.0 /	41.71954 (155, 1)	16.30558 (259, 1)	10.83712 (285, 1)
190.0 /	34.92819 (71, 1)	20.21833 (285, 1)	10.18770 (275, 1)
180.0 /	54.64593 (268, 1)	26.88159 (275, 1)	13.05921 (31, 1)
170.0 /	83.93459 (268, 1)	31.23164 (301, 1)	13.86982 (253, 1)
160.0 /	132.78583 (121, 1)	23.09526 (4, 1)	19.61605 (346, 1)
150.0 /	13.38003 (255, 1)	24.14291 (281, 1)	16.33374 (281, 1)
140.0 /	81.19286 (255, 1)	21.10072 (19, 1)	6.76696 (19, 1)
130.0 /	65.61731 (255, 1)	19.50598 (330, 1)	12.68189 (50, 1)
120.0 /	31.53257 (255, 1)	19.58327 (39, 1)	13.73883 (296, 1)
110.0 /	28.53326 (37, 1)	13.65036 (356, 1)	10.38108 (39, 1)
100.0 /	21.46343 (37, 1)	24.88420 (304, 1)	6.36262 (356, 1)
90.0 /	15.04285 (184, 1)	28.80371 (290, 1)	17.74656 (304, 1)
80.0 /	16.38233 (191, 1)	17.78389 (255, 1)	20.83493 (290, 1)
70.0 /	11.52795 (191, 1)	6.20086 (41, 1)	7.97697 (255, 1)
60.0 /	31.56363 (314, 1)	8.74025 (250, 1)	4.03860 (41, 1)
50.0 /	32.01107 (314, 1)	4.90944 (184, 1)	5.60337 (250, 1)
40.0 /	25.89028 (11, 1)	5.31970 (206, 1)	3.58392 (191, 1)
30.0 /	21.56571 (249, 1)	16.92371 (314, 1)	8.27840 (314, 1)
20.0 /	19.38905 (142, 1)	16.56249 (11, 1)	14.44568 (314, 1)
10.0 /	19.70264 (142, 1)	11.23895 (155, 1)	11.19150 (249, 1)

STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Governor

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

January 23, 1987

Ms. Pamela Meitner
E. I. du Pont de Nemours and Co.
Wilmington, Delaware 19898

Dear Ms. Meitner:

Comments on the Draft Carbon Tetrachloride Report

Thank you for your comments on the Draft Carbon Tetrachloride Report. We referred your comments on "Part B - Health Effects of Carbon Tetrachloride" to the Department of Health Services (DHS). Their response to your comments are attached to this letter. Your comments and the DHS response will be included in Part C of the Final Draft Report on Carbon Tetrachloride.

We will have the Final Draft Report on Carbon Tetrachloride (Part A with the Overview, Part B, and the completed Part C) available for review within the next month. A copy of this will be sent to you when it becomes available.

If you have any further questions on this matter, please contact Gary Murchison, Manager of the Compound Evaluation Section, at (916) 322-8521.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Peter D. Venturini
Michael Lipsett, DHS

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

Air Resource Board Staff Responses to Public Comments on the Draft Part A Report on Carbon Tetrachloride

Comment: The rigid 30 and 20 day comment periods may not always be long enough to review the draft and final draft reports.

Response: In order for the toxic air contaminant (TAC) identification process to proceed in a timely manner, it is necessary for the ARB to have the rigid comment periods. The ARB staff believes that the 30 day and 20 day comment periods allow sufficient time to review the report and identify major issues of concern. However, to ensure the maximum time possible is available for the review of the reports, the previous review process was modified in two ways. First, an announcement letter is sent out in advance of the draft report so that interested parties can be identified. This letter requests the name and address of the person reviewing the report so they can receive it in the most direct way. Second, extra time is allowed for the report to reach the reviewer before the comment period starts.

Comment: Part A correctly references previous projections of a 1 to 2 percent growth in carbon tetrachloride demand through 1990. However, Dow Chemical feels that because of environmental concerns, carbon tetrachloride demand will probably not increase as previously expected.

Response: The 1 to 2 percent growth for carbon tetrachloride demand was reported in the "Chemical Marketing Reporter", 1986. In the absence of more detailed information on why this estimate is no longer correct, the ARB staff believes the 1 to 2 percent growth is still the best estimate.

Comment: As stated in EPA research studies and the Federal Register, there are uncertainties involved in the decision to regulate chlorofluorocarbons and other chemicals that may affect the ozone layer. Dow Chemical requested that the uncertainties in this area be considered by the CARB during its consideration of carbon tetrachloride as a TAC.

Response: Stratospheric interaction of carbon tetrachloride and other chlorofluorocarbons with ozone is an important issue. However, carbon tetrachloride is being considered for identification as a TAC because of its potential danger to human health from inhalation and not because of its affect on the ozone layer.

Comment: The current level of regulation and federal EPA proposals to regulate carbon tetrachloride manufacturing processes are sufficient to protect human health. It is not necessary for regulations to be so stringent as to eliminate the carbon tetrachloride industry and its beneficial end products.

Response: The identification of carbon tetrachloride as a TAC will not in and of itself eliminate the use of this compound. If carbon tetrachloride is identified as a TAC, the ARB staff will then proceed to assess the need and appropriate degree of controls that would be required for carbon tetrachloride sources. Some of the factors which will be considered during this assessment are availability and feasibility of control, cost, availability of substitutes, exposure to the public, and risk to public health. It is only after this assessment that a decision will be made by the Air Resources Board as to the need for control measures. The ARB staff will continue to work closely with the public and the affected industries throughout the development of the carbon tetrachloride needs report.

V. Department of Health Services Responses to Part B - Related Comments

DEPARTMENT OF HEALTH SERVICES
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE "HEALTH EFFECTS OF CARBON TETRACHLORIDE" (MAY 1986)

Comment: Carbon tetrachloride has been classified as a carcinogen which acts by an epigenetic mechanism, according to Shank and Barrows (1986). [Their review article] indicates it satisfies several of the criteria for this classification which are:

It appears to induce cancer only at exposure levels which are near lethal doses (maximum tolerated dose which depresses growth rate 10 to 20%);

It increases the incidence of spontaneous tumors but does not induce formation of tumors which are rarely seen in control populations of the test species;

Cancers arise only after a long exposure relative to the lifespan of the test animal;

It does not form detectable levels of DNA adducts in *in vivo* tests. (Dupont)

Response:

Mechanism. Although the above authors have hypothesized that carbon tetrachloride acts via an epigenetic mechanism, this classification is debatable. Other authors have indicated that it cannot be classified as an epigenetic carcinogen (Williams GM and Weisburger JH, "Chemical Carcinogens," in Casarett and Doull's Toxicology, Klaassen CD et al., eds., 1986, pp. 99-173).

Dose levels. Carbon tetrachloride has been tested at high doses, but not at maximum tolerated doses. An adequate study of carbon tetrachloride's carcinogenicity has not been conducted at low concentrations. Thus, it cannot be stated with certainty that carbon tetrachloride induces tumors only at "near-lethal doses."

Absence of spontaneous tumors. Carbon tetrachloride produced a 100% incidence of tumors in hamsters where the control incidence was zero. The control incidence rate for tumors in mice in six studies was zero while the dosed animals had tumor incidence rates ranging from 38 to 100% (Edwards, 1941; Edwards and Dalton, 1942; Eschenbrenner and Miller, 1943; Eschenbrenner and Miller, 1946). In all the other studies with mice the liver tumor incidence rate ranged from 1 to 5% for the control animals but 47 to 100% for the exposed animals (Edwards, 1941; Edwards and Dalton, 1942; Edwards et al., 1942; NCI 1976a,b, 1977). In all studies with rats, the control rate of liver tumors was zero while the hepatic carcinoma incidence in treated animals ranged as high as 80% (Reuber and Glover, 1967; Reuber and Glover, 1970; NCI, 1976a,b, 1977). Thus, the argument regarding increasing the rate of spontaneous tumors is spurious.

Exposure relative to lifespan. Studies with mice showed development of tumors after 8 weeks of biweekly exposure (8% of lifespan). Studies with rats indicated that tumors can develop after 12 weeks of biweekly exposure (12% of lifespan). The criterion of a "long exposure relative to lifespan" has not been met, since a tumor incidence of greater than 88% had occurred after approximately 16 doses.

Detectable levels of DNA adducts in in vivo tests. Metabolically activated carbon tetrachloride has been found to bind with DNA in vivo (Diaz Gomez and Castro, 1980a; Rocchi et al. 1973).

Consequently, even using the criteria of Shank and Barrows, there appears to be no basis to classify carbon tetrachloride as an epigenetic carcinogen.

Comment: What constitutes sufficient valid data upon which to base a quantitative risk assessment? (Chevron)

Response: Studies used in the quantitative risk assessment for carbon tetrachloride were conducted over a period of almost 40 years, and the studies did not follow a standard format. Each study was evaluated individually by the Department of Health Services' (DHS) staff to determine whether it was scientifically valid and whether it could contribute to our understanding and evaluation of the carcinogenicity of carbon tetrachloride. DHS staff evaluated each study using the Department's Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale (1985), and reviewed the Health Assessment Document for Carbon Tetrachloride (US Environmental Protection Agency, 1984). The results of this evaluation are presented in Section 9.2.2 of the Health Effects of Carbon Tetrachloride (May, 1986) prepared by DHS staff (hereafter referred to as "Part B" of the Report to the Scientific Review Panel). The staff of DHS determined that the three studies used in the quantitative risk assessment contained sufficiently valid data and that the best available data were used in the risk assessment. The major criteria included: publication of the study in the scientific literature following peer review, a clear description of the protocol indicating that the study was designed to evaluate the potential tumorigenicity of carbon tetrachloride, and a significant increase in tumors over controls. The same studies were used by EPA in its risk assessment for carbon tetrachloride.

Comment: Data presented by Condie et al. (1986) raise concerns over the appropriateness of using the results of animal gavage studies which utilize an oil vehicle to predict the carcinogenic risk encountered by humans from the inhalation of ambient concentrations of carbon tetrachloride. The use of oil as a vehicle was found to significantly increase both the incidence and severity of carbon tetrachloride's hepatotoxicity over that encountered when the agent is administered in water. (Chevron)

Response: Condie et al. (1986) examined the effect of the vehicle on hepatotoxicity and found that the toxicity was greater when the compound was administered in oil compared to an aqueous Tween-60 emulsion (not in water as indicated in the comment). This potentiating effect is not expected to occur for inhalation exposures. Condie et al. concluded that the effect could have resulted from decreased total absorption of carbon tetrachloride when administered in aqueous solution due to micelle formation, or from a slower rate of absorption (allowing more compound metabolism during the first pass through liver) when administered in corn oil. While it is also possible that the corn oil itself could have increased the toxicity of carbon tetrachloride, the mechanism of this effect has not been elucidated. This study consisted of subchronic experiments looking at hepatotoxicity, not carcinogenicity. Increased hepatotoxicity may or may not have any bearing on the carcinogenicity of carbon tetrachloride, as discussed below.

Comment: Why was the Kotin et al. (1962) study excluded from the DHS discussion of the carcinogenicity studies performed in mice? (Chevron)

Response: The Kotin et al. (1962) study evaluated the influence of carbon tetrachloride on benzo(a)pyrene metabolism and tumorigenicity. Consequently, the study is discussed in Section 8.1.2 of Part B, which considers synergistic effects. The study was not discussed further in the carcinogenicity section since it involved subcutaneous injection of 40 μl in 30 mice without controls, and it was not designed to examine the tumorigenicity of carbon tetrachloride.

Comment: Carbon tetrachloride has elicited a carcinogenic response in certain test animals. There is insufficient evidence to support the premise that carbon tetrachloride is a human carcinogen; it has not demonstrated carcinogenicity in humans at low levels. (Dupont, Dow)

Response: The commenters are correct, but the qualitative assessment of carbon tetrachloride's carcinogenicity in animals and humans has already been discussed by DHS staff. The summary of Section 7 of Part B states in part: "Animal studies demonstrate that carbon tetrachloride produces hepatocellular carcinomas in the mouse, rat and hamster; human evidence is inconclusive. IARC evaluated [carbon tetrachloride] and concluded that it is an animal carcinogen. The IARC classification would place [carbon tetrachloride] in group 2B, indicating that it is probably carcinogenic to humans. DHS staff members concur with this assessment, based on the evidence cited in the preceding subsections... there is sufficient animal data to conclude that [carbon tetrachloride] is a potential human carcinogen..." Furthermore, as indicated in Section 7.4 of Part B, there have been some reports linking increased tumor incidence in humans with carbon tetrachloride, but a causal relationship could not be established.

Comment: The preponderance of the data in the literature indicates that the tumorigenic response to carbon tetrachloride occurred as a consequence of the induction of post-necrotic cirrhosis. The most likely mechanism for carbon tetrachloride carcinogenesis requires a toxic response prior to initiation of the carcinogenic response and no toxic response is expected at ambient levels. (Dupont, Dow)

Response: There is no study that "indicates that the tumorigenic response to carbon tetrachloride occurred as a consequence of the induction of post-necrotic cirrhosis." In several of the studies cirrhotic changes were reported concomitantly with tumorigenesis; however, no cause-effect relationship has been demonstrated. In fact, as shown by Eschenbrenner and Miller (1946), discussed in Part B, Section 7.0, liver necrosis was not a required precondition for the production of tumors with carbon tetrachloride.

Comment: The dose levels administered in the studies on mice and rats which resulted in a tumorigenic response were in excess of 1000 mg/kg/day. Compared to the amount given to animals to cause cancer (1250 mg/kg bw in mice) the amount inhaled [less than one ppb in ambient air] is one billion times smaller. (Dupont, Dow)

Response: Tumorigenic responses were also observed in mice at 20, 30, 40, 80, 159, 160, 260, 315 and 625 mg/kg (Edwards and Dalton, 1942;

Eschenbrenner and Miller, 1943; Eschenbrenner and Miller, 1946), in rats at 47, 80, and 94 mg/kg (NCI 1976a, b, and 1977), and in hamsters at 190 and 380 mg/kg (Della Porta et al., 1961). Thus, the implication that only doses above 1000 mg/kg produce tumors is incorrect. The 20 mg/kg-day level is roughly equivalent to 28 ppm in air. Thus, the range of extrapolation of the tumorigenic response is approximately four orders of magnitude, not nine. Noncarcinogenic, subchronic effects have been observed following inhalation of concentrations approximately three orders of magnitude higher than ambient levels of carbon tetrachloride (Prendergast et al. 1967).

Comment: The occurrence of hepatomas (in mice) as a result of the induction of post-necrotic cirrhosis suggests that carbon tetrachloride is not a direct-acting carcinogen (Louria and Bogden, 1980). This observation is not contradicted by the results of various short-term mutagenicity tests nor by the preponderance of the evidence indicating little or no covalent binding to liver DNA....a tumorigenic response to carbon tetrachloride occurs as a consequence of the induction of post-necrotic cirrhosis and levels and durations of exposure which do not cause significant tissue damage would not be expected to produce tumors. (Dow)

Response: As stated above, Eschenbrenner and Miller (1946) showed that liver necrosis is not required for the induction of tumors with carbon tetrachloride. Thus, the conclusions drawn from the "post-necrotic cirrhosis" hypothesis are unsubstantiated. In the absence of data that the carcinogenic process would result only if post-necrotic cirrhosis occurs, the above comments represent speculation, not established fact. The genotoxicity of carbon tetrachloride was reviewed in Part B, Section 5, and results and limitations of test systems were discussed. The DHS staff concluded that carbon tetrachloride has genotoxic potential.

Comment: The rhesus monkey, the species and strain most like man in regard to the level of liver cytochrome P-450, has been reported to have a no-observed effect level [NOEL] in the range of 25 to 50 ppm in a chronic study. (Dow)

Response: The Dow study (Adams et al., 1952) does not establish a no-effect level for monkeys. The authors of the study reported that "the maximum vapor concentrations without adverse effect were 25 ppm for monkey..." However, a NOEL cannot be established on the basis of a single monkey tested at 25 ppm. This is particularly important since a later study (Prendergast et al. 1967) with much shorter exposure times demonstrated toxicity at concentrations 5 to 25 times lower for the rat, guinea pig and rabbit when compared to similar species in the Adams et al. (1952) study.

Comment: [On] the basis that there are thresholds for the toxic effects of carbon tetrachloride and the mechanism of tumor formation is nongenetic and all the supportive evidence that indicates man metabolizes carbon tetrachloride more like the monkey than the rodent, the assessment of risk/safety for man should be based on the adequacy of the margin which exists between man's exposure to carbon tetrachloride in the ambient environment and the no-observed effect level in the study on the most appropriate animal model, the rhesus monkey, with a safety factor to compensate for the lack of lifetime data (emphasis in original). (Dupont, Dow)

Response: As indicated above, the mechanism of carbon tetrachloride's carcinogenicity has not been elucidated. The metabolism of carbon tetrachloride has not been studied across species. The study proposed as the basis for carcinogenic risk assessment of carbon tetrachloride did not examine the test animals for carcinogenic effects. It would be inappropriate to base a carcinogenic risk assessment on a study with one monkey at the target concentration, exposed to carbon tetrachloride for less than three percent of its lifetime, where tissues were not evaluated for carcinogenic effects.

Comment: Rodents are more sensitive than primates to the toxic effects of carbon tetrachloride. In particular, hamsters seem to be the most sensitive to carcinogenic effects, followed by mice and then rats.... this is an important distinction and should be incorporated into risk assessment calculations. (Dupont)

Response: The toxicity or carcinogenicity of carbon tetrachloride has not been adequately tested in primates. Although there may be some metabolic differences between rodents and primates in the handling of carbon tetrachloride, differences in susceptibility to carcinogenesis have not been evaluated. In addition, no epidemiologic study has been identified that clearly examines the carcinogenic effects of carbon tetrachloride in humans. Several case reports indicated the development of liver cancer following exposure to carbon tetrachloride, but (as noted in the response to a previous comment) a cause-effect relationship could not be established. There is no additional information to be incorporated at this time.

Comment: Mouse liver tumors are seriously questioned as useful estimators of potential tumorigenicity for man. (Dupont)

Response: The conclusion that carbon tetrachloride is potentially tumorigenic in man is based not only on mouse liver tumors, but also on cancers reported in rats and hamsters.

Comment: We are including a copy of a recent Du Pont study on workers chronically exposed to carbon tetrachloride...These results show that at long-term exposures at about 1/2 of the TLV, no toxic effects were seen. (Dupont)

Response: The document submitted, authored by J. Gooch (1981), apparently was never published in the peer-reviewed literature. It is the opinion of DHS staff that if the study had been sufficiently rigorous to demonstrate the absence of effects as alleged, it would have been published. In any case, the report examined biochemical indices, not carcinogenicity.

Comment: It is obvious that the lack of a chronic inhalation study makes it difficult to make an adequate risk assessment. (Dupont)

Response: It would be preferable to use an inhalation study for risk assessment purposes, but none is available. Consequently, gavage studies must be used for risk assessment purposes. A number of assumptions and adjustments to data were made to estimate inhalation absorption, as described in Section 9.2.2 of Part B. Since carbon tetrachloride is a systemic toxin, once absorbed it should act similarly independent of the route of exposure. Similar toxic (noncarcinogenic) effects have been

observed when carbon tetrachloride is administered by inhalation and by the oral route.

Comment: Dose-response for tumors was limited. (Dupont)

Response: This statement is potentially misleading since carbon tetrachloride has not been tested at low doses. Furthermore, at the doses that carbon tetrachloride has been tested, it has fairly consistently produced a high number of tumors.

Comment: EPA converts doses across species by assuming that biologically equivalent doses can be obtained by correcting for the surface area differences among species. Two other methods are often used to make interspecies comparisons: correcting for body weight differences and doing no conversion. (Dupont)

Response: There are a number of methods to make interspecies extrapolations. In the risk calculation the interspecies conversion was based on metabolic differences using the body surface area adjustment. This approach is consistent with practices generally followed by regulatory agencies and is supported in the published literature. Correcting for body weight differences is an alternate approach which is somewhat less health-conservative. The suggestion that no conversion be made appears inappropriate for gavage studies. If no conversion were made, then a given quantity of a substance would be considered to produce identical effects in different organisms regardless of variations in weight or metabolism.

CHRONIC TOXICITY SUMMARY

ACROLEIN

(2-propenal, acraldehyde, allyl aldehyde, acryl aldehyde)

CAS Registry Number: 107-02-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.02 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Histological changes in nasal epithelium in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless liquid/gas
Molecular formula	C_3H_40
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Vapor pressure	220 mm Hg @ 20°C
Solubility	Soluble in ethanol, diethyl ether, and up to 20% w/v in water
Conversion factor	1 ppm = 2.3 mg/m^3 @ 25° C

III. Major Uses or Sources

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein (IARC, 1985).

IV. Effects of Human Exposure

Information regarding the toxicity of acrolein to humans is scarce. Acrolein acts primarily as an irritant to the eyes and respiratory tract. The LOAEL for eye irritation is 0.06 ppm (0.14 mg/m^3) acrolein for five minutes (Darley *et al.*, 1960). In this study, 36 healthy human volunteers were exposed to 0.06 ppm (0.14 mg/m^3) for 5 minutes. Only volunteers without a prior history of

chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. Subjects reported a significant incidence of eye irritation in a questionnaire following the exposure.

V. Effects of Animal Exposure

Male rats were exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3) (Kutzman, 1981). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests (PFT) included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lung were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed post-exposure for 6 days to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extrarespiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates and rhinitis, beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions was also observed. No lung lesions were observed in the 0.4 ppm group. The NOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

The concentration required for depression of the respiratory rate of mice by 50% (RD_{50}) during 15 minutes of acrolein exposure was estimated as 1.7 ppm (Kane *et al.*, 1979). These authors proposed that the highest concentration suitable for a human air quality standard was 0.001 x RD_{50}, or 0.002 ppm (0.005 mg/m^3).

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was dose-dependently impaired following exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

Leach and associates (1987) found histological changes in pulmonary epithelium and mucosa in rats exposed to 3 ppm acrolein 6 hours/day, 5 days/week, for 3 weeks. In this study, tests for pulmonary and systemic immune function revealed no significant differences between treated and control animals. Similarly, no difference was observed in survival from a bacterial challenge with *Listeria monocytogenes*, although this challenge was intravenous and not intratracheal, and may not have revealed the pulmonary macrophage impairment indicated by Astry and Jakab (1983).

Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy,

although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure.

Lyon and associates (1970) investigated the effects of repeated or continuous exposures of acrolein on rats, guinea pigs, dogs, and monkeys. Animals were exposed to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. In these studies, 2 monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea was observed in monkeys and dogs; 7 of the 9 monkeys also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchiopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs.

There are no reports of reproductive or developmental toxicity following exposure to acrolein. Kutzman *et al.* (1981) found no significant changes in embryo viability in rats exposed to 4.0 ppm acrolein throughout pregnancy. Similarly, sperm morphology was reportedly not affected at this level.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Kutzman *et al.*, 1981 (evaluated by U.S. EPA, 1995)
Study population	Fischer-344 rats (24 males per group)
Exposure method	Discontinuous whole-body inhalation exposure of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)
Critical effects	Histological lesions in the upper airways
LOAEL	0.4 ppm
NOAEL	Not observed (see below)
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	62 days
Average experimental exposure	0.071 ppm (0.16 mg/m^3)
Human equivalent concentration	0.0087 ppm (gas with extrathoracic respiratory effects, RGDR = 0.14 based on MV = 0.18 m^3/day, SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	10

Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factors	1
Cumulative uncertainty factor	1,000
Reference exposure level	9×10^{-6} ppm (0.009 ppb, 2×10^{-5} mg/m^3, 0.02 μg/m^3)

The LOAEL for nasal histological changes in mice was considered by U.S. EPA to be 0.4 ppm (0.92 mg/m^3). Only one rat showed slight metaplastic and inflammatory changes, which would be insufficient to demonstrate a statistically significant increase. The potentially slight effect, however, was accounted for by use of only an intermediate 3-fold LOAEL factor.

Significant strengths in the acrolein RfC include (1) the use of a well-conducted study with histopathological analysis and (2) the demonstration of consistent adverse effects among multiple studies of several species conducted by independent investigators.

Major areas of uncertainty are (1) the lack of adequate human exposure data, (2) limited reproductive toxicity data, (3) the absence of a NOAEL in the major study, and (4) the lack of chronic inhalation exposure studies.

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ACRYLONITRILE

(acrylonitrile monomer, cyanoethylene, propenenitrile, 2-propenenitrile, VCN, vinyl cyanide)

CAS number: 107-13-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**2 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Degeneration and inflammation of nasal epithelium in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Clear, colorless to pale yellow liquid (technical grades)
Molecular formula	C_3H_3N
Molecular weight	53.1
Density	0.81 g/cm^3 @ 25°C
Boiling point	77.3 ^{o}C
Melting point	-82 ^{o}C
Vapor pressure	100 mm Hg @ 23°C
Solubility	Soluble in isopropanol, ethanol, ether acetone and benzene
Conversion factor	1 ppm = 2.17 mg/m^3 @25 ^{o}C

III. Major Uses or Sources

Acrylonitrile is produced commercially by propylene ammoxidation, in which propylene, ammonia and air are reacted by catalyst in a fluidized bed. Acrylonitrile is used primarily as a co-monomer in the production of acrylic and modacrylic fibers. Uses include the production of plastics, surface coatings, nitrile elastomers, barrier resins, and adhesives. It is also a chemical intermediate in the synthesis of various antioxidants, pharmaceuticals, dyes, and surface active agents. Formerly, acrylonitrile was used as a fumigant for food commodities, flour milling and bakery food processing equipment (HSDB, 1994).

IV. Effects of Human Exposure

Many occupational epidemiology studies have investigated retrospectively the morbidity and mortality of acrylonitrile exposed workers. An increased incidence of lung cancer was associated with acrylonitrile exposure. No significant excess mortality has been observed for any noncarcinogenic endpoint. One early cross-sectional study (Wilson *et al.*, 1948) observed multiple deleterious effects in synthetic rubber manufacturing workers acutely exposed (20 to 45 minutes) to various concentrations of acrylonitrile (16 to 100 ppm, 34.7 to 217 mg/m^3). Mucous membrane irritation, headaches, nausea, feelings of apprehension and nervous irritability were observed in the majority of workers. Other less common symptoms observed included low grade anemia, leukocytosis, kidney irritation, and mild jaundice. These effects were reported to subside with cessation of exposure. Human volunteers exposed for a single 8 hour period to acrylonitrile vapors exhibited no deleterious CNS effects at concentrations ranging from 5.4 to 10.9 mg/m^3 (2.4 to 5.0 ppm) (Jakubowski *et al.*, 1987).

A cross-sectional study (Sakurai *et al.*, 1978) found no statistically significant increases in adverse health effects in chronically exposed workers (minimum 5 years) employed at 6 acrylic fiber factories (n=102 exposed, n=62 matched controls). Mean acrylonitrile levels ranged from 0.1 to 4.2 ppm (0.2 to 9.1 mg/m^3) as determined by personal sampling. Though not statistically significant, slight increases in reddening of the conjunctiva and pharynx were seen in workers from the plant with the highest mean levels (4.2 ppm arithmetic mean). However, this study has limitations, including small sample size and examiner bias (the medical examiner was not blind to exposure status). The time-weighted average exposure of the group occupationally exposed to 4.2 ppm (9.1 mg/m^3) acrylonitrile can be calculated as: TWA = 9.1 mg/m^3 x (10/20)m^3/day x 5 days/7 days = 3 mg/m^3. This level is comparable to the LOAEL(HEC) derived by the U.S. EPA.

V. Effects of Animal Exposure

Quast *et al.* (1980) exposed Sprague-Dawley rats (100/sex/ concentration) 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20, or 80 ppm acylonitrile vapors (0, 43, or 174 mg/m^3). A statistically significant increase in mortality was observed in the first year among 80 ppm exposed rats (male and female). Additionally, the 80 ppm exposed group had a significant decrease in mean body weight. Two tissues, the nasal respiratory epithelium and the brain, exhibited treatment-related adverse effects due to acrylonitrile exposure.

Proliferative changes in the brain glial cells (i.e., tumors and early proliferation suggestive of tumors) were significantly increased in the 20 ppm (8/100) and 80 ppm (20/100) females versus female controls (0/100), and in the 80 ppm males (22/99) versus male controls (0/100). Noncarcinogenic, extrarespiratory effects were observed in the nasal turbinate epithelium at both exposure concentrations, 20 and 80 ppm, but were statistically significant only in the 80 ppm exposed rats. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory epithelium were observed at either concentration.

Maltoni and associates exposed Sprague-Dawley rats (30/sex/concentration) to 0, 5, 10, 20 or 40 ppm acrylonitrile vapor for 5 days/week over 52 weeks, and at 60 ppm for 4 to 7 days, 5

days/week for 104 weeks (Maltoni *et al.*, 1977; Maltoni *et al.*, 1988). Histopathologic examinations were performed, including on lungs, brain, kidney, and liver. No noncarcinogenic effects were reported.

One developmental study exposed rats to acrylonitrile vapors at 0, 40, or 80 ppm (duration adjusted concentrations of 0, 15.4, and 31 mg/m^3, respectively) for 6 hours/day during gestational days 6 to 15. In the 80 ppm exposed group, significant increases in fetal malformations were observed including short tail, missing vertebrae, short trunk, omphalocoele and hemivertebra (Murray *et al.*, 1978). No difference in implantations, live fetuses or resorptions were seen in the exposed (40 and 80 ppm) versus the control group. Maternal toxicity was observed as decreased body weight at both exposure levels. This study identified a developmental NOAEL of 15.5 mg/m^3 with a LOAEL of 31 mg/m^3 (with maternal toxicity).

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Quast *et al.*, 1980 (evaluated by U.S. EPA, 1994)
Study population	Sprague-Dawley rats (100/sex/concentration)
Exposure method	Discontinuous whole-body inhalation exposures (0, 20 or 80 ppm)
Critical effects	Degeneration and inflammation of nasal respiratory epithelium, hyperplasia of mucous secreting cells
LOAEL	20 ppm
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	3.6 ppm for LOAEL group (20 x 6/24 x 5/7)
Human equivalent concentration	0.9 ppm (gas with extrathoracic respiratory effects, RGDR = 0.25 based on MV = 0.33 m^3/day, SA(ET) = 11.6 cm^2)
Exposure duration	2 years
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	10 (lack of inhalation bioassay in second species and lack of reproductive data for inhalation exposures when oral study showed adverse reproductive effects)
Cumulative uncertainty factor	1,000
Inhalation reference exposure level	0.0009 ppm (0.9 ppb; 0.002 mg/m^3; 2 µg/m^3)

Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to 0, 20 or 80 ppm acrylonitrile (0, 43, and 174 mg/m^3, respectively). Significant degenerative

and inflammatory changes were observed in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm). This treatment-related irritation of the nasal mucosa appeared in the 20 ppm exposed male rats as either epithelial hyperplasia of the nasal turbinates, or as hyperplasia of the mucous secreting cells. In the 20 ppm exposed females it appeared as either focal inflammation in the nasal turbinates or flattening of the respiratory epithelium of the nasal turbinates. In 80 ppm exposed rats the effects were more severe, including suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment related effects in the olfactory epithelium, trachea or lower respiratory system were observed at either concentration. This study identified a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory tract of 20 ppm (43 mg/m^3).

Significant strengths in the acrylonitrile REL include (1) the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis and (2) the demonstration of a dose-response relationship.

Major uncertainties are (1) the lack of adequate human exposure data and (2) the lack of a NOAEL.

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CHRONIC TOXICITY SUMMARY

ARSENIC AND ARSENIC COMPOUNDS

Molecular Formula	Synonyms	Molecular Weight	% As by Weight	CAS Reg. No.
As	Arsenic black, metallic arsenic	74.92	100%	7440-38-2
As_2O_3	Arsenious acid, crude arsenic, white arsenic	197.82	75.7%	1327-53-3
As_2O_5	Arsenic anhydride, arsenic oxide, arsenic oxide anhydride	229.82	41.3%	1303-28-2
$AsH_3Na_2O_4$	Arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	185.91	40.3%	7778-43-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.03 µg As/m^3**
Oral reference exposure level	**0.0003 mg/kg bw-day** (based on U.S. EPA RfD)
Critical effect(s)	Decreased fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations in mice
Hazard index target(s)	Development (teratogenicity); cardiovascular system; nervous system

II. Physical and Chemical Properties (For metallic arsenic except as noted) (from HSDB, 1995, except as noted)

Description	As: Yellow, black or gray solid As_2O_3: White solid
Molecular formula	See above
Molecular weight	See above
Density	As: 5.727 g/cm^3 @ 14°C As_2O_3: 3.74 g/cm^3
Boiling point	613° C (sublimes) (ACGIH, 1992)
Melting point	As: 817°C @ 28 atm As_2O_3: 312.3°C
Vapor pressure	1 mm Hg @ 372° C
Solubility	As: soluble in nitric acid; insoluble in water Oxides: soluble in water

	Salts: soluble in water)
Conversion factor	Not applicable

III. Major Uses or Sources

Ore refining processes, including the smelting of copper and lead, are the major sources by which arsenic dust and inorganic arsenic compounds are released (Grayson, 1978). Arsenic trioxide (As_2O_3) is the most commonly produced form of arsenic. As_2O_3 is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds.

IV. Effects of Human Exposure

Smelter workers, exposed to concentrations of arsenic up to 7 mg As/m^3, showed an increased incidence in nasal septal perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (Lundgren, 1954; as cited in U.S. EPA, 1984).

In a case-control study, copper smelter workers (n=47) exposed to arsenic for 8-40 years (plus 50 unexposed controls matched for age, medical history, and occupation) were examined by electromyography and for nerve conduction velocity in the arms and legs (Blom *et al.*, 1985). The workers were found to have a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocities in three peripheral nerves (upper and lower extremities). Slightly reduced nerve conduction velocity in 2 or more peripheral nerves was reported as “more common” among arsenic exposed workers. Minor neurological and electromyographic abnormalities were also found among exposed workers. Occupational exposure levels were estimated to be 0.05-0.5 mg As/m^3, with As_2O_3 the predominant chemical form. Except for three arsenic exposed workers who had long-term exposure to lead, exposure to other heavy metals was insignificant.

The smelter workers described by Blom *et al.* (1985) (number of controls reduced to 48) were further examined for prevalence of Raynaud’s phenomenon and for vasospastic tendency by measurement of finger systolic pressure at 10°C and/or 15°C relative to that at 30°C (FSP%) (Lagerkvist *et al.*, 1986). The FSP% was found to covary with the duration of exposure to arsenic and the prevalence of Raynaud’s phenomenon was significantly increased among exposed workers. Daily arsenic uptake was estimated at less than 300 μg/day and was confirmed with urinary excretion data.

Hyperpigmentation and hyperkeratinization were observed in workers exposed to 0.4-1 mg/m^3 inorganic arsenic for 2 or more years (Perry *et al.*, 1948).

Dermatitis and irritation of the mucous membranes have been observed in arsenic exposed workers (Vallee *et al.*, 1960).

Chronic exposure to arsenic has been associated with decreased birth weight and an increased rate of spontaneous abortion in female smelter workers. However, this association is confounded by the presence of other toxicants in the smelting process, including lead (Nordstrom *et al.*, 1979).

Hepatic fatty infiltration, central necrosis, and cirrhosis were observed in two patients who ingested As_2O_3 (1% in Fowler's solution) for three or more years (Morris *et al.*, 1974). Daily consumption of 0.13 mg As/kg in contaminated well water resulted in the chronic poisoning and death of four children; at autopsy, myocardial infarction and arterial thickening were noted (Zaldívar and Guillier, 1977).

Anemia and leukopenia have been reported in infants ingesting approximately 3.5 mg As/day in contaminated milk over a period of 33 days (Hammamoto, 1955; as cited in ATSDR, 1989).

Premature birth and subsequent neonatal death was reported in a single individual following ingestion of arsenic (Lugo *et al.*, 1969).

V. Effects of Animal Exposure

Changes in host resistance from inhalation exposure to As_2O_3 aerosol were examined in female CD1 mice using a streptococcus infectivity model and an assay for pulmonary bactericidal activity (Aranyi *et al.*, 1985; Aranyi *et al.*, 1981). Mice (100-200/group) were exposed to As_2O_3 aerosol (or filtered air) for 3 hours/day, 5 days/week, for 1, 5 or 20 days. Aerosol exposed and control mice were then combined before challenge with *Streptococcus zoopidemicus* aerosol (4-8 replicate exposures). Statistically significant increases in mortality ($p < 0.05$) were observed in mice exposed (1) once to 271, 496, and 940 μg As/m^3, (2) 5 times to 519 μg As/m^3, and (3) 20 times to 505 μg As/m^3. Multiple exposures at a given exposure level did not correlate with increased mortality, suggesting an adaptation mechanism. Single exposure did, however, show a dose-response for increased mortality with increasing level of arsenic exposure. Bactericidal activity was evaluated by measuring the ratio of viable bacteria count to radioactive count in the lung 3 hours after infection with ^{35}S-labeled *Klebsiella pneumoniae*. A single exposure to 271, 496, and 940 μg As/m^3, but not 123 μg As/m^3, resulted in significantly decreased bactericidal activity. Five exposures to 519 μg As/m^3 and twenty exposures to both 245 and 505 μg As/m^3 resulted in decreased bactericidal activity.

Female albino rats (20/group) were exposed to 0, 1.3, 4.9, or 60.7 μg As_2O_3/m^3 as aerosol continuously for 3 months (Rozenshtein, 1970). Decreased whole blood sulfhydryl group content, histological changes in the brain, bronchi, and liver, changes in conditioned reflexes, and changes in chronaxy ratio were observed in both the high- and mid-dose groups. Among animals in the high dose group, eosinophilia, decreased blood cholinesterase activity, decreased serum sulfhydryl content, and increased blood pyruvic acid were observed. No significant changes were observed in the low-dose group.

Male mice (8-10/group) were exposed to 0, 0.5, 2.0, or 10.0 ppm sodium arsenite in drinking water for 3 weeks followed by a 28 day recovery period (Blakley *et al.*, 1980). The primary

immune response of the spleen (as indicated by changes in IgM-production assayed by plaque-formation) was suppressed at all dose levels. The secondary immune response was also suppressed at all dose levels as indicated by a decrease in the number of IgG producing cells.

Male Sprague-Dawley rats (7-28/group) were exposed to 0, 40, 85, or 125 ppm sodium arsenate in drinking water for 6 weeks (Brown *et al.*, 1976). Rats from all arsenic exposed groups showed increased relative kidney weights, decreased renal mitochondrial respiration, and ultrastructural changes to the kidney.

Male ddY mice (number not stated) received 0, 3, or 10 mg As_2O_3/kg/day orally for 14 days and were examined for changes in concentrations of monoamine-related substances in various brain regions and for changes in locomotor activity (Itoh *et al.*, 1990). Locomotor activity was increased in the low-dose group and decreased in the high-dose group. Several monoamine-related compounds were altered in both dose groups in the cerebral cortex, hippocampus, hypothalamus, and corpus striatum.

Male and female Wistar rats (7-10/group) were treated from age 2 to 60 days by oral gavage with daily administration of 0 or 5 mg As/kg body weight (as sodium arsenate) (Nagaraja and Desiraju, 1993; Nagaraja and Desiraju, 1994). After 160 days, body weights, brain weights, and food consumption were decreased in the arsenic exposed group. Acetylcholinesterase (AChE) and GAD activity and GABA levels were decreased in the hypothalamus, brain stem, and cerebellum during the exposure period; all but AChE activity returned to normal during the post-exposure period. Changes in operant conditioning were also observed among the exposed animals.

Female Holtzman rats (>5/group) were treated with 0, 100, 500, 1000, 2000, or 5000 ppm As_2O_3 in feed for 15 days (Wagstaff, 1978). Hexibarbitone sleeping time was altered in all arsenic exposed groups. Body weight and feed consumption were decreased among animals in the groups exposed to ≥ 500 ppm As_2O_3. Clinical signs of toxicity observed among arsenic exposed animals included roughened hair, diarrhea, and decreased physical activity.

Male Sprague-Dawley rats and C57 black mice (12/group) were treated with 0, 20, 40, or 85 ppm sodium arsenate in drinking water for up to 6 weeks (Woods and Fowler, 1978). Among arsenic exposed rats, heme synthetase activity was decreased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, hepatic ALA synthetase activity was decreased and urinary uroporphyrin and coproporphyrin were increased. Among exposed mice, heme synthetase activity was decreased and uroporphyrinogen I synthetase activity was increased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, urinary uroporphyrin and coproporphyrin were increased.

Administration of 3.7 mg As_2O_3/kg/day to rhesus monkeys for 12 months did not result in any neurologic change detectable by an EEG (Heywood and Sortwell, 1979). Two of the 7 animals exposed to this concentration died before the conclusion of the 52 week period. Of the surviving animals, two were retained for a 52 week recovery period after which they were sacrificed and necropsied. No significant changes in organ weights or gross appearance were noted.

Pregnant CFLP mice (8-11 females/group) were exposed to As_2O_3 for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg As_2O_3/m^3 (~0.2, 2.2, and 21.6 mg As/m^3 (Nagymajtényi *et al.*, 1985). A significant decrease in fetal weight was observed in all the dose groups, with a 3, 9, and 29% reduction in average fetal weight with increasing dose groups. Significantly increased fetal malformations were observed only in the highest dose group; delayed ossification was the primary defect.

Rats exposed to 1 μg As_2O_3/m^3 (0.76 μg As/m^3) for 5 months showed increased preimplantation mortality and delayed ossification in fetuses (Kamkin, 1982). Experimental detail was not presented, thus limiting the usefulness of this study.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to 32.4 mg As_2O_3/m^3 for 48 hours (Kamil'dzhanov, 1982). Similarly, motility was decreased after (1) a 120 hour exposure to 7.95 mg/m^3, (2) a 252 hour exposure to 1.45 mg/m^3, and (3) an 800 hour exposure to 0.36 mg/m^3.

Male and female Charles River CD mice (10/group) were treated with 0 or 5 ppm arsenite in drinking water continuously through 3 generations (Schroeder and Mitchener, 1971). Endpoints examined included the interval between litters, the age at first litter, the ratio of males to females, the number of runts, stillborn offspring, failures to breed, and congenital abnormalities. The study showed an alteration in the number of small litters in the arsenic exposed group.

Female CD-1 mice (8-15/group) were treated by oral gavage with 0, 20, 40, or 45 mg sodium arsenite/kg on a single day of gestation between days 8 and 15 (Baxley *et al.*, 1981). Maternal mortality, fetal malformations, and increased prenatal death were observed among animals treated with 40 and 45 mg sodium arsenite/kg.

Pregnant golden hamsters (>10/group) were treated by oral gavage with a single administration of 0, 20, or 25 mg/kg sodium arsenite on one of gestational days 8-12 (Hood and Harrison, 1982). Prenatal mortality was increased among animals receiving 25 mg/kg on gestational days 8 and 12 and fetal weights were decreased among animals receiving 25 mg/kg on gestational day 12. One dam died following administration of 20 mg/kg.

Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggested that long term exposure of sperm to arsenic may occur *in vivo* following acute exposure (Danielsson *et al.*, 1984).

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Chronic Reference Exposure Level

Study	Nagymajtényi et al., 1985
Study population	CFLP mice (8-11/group)
Exposure method	Discontinuous inhalation exposure
Critical effects	Reduction in fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations
LOAEL	200 μg As/m^3
NOAEL	Not observed
Exposure continuity	4 hr/day
Exposure duration	4 days (gestational days 9-12)
Average experimental exposure	33 μg As/m^3 for LOAEL group (200 x 4/24)
Human equivalent concentration	33 μg As/m^3 for LOAEL group (particle with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	10 (since USEPA severity level > 5)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.03 μg As/m^3

Reports of human inhalation exposure to arsenic compounds, primarily epidemiological studies of smelter workers, indicate that adverse health effects occur as a result of chronic exposure. Among the targets of arsenic toxicity are the respiratory system (Lundgren, 1954), the circulatory system (Lagerkvist *et al.*, 1986), the skin (Perry *et al.*, 1948), the nervous system (Blom *et al.*, 1985), and the reproductive system (Nordstrom *et al.*, 1979). Occupational exposure levels associated with these effects ranged from 50 to 7000 μg As/m^3. These epidemiological studies suffer, however, from confounding as a result of potential exposure to other compounds, which limits their usefulness in the development of the chronic REL.

Studies in experimental animals show that inhalation exposure to arsenic compounds can produce immunological suppression, developmental defects, and histological or biochemical effects on the nervous system and lung, thus providing supportive evidence of the types of toxicity observed in humans. Among the inhalation studies, the lowest adverse effect level (LOAEL) was quite consistent:

245 μg As/m^3 for decreased bactericidal activity in mice (Aranyi *et al.*, 1985);
200 μg As/m^3 for decreased fetal weight in mice (Nagymajtényi *et al.*, 1985); and
270 μg As/m^3 for decreased sperm motility in rats (Kamil'dzhanov, 1982).

A single study showed effects occurring at 4.9 μg As_2O_3/m^3 (Rozenshtein, 1970), however, lack of detail with respect to endpoints and experimental design limits this study's usefulness. A significant dose-related reduction in fetal weight and increased incidences of intrauterine growth

retardation, skeletal malformations, and hepatocellular chromosomal aberrations were observed in mice following maternal inhalation exposure to 200 μg As/m^3 (260 μg As_2O_3/m^3) for 4 hours on gestation days 9, 10, 11, and 12 ($p<0.05$) (Nagymajtényi *et al.*, 1985). The most sensitive effect, decreased fetal weight, was observed at 200 μg As/m^3, so 200 μg As/m^3 was taken as a LOAEL. Maternal toxicity data were not reported.

The weight decrement of 3% might not be biologically significant if the loss is generally distributed. If it were specific, it could be. In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant.

Route-to-route conversion of the LOAEL in the key study indicates that this chronic REL should also be protective of adverse effects that have been observed in studies with oral exposures, either in food or drinking water. Since adverse health effects have been reported among workers exposed to levels near 50 μg As/m^3, use of the human data would produce a chronic REL near that derived using animal data. The chronic REL from animal data should, therefore, be protective of potential adverse health effects from human exposures.

The major strength of the REL is the identification of a LOAEL that is supported by data from other studies. The major uncertainties are the lack of adequate human data, the lack of a NOAEL observation, the lack of comprehensive, long-term, multiple-dose, multiple-species studies, and the possibly marginal significance of the findings in the low dose group in the Nagymajtényi *et al.* (1985) study.

Derivation of U.S. EPA Oral Reference Dose (RfD)

Study	Tseng *et al.*, 1968; Tseng, 1977
Study population	>40,000 residentially exposed individuals
Exposure method	Drinking water (residential exposures)
Critical effects	Hyperpigmentation, keratosis, and possible vascular complications
LOAEL	0.17 mg/L (0.014 mg/kg-day)
NOAEL	0.009 mg/L (0.0008 mg/kg-day)
Exposure continuity	Not applicable
Exposure duration	Lifetime
Average exposure	0.006 mg/kg-day for LOAEL group
Human equivalent concentration	0.006 mg/kg-day for LOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Oral reference exposure level	0.0003 mg/kg bw-day

*Conversion Factors: NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentrations from 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy *et al.*, 1989).

NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg-day.

The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L.

LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg-day.

The oral REL is the U.S. EPA's oral Reference Dose (RfD) (U.S. EPA, 1996). The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, one report indicates that it may not be strictly due to arsenic exposure (Lu, 1990).

The data in Tseng *et al.* (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL. The control group described in Tseng *et al.* (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This exposure of this group is considered a NOAEL. The arithmetic mean of the arsenic

concentration in the wells used by the individuals in the NOAEL group is 9 µg/L (range: 1-17 µg/L) (Abernathy *et al.*, 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 µg/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy *et al.* (1989), the NOAEL and LOAEL doses for both food and water are as follows:

LOAEL - [170 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 14 µg/kg/day;
NOAEL - [9 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 0.8 µg/kg/day.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7).

This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on humans exposed to arsenic. This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 mg/L and at the low dose is 5 mg/L (Cebrian *et al.*, 1983; Figure 2 and Table 1) or 7 mg/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below an average water consumption of 3 L/day was assumed by USEPA. No data are given on the arsenic exposure from food or the body weight of the participants (therefore 55 kg was assumed). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study were more than 20 years old (Figure 1). Exposure estimates (water only) are:

high dose - 410 mg/L x 3 L/day x (1/55 kg) = 22 mg/kg/day;
low dose - 5-7 mg/L x 3 L/day x (1/55 kg) = 0.3-0.4 mg/kg/day.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng *et al.* (1968) control group, but the dose is lower (0.4 vs. 0.8 mg/kg/day). The Southwick *et al.* (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16%) (Southwick *et al.*, 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic. Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance. Table 3 (Southwick *et al.*, 1983) shows the annual arsenic exposure from

drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are >5 years, and dose groups are ranges of exposure. Exposure estimates (water only) are:

dosed group - 152.4 mg/year x 1 year/365 days x (1/70) kg = 6 µg/kg/day;
control group - 24.2 mg/year x 1 year/365 days x (1/70) kg = 0.9 µg/kg/day.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian *et al.* (1983) study. The incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh *et al.* (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng *et al.* (1968) and Hindmarsh *et al.* (1977) studies. The dosed group may or may not be a LOAEL, since it is does not report statistically significant effects when compared to the control. This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh *et al.*, 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups. The exact doses are not given in the Hindmarsh *et al.* (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 µg/L, respectively. Figure 1 (Hindmarsh *et al.*, 1977) shows that the average arsenic concentration of the low-dose wells is about 25 µg/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated. Exposure estimates (water only) are:

low - 25 µg/L x 2 L/day x (1/70) kg = 0.7 µg/kg/day;
mid - 70 µg/L x 2 L/day x (1/70) kg = 2 µg/kg/day; and
high - 680 µg/L x 2 L/day x (1/70) kg = 19 µg/kg/day.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick *et al.* (1983) studies.

The responses at the mid-dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses. As discussed previously there is no way of knowing whether the low doses in the Cebrian *et al.* (1983), Southwick *et al.* (1983), and Hindmarsh *et al.* (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the U.S.EPA felt comfortable in assigning the low doses in these studies as NOAELs. The Tseng (1977) and Tseng *et al.* (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people less than 20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

1) Tseng (1977):	NOAEL = 0.0008;	LOAEL = 0.014
2) Cebrian *et al.* (1983):	NOAEL = 0.0004;	LOAEL = 0.022
3) Southwick *et al.* (1983):	NOAEL = 0.0009;	LOAEL = none (equivocal effects at 0.006)
4) Hindmarsh *et al.* (1977):	NOAEL = 0.0007;	LOAEL = 0.019 (equivocal effects at 0.002)

There was not a clear consensus among U.S. EPA scientists on the oral RfD. Applying the U.S. EPA's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 µg/kg/day. However, the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the U.S. EPA Work Group as it becomes available.

The U.S. EPA used an Uncertainty Factor (UF) of 3 to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the oral RfD as: Study - Medium; Data Base - Medium; and RfD - Medium. Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian *et al.* (1983) study. The U.S. studies are too small in number to resolve several issues. However, the data base does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

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CHRONIC TOXICITY SUMMARY

BERYLLIUM and BERYLLIUM COMPOUNDS

(beryllium-9; glucinium; glucinum; beryllium metallic)
CAS Registry Number: 7440-41-7

(beryllium oxide; beryllia; beryllium monoxide)
CAS Registry Number: 1304-56-9

(beryllium hydroxide; beryllium hydrate; beryllium dihydroxide)
CAS Registry Number: 13327-32-7

(beryllium sulfate; sulfuric acid; beryllium salt)
CAS Registry Number: 13510-49-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.001 µg Be/m^3**
Critical effect(s)	Berylliosis in non-occupationally exposed humans
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties Summary (ATSDR, 1993)

Description	Solid gray, hexagonal structure	White light, amorphous powder	White amorphous powder or crystalline	Colorless tetragonal crystals
Molecular formula	Be	BeO	$Be(OH)_2$	$BeSO_4$
Molecular weight	9.012	25.01	43.03	105.07
Vapor pressure	10 mm Hg at 1860 ^oC	No data	No data	No data
Solubility	Insoluble in water; metal soluble in dilute acid and alkali, oxide and hydroxide species soluble in concentrated acid and alkali			
Conversion factor	Not applicable			

III. Major Uses and Sources

Beryllium is a metallic element mined from bertrandite and beryl mineral ores. As the lightest structural metal, beryllium is used in the space, aircraft and nuclear industries in a variety of components including air craft disc brakes, x-ray transmission windows, vehicle optics, nuclear reactor neutron reflectors, fuel containers, precision instruments, rocket propellants, navigational

systems, heat shields, and mirrors. In addition to the 4 species listed, there are at least 13 other beryllium containing compounds including other salts, ores and alloys.

Beryllium alloys, especially the hardest alloy beryllium copper, are used in electrical equipment, precision instruments, springs, valves, non-sparking tools, and in molds for injection-molded plastics for automotive, industrial and consumer applications. Beryllium oxide is used in high-technology ceramics, electronic heat sinks, electrical insulators, crucibles, thermocouple tubing, and laser structural components. Other beryllium compounds, containing chloride, nitrate, fluoride and sulfate, are utilized as chemical reagents or generated from the refining of beryllium-containing ores.

Beryllium is naturally emitted into the atmosphere by windblown dusts and volcanic particles. However, the major emission source is the combustion of coal and fuel oil, which releases beryllium-containing particulates and ash. Other beryllium-releasing industrial processes include ore processing, metal fabrication, beryllium oxide production, and municipal waste incineration (ATSDR, 1993). Beryllium also occurs in tobacco smoke.

IV. Effects of Human Exposure

The respiratory tract is the major target organ system in humans following the inhalation of beryllium. The common symptoms of chronic beryllium disease include shortness of breath upon exertion, weight loss, cough, fatigue, chest pain, anorexia, and overall weakness. Most studies reporting adverse respiratory effects in humans involve the occupational exposure to beryllium. Exposure to soluble beryllium compounds is associated with acute beryllium pneumonitis (Eisenbud *et al.*, 1948). Exposure to both soluble or insoluble beryllium compounds may result in obstructive and restrictive diseases of the lung, called chronic beryllium disease (berylliosis) (Cotes *et al.*, 1983; Johnson, 1983; Infante *et al.*, 1980; Kriebel *et al.*, 1988a; Metzner and Lieben, 1961). Overall, the total number of beryllium-related disease cases has declined since the adoption of industrial standards (Eisenbud and Lisson, 1983; ATSDR, 1993).

Historically, beryllium pneumonitis has been associated with occupational concentrations over 0.1 mg Be/m^3, primarily as beryllium sulfate or beryllium fluoride (Eisenbud *et al.*, 1948). But the atmospheric concentrations related to chronic beryllium disease have been more difficult to define, in part due to the lack of individual exposure estimates, especially in the studies derived from the berylliosis case registries (Infante *et al.*, 1980; Lieben and Metzner, 1959). However, Infante and associates (1980) reported significantly increased mortality due to non-neoplastic respiratory disease in beryllium-exposed workers, and noted one case of chronic berylliosis in a worker following 7 years exposure to $\leq$ 2 µg Be/m^3. In a 30-year follow-up study of 146 beryllium-exposed workers, Cotes *et al.* (1983) identified seven cases of chronic beryllium related disease (146 workers examined). All the cases were exposed to beryllium oxide or hydroxide, but in a wide range of retrospectively estimated doses (over 3000 samples from 1952 to 1960). The estimated average daily exposure did not exceed 2 µg/m^3 for the ten site/process classifications, but 318 samples did exceed 2 µg Be/m^3 (and 20 samples were greater than 25 µg Be/m^3). No atmospheric samples were available after 1963, even though the exposure occurred

through 1973. The LOAEL for occupationally-induced berylliosis observed in this study was estimated from uncertain exposure data to be less than 2 µg Be/m^3.

One cross-sectional study (Kriebel *et al.*, 1988a; Kriebel *et al.*, 1988b) estimated beryllium exposure levels for 309 workers originally surveyed in 1977, with a median duration of exposure of 17 years (range 2 to 39 years). Historic plant beryllium levels were estimated to be as high as 100 µg Be/m^3, and, even as late as 1975, some job classifications exceeded 10 µg Be/m^3. The workers' median cumulative exposure was 65 µg Be/m^3-years (range 0.1 to 4400 µg Be/m^3-years); the median lifetime exposure estimate was 4.3 µg/m^3 (range 0.01 to 150 µg/m^3). Spirometric measurement of pulmonary function, chest x-rays, and arterial blood gas measurements were collected. Decrements in lung function, as defined by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), were associated with cumulative exposure up to 20 years prior to the health survey, even in workers with no radiographic abnormalities. Differences in alveolar-arterial oxygen gradient were associated with cumulative exposure in the 10 years prior to the study. These endpoints give a LOAEL of 39 µg/m^3-years (geometric mean cumulative exposure) for decrements in pulmonary function and changes in arterial blood gases.

Non-occupational beryllium-related chronic disease has been reported in individuals residing in the vicinity of beryllium manufacturing industries (Eisenbud *et al.*, 1949; Metzner and Lieben, 1961). An early cross-sectional study (Eisenbud *et al.*, 1949) described 11 cases of non-occupational berylliosis after examining (x-ray and clinical) approximately 10,000 residents near a beryllium fabrication facility. Ten of the cases resided within 3/4 mile of the plant (up to 7 years duration), and five cases resided within 1/4 mile. The authors approximated a 1% disease incidence within 1/4 mile (500 individuals). Atmospheric sampling in 1947 identified an average beryllium level of 0.2 µg Be/m^3 at 1/4 mile decreasing to 0 µg Be/m^3 at 10 miles, but samples varied widely (up to 100 fold) over the 10 week sampling period. Utilizing current and historic exposure estimates based on discharge, process, inventory and building design changes, this study estimated a chronic LOAEL in the range of 0.01 to 0.1 µg Be/m^3 for continuous exposure to beryllium compounds, based on the development of chronic berylliosis.

Metzner and Lieben (1961) also reported 26 cases of chronic berylliosis in a population of approximately 100,000 living within 7 miles of a refining and alloy fabrication plant (duration 6 to 19 years). Neighborhood exposure assessment conducted over 14 months during1958 and 1959 identified a mean level of 0.0155 µg Be/m^3, with 10% of the samples registering over 0.03 µg Be/m^3. Limited measurements conducted earlier at the site were higher (1.0 to 1.8 µg Be/m^3 in 1953 and 0.91 to 1.4 µg Be/m^3 in 1954).

Chronic beryllium disease appears to involve a cell-mediated immune response, especially granulomatous reactions found in the lungs of sensitive individuals. Humans exposed to beryllium compounds have demonstrated increased T-cell activity (*in vitro*) and histological abnormalities of the lymph nodes (Cullen *et al.*, 1987; Johnson, 1983). Johnson (1983) described granuloma of lymph nodes and chronic interstitial pneumonitis in a small number of beryllium metal handling machinists (LOAEL = 4.6 µg Be/m^3). A second study identified granulomatous lung lesions, scarred lung tissue, and breathing difficulties in workers from a precious metal refining facility exposed to a mixture of beryllium and other metals (Cullen *et al.*,

1987). Also, altered proliferative responses of lymphocytes obtained by bronchoalveolar lavage indicated increased T-cell activity in vitro. This study reported a LOAEL of 1.2 µg Be/m^3 for the immunological and respiratory endpoints.

V. Effects of Animal Exposure

Three chronic studies, two in rats (Vorwald and Reeves, 1959; Reeves *et al.*, 1967) and one in guinea pigs (Reeves *et al.*, 1970), observed adverse inflammatory and proliferative respiratory changes following inhalation exposure to beryllium compounds. Vorwald and Reeves (1959) observed inflamed lungs and fibrosis in rats exposed to 0.006 mg Be/m^3 (as BeO) for an unspecified duration. A later study exposed Sprague-Dawley CD rats for 72 weeks (7 hr/d, 5 d/wk) to 34.25 µg Be/m^3 from $BeSO_4$ (Reeves *et al.*, 1967). Gross and histological changes observed in exposed versus unexposed rats included increased lung weight, inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (LOAEL = 34.25 µg Be/m^3). In guinea pigs exposed to either 0, 3.7, 15.4 or 29.3 µg Be/m^3 (from the sulfate) for 6 hours/day, 5 days/week for up to 1 year, respiratory alterations observed in the beryllium-exposed groups included increased tracheobronchial lymph node and lung wet weights, interstitial pneumonitis, and granulomatous lesions. These adverse respiratory effects were observed in all the beryllium dosed groups and indicated a chronic inhalation LOAEL of 3.7 µg Be/m^3.

Wagner *et al.* (1969) exposed monkeys, rats and hamsters to 0.21 and 0.62 mg Be/m^3 as fumes from bertrandite or beryl ore, respectively. Rats, exposed 6 hours/day, 5 days/week for up to 17 months, displayed more severe effects, including (1) bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions after exposure to 0.21 mg Be/m^3 from bertrandite ore, and (2) inflamed lungs, fibrosis, and granuloma after exposure to 0.62 mg Be/m^3 from beryl ore. Lung inflammation was observed in the exposed monkeys, and a few granulomatous lung lesions were observed in the hamsters after similar exposure conditions (up to 23 months).

Immunological effects have been observed in a few subchronic studies (Schepers, 1964; Schepers *et al.*, 1957; Stiefel *et al.*, 1980). Schepers (1964) exposed monkeys (*Macacus mullata*) to three soluble forms of beryllium (BeF_2, $BeSO_4$, $BeHPO_4$) daily for 6 hours/day over 7 to 30 days. Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed after 17 days at 0.198 mg Be/m^3 (as $BeSO_4$). Histological examination found pleuritis, congestion, emphysema, consolidation and edema of the lung. Immunological effects were seen as hyperplasia of the lymph nodes typical of immune activation after 7 to 18 days exposure to either 0.198 or 0.184 mg Be/m^3 as the sulfate or fluoride. A subchronic inhalation study reported immunological effects as increased, beryllium-specific stimulation of T-lymphocytes *in vitro* from Wistar rats and guinea pigs exposed daily (6 hours/day) over 10 weeks (LOAEL = 0.5 mg/m^3) (Stiefel *et al.*, 1980). However, a subchronic inhalation study on Wistar and Sherman rats (Schepers *et al.*, 1957) observed multiple lung alterations including granulomas (LOAEL = 35 µg Be/m^3) but did not find any accompanying immunological effects after 30 days discontinuous exposure (5-6 d/wk, 4-8 hr/d) to beryllium fumes from $BeSO_4$.

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Reference Exposure Level

Study	Eisenbud *et al.* (1949)
Study population	Approximately 10,000 individuals within 2 miles of a beryllium manufacturing plant
Exposure method	Environmental exposure
Critical effects	Pulmonary berylliosis
LOAEL	0.03 µg/m^3 (geometric mean of range of measured exposures associated with berylliosis of 0.01 to 0.1 µg/m^3)
NOAEL	Not observed
Exposure continuity	Continuous
Average exposure	Estimated to be approximately 0.3 µg/m^3 (historical exposures estimated to be 10-fold higher than measured values) for LOAEL group
Human equivalent concentration	0.3 µg/m^3 for LOAEL group
Exposure duration	Up to 7 years
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.001 µg/m^3

Eisenbud *et al.* (1949) reported 11 cases of non-occupational chronic pulmonary granulomatosis (berylliosis) among approximately 10,000 residents screened (health survey and x-ray) in the vicinity of a beryllium manufacturing plant. Ten of the cases resided within 3/4 mile of the facility, but neither these individuals nor their spouses had occupational contact with the plant. Five cases occurred within 1/4 mile of the plant from an approximate population of 500 residents. Although this study gave minimal case and population descriptions, environmental exposure assessment was conducted (fixed and mobile stations over 10 weeks) at the time of study (1947). In addition historical estimates were developed from earlier measurements, downwind effluent models, inventory, process and building design changes over time (plant operated from 1935 to 1947). In 1947, air concentrations ranged from 2 µg Be/m^3 at 1/4 mile to 0 µg Be/m^3 at 2 miles distance (detection limit = 0.001 µg Be/m^3). The estimated concentration at 3/4 mile distance from the plant was 0.01 µg Be/m^3. The authors estimated the airborne beryllium concentration associated with berylliosis as 0.01 to 0.10 µg Be/m^3. This estimate included multiplication of the 0.01 µg/m^3 concentration by a factor of 10 to account for greater historical exposures.

One other report describes 26 cases of berylliosis due to environmental exposure to beryllium plant effluent (Metzner and Lieben, 1961). This study reported a similar mean air concentration of 0.0155 µg Be/m^3, while limited historic measurements ranged from 0.91 to 1.8 µg Be/m^3.

Occupational studies have reported berylliosis and/or alterations in pulmonary function after exposure to higher concentrations of beryllium (2- to 10-fold). Cotes *et al.* (1983) reported on 146 workers surveyed three times since 1963 (1963, 1973, and 1977). Exposure assessment was based on plant sampling from 1952 to 1963. The estimated overall daily average was < 2 µg Be/m^3, however, a wide range of individual integrated exposures was estimated. Seven cases of berylliosis-related disease were observed in 130 workers examined in 1973. No association was seen between lung function and estimated exposure in normal subjects. However, Kriebel *et al.* (1988a; 1988b) did find decrements in lung function significantly associated with cumulative exposure to beryllium. Lifetime beryllium exposure histories were estimated for 309 of 350 workers (mean duration = 17 years) and 297 underwent medical testing. The median cumulative exposure was 65 µg Be/m^3-years (mean cumulative exposure = 37 µg Be/m^3) and the mean lifetime exposure was 3 µg Be/m^3. After controlling for age, height, and smoking in multivariate regression models, decrements in lung function (FVC and FEV_1) were associated with cumulative exposure to beryllium, in the period up until 20 years before the survey.

The major strength of the REL is the use of human data among residentially-exposed persons. The major uncertainties are the lack of a NOAEL observation, the lack of long-term exposure data, the difficulty of estimating exposures, and the lack of chronic exposure data.

Derivation of Chronic Oral Reference Exposure Level* (U.S. EPA RfD*)

Study	Schroeder and Mitchner, 1975
Study population	Rats
Exposure method	Drinking water
Critical effects	No adverse effects at dose given
LOAEL	Not observed
NOAEL	5 ppm in water (0.54 mg/kg bw-day)
Exposure continuity	Continuous
Exposure duration	Lifetime
Average experimental exposure	0.54 mg/kg bw-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.005 mg/kg bw-day

*Conversion Factors: 5 ppm (5 mg/L) x 0.035 L/day / 0.325 kg bw = 0.54 mg/kg bw/day

The Oral Reference Exposure Level (REL) for beryllium is the U.S. EPA's Reference Dose for chronic oral exposure (RfD) (U.S.EPA, 1996). Fifty-two weanling Long-Evans rats of each sex

received 0 or 5 ppm beryllium (as $BeSO_4$, beryllium sulfate) in drinking water (Schroeder and Mitchner, 1975). Exposure was for the lifetime of the animals. At natural death the rats were dissected and gross and microscopic changes were noted in heart, kidney, liver, and spleen. There were no effects of treatment on these organs or on life span, urinalysis, serum glucose, cholesterol, and uric acid, or on numbers of tumors. Male rats showed decreased growth rates from 2 to 6 months of age. Similar studies were carried out on Swiss (CD strain) mice in groups of 54/sex at doses of approximately 0.95 mg/kg/day (Schroeder and Mitchner, 1975). Female animals showed decreased body weight compared with untreated mice at 6 of 8 intervals. Male mice exhibited slight increases in body weight. These effects were not considered adverse, therefore, 0.95 mg/kg/day is considered a NOAEL. An unpublished investigation by Cox *et al.* (1975) indicates a much higher dose level (approximately 25 mg/kg/day) in the diet may be a NOAEL.

The uncertainty factor (UF) of 100 reflects a factor of 10 each for interspecies conversion and for the protection of sensitive human subpopulations. No modifying factor (MF) was used.

This RfD is limited to soluble beryllium salts. Data on the teratogenicity or reproductive effects of beryllium are limited. It has been reported to produce embryolethality and terata in chick embryos.

U.S. EPA stated its confidence in the RfD as: Study - Low; Data Base – Low, and RfD - Low. Confidence in the study is rated as low because only one dose level was administered. Although numerous inhalation investigations and a supporting chronic oral bioassay in mice exist, along with the work by Cox *et al.* (1975) which indicates that a higher dose level might be a NOEL, these studies are considered as low to medium quality. Thus, the data base is given a low confidence rating. The overall confidence in the RfD is low, reflecting the need for more toxicity data by the oral route.

VII. References

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CHRONIC TOXICITY SUMMARY

1,3-BUTADIENE

(butadiene; buta-1,3-diene; biethylene; bivinyl; vinylethylene)

CAS Registry Number: 106-99-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**8 µg/m^3**
Critical effect(s)	Increased incidence of ovarian atrophy in mice
Hazard index target(s)	Reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Colorless gas
Molecular formula	C_4H_6
Molecular weight	54.09
Boiling point	-4.4^{o}C
Vapor pressure	910 mm Hg at 20°C
Solubility	Soluble in water (735 mg/L); soluble in ethanol, ether, acetone, benzene
Conversion factor	1 ppm = 2.21 mg/m^3 at 25°C

III. Major Uses and Sources

1,3-Butadiene is a major commodity product of the petrochemical industry, usually produced as a by-product of ethylene. The majority of 1,3-butadiene is used in the production of styrene-butadiene rubber copolymers (SBR). Other applications include as a polymer component for polybutadiene, hexamethylene diamine, styrene-butadiene latex, acrylonitrile-butadiene-styrene (ABS) resins, chloroprene and nitrile rubbers. A variety of industrial syntheses use 1,3-butadiene resins (AB as a chemical intermediate, such as in the production of adiponitrile (a nylon precursor), captan and captofol fungicides, ethylidene norbornene and sulfolane, boron alkyls, and hexachlorobutadiene. Additionally, 1,3-butadiene has been found in automobile exhaust, gasoline vapor, fossil fuel incineration products, and cigarette smoke (HSDB, 1995).

IV. Effects of Human Exposure

An early occupational study reported complaints of irritation of eyes, nasal passages, throat, and lungs in rubber manufacturing workers following acute exposure to unknown levels of 1,3-butadiene (Wilson, 1944). Additional symptoms reported included coughing, fatigue, and drowsiness, however, all symptoms ceased on removal from the exposure.

Studies on the chronic effects of 1,3-butadiene have been centered in the styrene-butadiene rubber manufacturing industry, which uses large quantities of 1,3-butadiene, and the 1,3-butadiene monomer industry. One retrospective epidemiological study reported an increase in overall mortality, emphysema, and cardiovascular diseases (chronic rheumatic and arteriosclerotic heart disease) among rubber workers (McMichael *et al.*, 1976). Two other occupational studies have described the potential for adverse hematological effects due to butadiene exposure (Checkoway and Williams, 1982; McMichael *et al.*, 1975). A survey of workers at a styrene-butadiene rubber plant revealed slightly lower levels (but within normal range) of red blood cells, hemoglobin, platelets, and neutrophils in exposed (mean 20 ppm) versus unexposed workers (Checkoway and Williams, 1982). And 1,3-butadiene has been implicated in hematopoietic malignancies among styrene-butadiene rubber workers at levels lower than 20 ppm (McMichael *et al.*, 1975). Since the workers in these studies were exposed to mixtures of chemicals, the specific contribution of butadiene to the adverse respiratory and hematopoietic effects remains unclear.

V. Effects of Animal Exposure

The few available chronic animal inhalation studies have focused on the potential carcinogenicity of 1,3-butadiene. The National Toxicology Program (NTP) has sponsored two chronic inhalation studies in $B6C3F_1$ mice (NTP, 1984; Melnick *et al.*, 1990; NTP, 1993), while Hazelton Laboratories Europe (HLE) Ltd. conducted a chronic inhalation study in Sprague-Dawley rats (HLE, 1981; Owen *et al.*, 1987; Owen and Glaister, 1990).

The two $B6C3F_1$ mice inhalation studies sponsored by NTP (Huff *et al.*, 1985; Melnick *et al.*, 1990; NTP, 1984; NTP, 1993), although focused on carcinogenicity, identified other adverse chronic effects. The earlier NTP (1984) study in mice administered 0, 625 or 1250 ppm 1,3-butadiene for 6 hours/day, 5 days/week for up to 61 weeks. Nonneoplastic changes observed were elevated testicular and ovarian atrophy at both doses (625 and 1250 ppm); liver necrosis in male mice at both doses and in female mice at 1250 ppm; and nonneoplastic lesions in the nasal cavity at 1250 ppm. At the highest dose, adverse changes in the nasal cavity included chronic inflammation, fibrosis, cartilaginous metaplasia, osseous metaplasia, and atrophy of the sensory epithelium. No nasal or respiratory lesions were seen in the controls. This study identified a chronic LOAEL of 625 ppm for gonadal atrophy in both sexes.

The later NTP study (Melnick *et al.*, 1990; NTP, 1993) used lower exposure concentrations of 1,3-butadiene (0, 6.25, 20, 62.5, 200 or 625 ppm) administered 6 hours/day, 5 days/week for up to 2 years. Two-year survival was significantly decreased in mice exposed to 20 ppm and greater, primarily due to chemical-related malignant neoplasms. Increased incidences of nonneoplastic lesions in exposed mice included bone marrow atrophy, gonadal atrophy (testicular, ovarian and uterine), angiectasis, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and cardiac endothelial hyperplasia. Gonadal atrophy was observed at 200 ppm and 625 ppm for males and at 6.25 ppm and higher for females. Bone marrow toxicity (regenerative anemia) was seen at 62.5 ppm and higher. This study identified a chronic LOAEL

of 6.25 ppm for reproductive toxicity, and a NOAEL of 200 ppm and a LOAEL of 625 for nonneoplastic hematotoxic effects.

The U.S. EPA (1985) reviewed data from a 2-year chronic inhalation toxicity study sponsored by the International Institute of Synthetic Rubber Producers (IISRP) at Hazelton Laboratories Europe, Ltd (1981) on Sprague-Dawley rats exposed to 0, 1000 or 8000 ppm 1,3-butadiene. Results from the study were also reported later by Owen *et al.* (1987; 1990). Minor clinical effects, including excessive eye and nose secretions plus slight ataxia, were observed between 2 and 5 months in rats exposed to 8000 ppm 1,3-butadiene. Alterations in organ weight were also observed in this high exposure group. A dose-related increase in liver weights was observed at both the 52-week interim kill and at study termination. Absolute and relative kidney weight was also significantly increased and associated with nephrosis. No reproductive organ atrophy was reported in this rat study.

The U.S. EPA (1985) described another secondary report, that of Miller (1978), which reviewed a group of Russian studies of subchronic 1,3-butadiene exposure in rats. One study (reported by Ripp in 1967) continuously exposed rats to relatively lower concentrations of 0.45, 1.4 or 13.5 ppm. At 13.5 ppm, blood cholinesterase was elevated, blood pressure was lowered, and motor activity was decreased. Histopathological changes reported at 0.45 ppm were congestion in the spleen and hyperemia and leukocyte infiltration of cardiac tissue. Alterations in lung tissue noted at 1.4 and 13.5 ppm included atelectasis, interstitial pneumonia, and emphysema. No other studies used such low exposure levels or measured such endpoints. Unfortunately, the specific research methods and results for this study are unavailable for direct review and comparison.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP (1993)
Study population	$B6C3F_1$ mice (70/sex/group)
Exposure method	Discontinuous inhalation (0, 6.25, 20, 62.5, 200, 625 ppm) over 2 years
Critical Effects	Increased incidence of ovarian atrophy
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	103 weeks
LOAEL	6.3 ppm
NOAEL	Not observed
Average experimental exposure	1.1 ppm for LOAEL group (6.3 x 6/24 x 5/7)
Human equivalent concentration	1.1 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic factor	1
LOAEL uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	4 ppb (0.004 ppm; 0.008 mg/m^3; 8 $\mu g/m^3$)

The chronic REL for butadiene is based on an increased incidence of ovarian atrophy in mice. Significant reproductive toxicity was observed in both sexes of mice at the interim 9-month, interim 15-month, and 2-year study termination as gonadal atrophy (NTP, 1993). Testicular atrophy was induced in male B6C3F1 mice at 625 ppm or above in this principal study and in a previous study (NTP, 1984). In female mice exposed for 9-months, ovarian atrophy was observed at 200 and 625 ppm (442 or 1381 mg/m^3, respectively). After 15 months, ovarian atrophy was observed at exposure levels of 20 ppm (44.2 mg/m^3) and above. In mice exposed for up to 2 years (103 weeks), the incidence of ovarian atrophy increased at all exposure concentrations relative to controls, which establishes a chronic LOAEL of 6.25 ppm (13.81 mg/m^3) for reproductive toxicity. The incidence of ovarian atrophy was 4/49 in controls and 19/49 (39%) at 6.25 ppm. Because atrophy of a major organ is the critical effect observed at the LOAEL, and no NOAEL was recorded, the full LOAEL uncertainty factor of 10 is used.

Few chronic animal studies are available for comparison to the above; however, an acute and subchronic (10 week) study identified male-mediated F1 effects in mice exposed to 12.5 or 1250 ppm 1,3-butadiene (6 hour/day, 5 days/week) (Anderson *et al.*, 1993). At 1250 ppm (2762.4 mg/m^3), statistically significant effects observed were a reduction in the number of implantations, an induction of dominant lethal mutations, an increased incidence of early and late deaths, and an increase in abnormalities. The lower dose, 12.5 ppm (27.63 mg/m^3), resulted in an increase of early deaths and fetal abnormalities. The IISRP sponsored study (Owen *et al.* 1987; 1990) did not report any noncancer adverse reproductive effects in Sprague-Dawley rats exposed to 1000 or 8000 ppm 1,3-butadiene (2210 or 17,680 mg/m^3, respectively); however, tumors were found in reproductive tissues (Owen *et al.*, 1987).

The mouse ovary is more sensitive to butadiene's epoxide metabolites than the rat ovary. Doerr *et al*. (1996) administered butadiene monoepoxide (BMO) or butadiene diepoxide (BDE) intraperitoneally to female B6C3F1 mice and Sprague-Dawley rats for 30 days and found that BMO and BDE exhibited a greater ovotoxic potential in the mice compared to the rats. Dahl et al. (1991) reported that, for equivalent inhalation exposures, the concentrations of total butadiene metabolites in blood were 5-50 times lower in the monkeys than in the mice and 4-14 times lower than in the rats. People may be more like the monkey than the mouse or the rat in their formation of epoxides from butadiene. Several pharmacokinetic models (reviewed by Himmelstein *et al*., 1997) have been developed to adjust for species differences in pharmacokinetics. However, an interspecies pharmacodynamic adjustment for this ovarian atrophy endpoint with butadiene is still needed. Therefore OEHHA staff use an interspecies uncertainty factor of 3 to account for pharmacodynamic differences between mice and men.

The major strength of the butadiene REL is the observation of a dose-response effect in a well-conducted lifetime inhalation exposure study. The major weaknesses are the lack of adequate human health effects data and the lack of a NOAEL observation.

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CHRONIC TOXICITY SUMMARY

CADMIUM AND CADMIUM COMPOUNDS

CAS Registry Number: 7440-43-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.02 μg/m^3** (respirable)
Critical effect(s)	Kidney effects (proteinuria) and respiratory effects (reduction in forced vital capacity and reduction in peak expiratory flow rate) in occupationally exposed humans
Hazard index target(s)	Kidney; respiratory system

II. Physical and Chemical Properties (ATSDR, 1993)

Description	Blue-white solid
Molecular formula	Cd
Molecular weight	112.41
Density	8.642 g/cm^3 @ 20ºC
Boiling point	767ºC
Melting point	320.9ºC
Vapor pressure	1 torr @ 394ºC
Conversion factor	Not applicable

III. Major Uses or Sources

The production of nickel-cadmium batteries is currently the primary use of cadmium (ATSDR, 1993). Cadmium, a by-product of zinc- and sulfide-ore processing, is also used for metal plating and in pigments and plastics.

IV. Effects of Human Exposure

Pulmonary and renal function were examined in three worker groups: women with less than 20 years of exposure [group E1]; men with less than 20 years of exposure [group E2], and men with more than 20 years of exposure [group E3] (Lauwerys *et al.*, 1974). Although urine cadmium concentrations were significantly elevated, the subjects in E1 did not exhibit pulmonary function changes or proteinuria indicative of renal impairment. The workers in E1 had been exposed for a mean of 4.08 years to 31 μg/m^3 total cadmium (1.4 μg/m^3 respirable cadmium). The 27 workers in E2 had been exposed for a mean of 8.6 years to 134 μg/m^3 total cadmium (88 μg/m^3 respirable cadmium). The blood and urinary cadmium levels of these workers were also significantly

elevated compared to matched controls. Glomerular proteinuria was observed in 15% of the workers in E2 and in 68% of workers in E3. The 22 workers of E3 had been exposed for a mean of 27.8 years to 66 $\mu g/m^3$ total cadmium (21 $\mu g/m^3$ respirable cadmium). Significantly increased levels of cadmium were observed in the blood and urine and workers in E3 also exhibited significant decreases in some measures of pulmonary function (forced vital capacity, forced expiratory volume in one second, and peak expiratory flow rate). This study identifies the kidney as the key target organ of chronic cadmium exposure. For respirable cadmium, this study indicates a LOAEL of 21 $\mu g/m^3$ for workers exposed for 28 years and a NOAEL of 1.4 $\mu g/m^3$ for workers exposed for 4 years.

A study of 82 cadmium exposed workers reports the time-weighted cumulative exposure index (TWE) and cadmium body burden determined in vivo (Ellis *et al.*, 1985). Evidence of renal dysfunction (usually elevated urinary β_2-microglobulin) was consistently observed when the worker's liver cadmium burden exceeded 40 ppm and the time-weighted cumulative exposure index exceeded 400-500 μg years/m^3.

A detailed investigation of renal function in 75 male cadmium-exposed workers identified significant increases in urinary excretion of several low- and high molecular weight proteins, including β_2-microglobulin, and significant decreases in renal reabsorption of calcium, urate, and phosphate compared to controls (Mason *et al.*, 1988). Exposures, which ranged from 36 to 600 $\mu g/m^3$, were determined from background or personal exposure measurements made between 1964 and 1983, or were estimated. A time-weighted cumulative exposure index (TWE) was determined for each subject. A two phase linear regression model was applied to the data to identify inflection points for each biochemical parameter. The biochemical indicators most highly correlated to exposure were urinary retinol binding protein and urinary β_2-microglobulin. Of these, the most sensitive parameter, urinary β_2-microglobulin, demonstrated an inflection point at 1108 μg years/m^3 with a 95% lower confidence limit of 509 μg years/m^3. The endpoint selected is indicative of defects in tubular reabsorption of proteins.

Diminished sensitivity of smell has also been observed in cadmium exposed workers (Rose *et al.*, 1992). Cadmium body burden, β_2-microglobulin levels, and olfactory function were measured in a group of 55 male workers exposed to cadmium fumes in a brazing operation. A group of 15 control workers was also tested. Exposed workers exhibited high urinary cadmium levels, tubular proteinuria, and a significant, selective defect in odor detection threshold.

V. Effects of Animal Exposure

Interstitial infiltration of lymphocytes and leukocytes and hyaline casts were observed in the kidneys of rabbits following exposure to 6.5 mg/m^3 cadmium-iron dust for 3 hours per day, 21 days per month for 9 months (Friberg, 1950). Proteinuria was observed in the majority of exposed rabbits by the fourth month of exposure. Increased lung weights and emphysema were also observed. The trachea and nasal mucous membranes exhibited chronic inflammatory changes (not specified) and lymphocyte infiltration. The kidney contained the greatest concentration of cadmium. This study also exposed a group of rabbits to 9.1 mg/m^3

cadmium-iron dust for 3 hours per day, 23 days per month, for 7 months. Two rabbits in this group died from acute pneumonia at one month, and one rabbit was terminated at 3 months of exposure. Findings at necropsy were similar, although more severe than those observed in rabbits exposed to 6.5 mg/m^3. Chronic bronchitis and hyperplasia of the bronchiolar epithelium were observed in the higher dose group in addition to the findings previously noted.

Male and female rats were exposed to 0, 0.3, 1.0, or 2.0 mg Cd/m^3 (as $CdCl_2$) 6 hours per day, 5 days per week for a total of 62 exposures (Kutzman *et al.*, 1986). Rapid, shallow breathing and marked weight loss were observed in the highest dose group; all animals in this group died within the first 45 days of exposure. A dose-dependent increase in lung weight was observed in the remaining dose groups and a statistically significant increase in lung collagen and elastin was observed in rats exposed to 1.0 mg/m^3. Pathological changes noted in the terminal bronchioles include flattening and hyperplasia of type II cells, and infiltration of macrophages, mononuclear cells, and polymorphonuclear leukocytes. Proliferation of fibroblasts with deposition of collagen was also noted.

Male rats were exposed continuously to 0, 30, or 90 µg Cd/m^3 cadmium oxide (CdO) dust for up to 18 months (Takenaka *et al.*, 1990). Animals exposed to 30 µg/m^3 were sacrificed at 6 and 18 months of exposure. Although some rats in the high dose group were terminated after 6 months of exposure, the remaining rats were terminated after 7 months due to increased mortality and were not included in the study. Inflammation and hyperplasia of the alveolar epithelium occurred in animals of both groups after 6 months of exposure with more marked changes observed in the high dose group. Abnormal proliferation of the epithelium was observed in the low dose group following 18 months of exposure. Lung tumors observed in both dose groups were characterized as being duration dependent.

VI. Derivation of Chronic Reference Exposure Levels (REL)

Derivation of Chronic Inhalation Reference Exposure Level

Study	Lauwerys *et al.*, 1974
Study population	Humans (22 exposed men and 22 unexposed men in LOAEL group; 31 exposed women and 31 non-exposed women in NOAEL group)
Exposure method	Occupational exposures
Critical effects	Kidney effects - proteinuria in 68% of LOAEL group Respiratory effects – reduction in forced vital capacity in 1 second (FEV_1); reduction in peak expiratory flow rate
LOAEL	21 µg/m^3 respirable cadmium
NOAEL	1.4 µg/m^3 respirable cadmium
Exposure continuity	Assumed to be 5 days/week for 8 hours/day during which 10 m^3 air is breathed

Average occupational exposure	0.5 μg/m^3 for NOAEL group (1.4 x 10/20 x 5/7)
Human equivalent concentration	0.5 μg/m^3 for NOAEL group
Exposure duration	Average of 4.1 years (1 to 12 years) for NOAEL group
Subchronic uncertainty factor	3
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 μg/m^3

This evaluation is strengthened by being based on a human exposure study of workers exposed to cadmium for periods of 1 to over 20 years. The exposed group was matched to a control group in terms of age, body size, cigarettes smoked per day, duration of smoking, and duration of employment. The factory process was unchanged over the study period suggesting that exposures may have remained relatively constant over time.

Significant areas of uncertainty include an incomplete knowledge of the past exposures over the full study interval and the relatively small study size.

A similar evaluation of the LOAEL group led to an alternate inhalation reference exposure level estimate of 0.05 μg/m^3. The LOAEL group had an average occupational exposure of 5.0 μg/m^3 and an average exposure duration of 27.8 years (21 to 40 years). Default uncertainty factors would include a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor (UF).

Using data presented by Ellis and associates (1985) and Mason and associates (1993) correlating human cumulative exposures (in terms of μg-years/m^3) and renal tubular protein reabsorption, a LOAEL of 500 μg-years / m^3 was predicted. This correlates to 7 μg/m^3 over 70 years. A time-weighted exposure to account for continuous exposure rather than 40 hour per week occupational exposure is 1.7 μg/m^3. Applying a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor results in a REL value of 0.02 μg/m^3, the same value obtained using the Lauwerys *et al*. data.

Derivation of Chronic Oral Reference Exposure Level **(U.S. EPA RfD)**

Study	U.S. EPA, 1985
Study population	Humans
Exposure method	Food and drinking water
Critical effects	Significant proteinuria
LOAEL	Not observed
NOAEL	0.005 mg/kg bw-day
Exposure continuity	Chronic
Exposure duration	Up to lifetime
Average exposure	0.005 mg/kg bw-day

LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies factor	10
Cumulative uncertainty factor	10
Oral reference exposure level	0.0005 mg/kg bw-day

The oral REL is the U.S. EPA's Reference Dose (RfD) (U.S. EPA, 1996). A concentration of 200 μg cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 μg Cd/gm wet weight human renal cortex. The model assumes that 0.01% of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 μg Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day.

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect. Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

The uncertainty factor of 10 is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the RfD as: Study - Not applicable; Data Base - High; and RfD – High. The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium including absorption, distribution, metabolism, and elimination. All this information considered together gives high confidence in the data base. High confidence in the RfD follows as well.

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CHRONIC TOXICITY SUMMARY

CARBON DISULFIDE

(carbon bisulfide; carbon sulfide; dithiocarbonic anhydride)

CAS Registry Number: 75-15-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**700 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	CNS/PNS (reduction in motor nerve conduction velocities in occupationally-exposed humans)
Hazard index target(s)	Nervous system; reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Clear, colorless or faintly yellow liquid
Molecular formula	CS_2
Molecular weight	76.14
Boiling point	46.5^{o}C
Vapor pressure	297 mm Hg @ 20°C
Solubility	Slightly soluble in water (2.94 g/L); miscible in anhydrous methanol, ethanol, ether, benzene, chloroform, and carbon tetrachloride
Conversion factor	3.1 mg/m^3 per ppm at 25°C

III. Major Uses and Sources

The most prominent industrial use of carbon disulfide is in the production of viscose rayon fibers. Other uses are in the production of carbon tetrachloride and cellophane, and, as a solvent for rubber, sulfur, oils, resins and waxes. In the past, carbon disulfide was used in soil fumigation and insect control in stored grain. Industrial processes that produce carbon disulfide as a by-product include coal blast furnaces and oil refining (HSDB, 1995).

IV. Effects of Human Exposure

A primary target of carbon disulfide (CS_2) toxicity is the nervous system. The major neurotoxic action of carbon disulfide is the development of mental disturbances. These include change of personality, irritability, and forgetfulness, often with accompanying neurophysiological and

neuropathological changes after prolonged exposure. Such changes include decreased peripheral nerve impulse conduction, motor and/or sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes (Aaserud *et al.* 1988, 1990, 1992; Foa *et al.*, 1976; Hirata *et al.* 1992; Ruijten *et al.* 1990, 1993). Alterations in behavioral indices have historically been associated with high levels of CS_2, often in the excess of 20 ppm (Foa *et al.* 1976; Hanninen *et al.*, 1978).

Studies have identified alterations in the nerve conduction of workers chronically exposed to lower CS_2 levels (Hirata *et al.*, 1992a; Johnson *et al.*, 1983; Ruijten *et al.*, 1990; Ruijten *et al.*, 1993). A cross-sectional study of Japanese spinning workers identified alterations in the central nervous system as measured by brain stem auditory evoked potential (BAEP) (Hirata *et al.*, 1992). The latencies of the three main BAEP components increased significantly in the CS_2 exposed workers (more than 20 years duration) when compared to controls. CS_2 exposures ranged from 3.3 to 8.2 ppm (mean 4.76 ppm). Ruijten *et al.* (1993) identified mild presymptomatic nerve impairment (decreased conduction velocities and response amplitudes) in 44 CS_2-exposed workers with an average cumulative exposure range from 192 to 213 ppm-year (mean duration 26.1 years).

Another occupational study evaluated the effects of CS_2 on the peripheral nervous system. Johnson *et al.* (1983) identified a significant dose related reduction in the motor nerve conduction velocities in the calves and ankles of workers exposed to high (median = 7.6 ppm) CS_2 levels versus a comparison group (median = 0.2 ppm). Since this motor nerve reduction was still within normal values, the authors considered the measured difference an indication of minimal neurotoxicity. The mean exposure concentration for all exposed workers (n = 145) ranged from 0.6 to 16 ppm (mean 7.3 ppm) with a mean duration of 12.1 years. This study established a chronic LOAEL of 7.6 ppm for minor neurological effects (decreased peroneal nerve MCV and sural nerve SVC).

Vascular atherosclerotic changes are also considered a major effect of chronic carbon disulfide exposure. Several occupational studies have demonstrated an increase in the mortality due to ischemic heart disease in CS_2 exposed workers (Hernberg *et al.*, 1970; MacMahon and Monson, 1988; Tiller *et al.*, 1968; Tolonen *et al.*, 1979). A 2.5-fold excess in mortality from coronary heart disease in workers exposed to CS_2 was first reported by Tiller *et al.* (1968). A subsequent prospective study by Hernberg *et al.* (1970) found a 5.6-fold increased risk in coronary heart disease mortality and a 3-fold increased risk of a first nonfatal myocardial infarction in CS_2 exposed workers.

Egeland *et al.* (1992) and Vanhoorne *et al.* (1992) have reported that human exposure to CS_2 for more than one year causes increases in biochemical changes often associated with cardiovascular disease - diastolic blood pressure, low density lipoprotein cholesterol, and apolipoproteins A1 and B. Egeland *et al.* (1992) used cross sectional data on 165 CS_2-exposed workers (245 controls) collected in 1979 by Fajen *et al.* (1981). The affected workers were exposed for at least 1 year in a viscose rayon factory to an estimated median TWA (8-hour) of 7.6 ppm. The Egeland *et al.* (1992) study indicated that modest CS_2 exposure (range 3.4 to 5.1 ppm, median 4.1 ppm) was associated with increased low density lipoprotein cholesterol (LDLc), the type of increase associated with atherosclerotic heart disease. No significant differences were seen

between controls and the low CS_2 exposed group (range 0.04 to 1.02 ppm, median 1.00 ppm). This study indicates a chronic NOAEL of 1.00 ppm and a LOAEL of 4.1 ppm for increased LDLc and diastolic blood pressure. Vanhoorne *et al.* (1992) identified increased LDL-cholesterol, apolipoprotein B, systolic and diastolic blood pressure indicative of a increased coronary risk in workers from a Belgium viscose rayon factory (115 exposed and 76 controls). CS_2 concentrations ranged from 1 to 36 ppm. Duration of exposure was not indicated. Even though these biochemical changes were observed, no significant increases in mild cardiovascular disease, such as angina, myocardial infarction, or ischemia, were determined by ECG changes.

CS_2 causes reproductive toxicity in both males and females. Lancranjan *et al.* (1969), Lancranjan (1972), Cirla *et al.* (1978), and Wagar *et al.* (1983) studied male reproductive effects of occupational exposure to CS_2 and showed significant adverse effects on spermatogenesis, levels of serum FSH and LH, and libido; these effects persisted in 66% of the workers subject to follow-up. Zhou *et al.* (1988) investigated pregnancy outcomes and menstrual disturbances in 265 women occupationally exposed to CS_2 and 291 controls. The CS_2-exposed women had significantly higher incidence of menstrual disturbances versus the control group (overall 34.9% vs. 18.2%). CS_2 levels varied between the five facilities (exposure category means of low = 3.1 mg/m^3, intermediate = 6.5 mg/m^3, and high = 14.8 mg/m^3), but all workers from these CS_2 facilities had significantly higher incidences of menstrual disturbance. Irregularity of menstruation was the most common disturbance, followed by abnormal bleeding. No evidence was observed to indicate an adverse effect on the term and outcome of pregnancy.

Price and colleagues (1996) conducted a statistical analysis of the National Institute for Occupational Safety and Health (NIOSH) carbon disulfide (CS_2) exposure database. They analyzed the effects of CS_2 on the peripheral nervous system and on ischemic heart disease risk factors. Changes in the responses associated with increases in work place CS_2 exposure were relatively small after adjustment for confounding. Only peroneal nerve motor conduction velocity and peroneal nerve amplitude ratio had statistically significant relationships with CS_2. In order to investigate the association between CS_2 exposure and ischemic heart disease (IHD) mortality, Price *et al*. (1997) reviewed historical CS_2 exposure data in the viscose rayon industry to identify trends and to use the data to suggest a standard mortality ratio (SMR)-exposure relationship and a threshold level for occupational exposure. Exposure data were extracted from published studies and used with the SMR versus exposure score relationship developed previously by Sweetnam and associates to relate SMRs directly to exposure. Upper and lower bound exposure profiles were derived and used to identify exposure thresholds. For an IHD SMR equal to 100, the upper and lower bound exposures were 60 and 20 ppm, respectively. The analysis indicated that the risk of IHD mortality and its relationship to CS_2 exposure is meaningful only for workers exposed to high level (20-60 ppm and above) for many years. These high levels, which existed in the past, are no longer found in the workplace. The results of their analysis suggested to them a safe workplace exposure level for CS_2 between 15 and 20 ppm.

The possibility of determining LOAEL and/or NOAEL values for the major CS_2-related adverse effects from epidemiology studies, which predominately use workers from the viscose rayon industry, is limited. The limitations include incomplete historical exposure measurements, concurrent exposure to other chemicals (including hydrogen sulfide or methylene chloride), lack

of personal exposure determinations, and a high variability of individual exposures due to decreases of plant CS_2 concentrations over time.

V. Effects of Animal Exposure

Studies investigating the potential for CS_2 toxicity in animals have usually been limited by intermediate or subchronic duration (less than 1 year) and a lack of multiple dose or exposure groups. The neuropathologic changes consistently observed in rodents following CS_2 exposure include axonal swelling, demyelination, swelling at neuromuscular junctions, muscle atrophy and degeneration, damage to terminal axons, and nerve fiber breakdown (Clerici and Fechter, 1991; Colombi *et al.* 1981; Eskin *et al.*, 1988; Jirmanova and Lukas, 1984; Maroni *et al.*, 1979; Szendzikowski *et al.*, 1973). These adverse effects have been observed over a range of exposures (250 to 800 ppm), but few studies have attempted to establish a dose response for this CS_2-induced neurotoxicity.

In a 90 day subchronic inhalation study, Sprague-Dawley and Fischer 344 rats exposed discontinuously (6 hours/day, 5 days/week) to CS_2 developed morphological alterations in nerves including axonal swelling and myelin degradation (Gottfried *et al.*, 1985). This study established a subchronic NOAEL of 50 ppm and a LOAEL of 300 ppm for morphological changes in nerves. A longer inhalation study in Wistar rats observed impairment in the conduction velocity of the sciatic and tibial nerves after 6 and 12 months of intermittent exposure to 289 ppm CS_2 (LOAEL of 289 ppm) (Knobloch *et al.*, 1979).

Wronska-Nofer (1973) showed a positive relationship between the level of triglycerides, the rate of cholesterol synthesis, and CS_2 exposure in Wistar rats exposed to 0, 73.8, 160, 321 or 546 ppm CS_2 for 5 hours/day, 6 days/week over 8 months. This study found a subchronic LOAEL of 73.8 ppm for disturbances in lipid metabolism (increase in serum cholesterol and serum triglycerides). Hepatic toxicity has also been induced in rats exposed to relatively high doses of CS_2, usually following pretreatment with liver inducers such as phenobarbital. Bond *et al.* (1969) showed that high doses of CS_2 to rats produced an increase in periportal liver fat, and decreases in hepatic cytochrome P450 content and in microsomal mixed function oxidase (MFO) activity. After phenobarbital induction, exposed rats exhibited more severe hepatoxicity characterized by hydropic degeneration and necrosis. Other hepatotoxic effects seen after CS_2 exposures greater than 400 ppm include increases in relative liver weight (Sokal, 1973), stimulation of liver microsomal lipid peroxidation (Wronska-Nofer *et al.*, 1986), and decreases in hepatic cholesterol synthesis (Simmons *et al.*, 1988).

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Johnson *et al.* (1983); U.S. EPA (1995)
Study population	145 occupationally exposed workers and 212 nonexposed workers
Exposure method	Discontinuous occupational inhalation exposures (mean of 7.3 ppm and range of 0.6 to 16 ppm)

Critical effects	Reduction in motor nerve conduction velocities (decreased peroneal nerve MCV and sural nerve SVC)
LOAEL	7.3 ppm
NOAEL	Not observed
Average occupational exposure	2.6 ppm for LOAEL group (7.3 x 10/20 x 5/7)
Benchmark concentration (BMC_{10})	17.7 ppm (continuity-weighted exposure of 6.3 ppm)
Exposure continuity	8 hr/day, 5 days/week
Human equivalent concentration	6.3 ppm for BMC
Exposure duration	Mean of 12.1 years (SD 6.9 years)
Subchronic factor	3
LOAEL factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Modifying factor	3 (database deficiencies)
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.7 mg/m^3; 700 µg/m^3)

The major strengths of the REL are the use of human data, the observation of a dose-response effect, and the duration of exposures. The major uncertainties are the poor quantitation of actual exposure magnitude over time and the limited nature of health effects studies conducted.

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CHRONIC TOXICITY SUMMARY

CARBON TETRACHLORIDE

(carbon chloride; carbon tet; freon 10; halon-104; methane tetrachloride; necatrine; tetrachlorocarbon; tetrachloromethane; tetraform; tetrasol; univerm)

CAS Registry Number: 56-23-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**40 µg/m^3**
Critical effect(s)	Increased liver weight and hepatic fatty infiltration in guinea pigs
Hazard index target(s)	Alimentary system; development (teratogenicity); nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless liquid
Molecular formula	CCl_4
Molecular weight	153.8
Density	1.59 g/cm^3 @ 20°C
Boiling point	76.7° C
Vapor pressure	91.3 mm Hg @ 20°C
Vapor density	5.3 at the boiling point (air = 1.0)
Solubility	Soluble in acetone, ethanol, benzene, carbon disulfide, slightly soluble in water
Conversion factor	1 ppm = 6.3 mg/m^3 @ 25°C

III. Major Uses or Sources

Carbon tetrachloride was formerly used for metal degreasing and as a dry-cleaning fluid, fabric-spotting fluid, fire-extinguisher fluid, grain fumigant and reaction medium (DeShon, 1979). Carbon tetrachloride is used as a solvent for the recovery of tin in tin-plating waste and in the manufacture of semiconductors. It is used in petrol additives, refrigerants, metal degreasing, and as a catalyst in the production of polymers. Carbon tetrachloride is also used as a chemical intermediate in the production of fluorocarbons and some pesticides (HSDB, 1995).

IV. Effects of Human Exposure

Kazantzis *et al.* (1960) evaluated 17 employees of a quartz processing factory who were occupationally exposed to 45-100 ppm (284-630 mg/m^3) carbon tetrachloride (CCl_4) vapor. Fifteen of the 17 workers complained of symptoms including nausea, anorexia, vomiting, flatulence, epigastric discomfort or distention, depressive symptoms, headache or giddiness for up to 4 months prior to the evaluation. A week after CCl_4 concentrations were reduced to 0-9 ppm with control measures, workers were symptom-free.

V. Effects of Animal Exposure

Adams *et al.* (1952) chronically exposed albino Wistar rats, guinea pigs, albino rabbits and rhesus monkeys to 0, 5, 10, 25, 50, 100, 200 and 400 ppm CCl_4 for varying duration. For each exposure group, two control groups were devised (unexposed and air-exposed controls) consisting of animals similar in age, sex, weight and number. The 2 control groups responded similarly to the experimental protocol.

In the 100, 200 and 400 ppm exposure groups, mortality was excessive with moderate to severe liver cirrhosis and other various pathological changes in all the species tested. Fifteen male and 15 female rats were exposed to 50 ppm CCl_4 134 times for 187 days. They experienced decreased body weight gain and liver weight increase as well as moderate fatty degeneration and slight to moderate liver cirrhosis. Females showed kidney weight increase and four rats showed slight to moderate swelling of the kidney tubular epithelium. Guinea pigs (8 males and 8 females; 143 exposures in 200 days) showed depressed growth in the first two weeks, enlarged livers, moderate fatty degeneration and liver cirrhosis, and increased levels of liver total lipids, neutral fat, esterified cholesterol and plasma prothrombin clotting time.

The rabbit group of 2 males and 2 females, which underwent 155 exposures to 50 ppm in 216 days, showed slightly depressed growth and increased kidney weights, prolonged plasma prothrombin clotting time, and moderate fatty degeneration and cirrhosis of the liver.

No change was seen in the group of 2 male monkeys exposed 198 times to 50 ppm in 277 days. One monkey experienced depressed weight gain compared to the other monkey and the controls, but no other adverse effects were seen with respect to organ weights, tissue examination, total liver lipid, blood urea nitrogen, blood non-protein nitrogen, serum phosphatase, plasma prothrombin clotting time, phospholipid, neutral fat, and free esterified cholesterol.

At 25 ppm CCl_4, 15 male and 15 female rats were exposed 137 times for 191 days. Early growth depression in males was observed, although final body weights did not significantly differ from the controls. Significant liver weight increase and slight to moderate fatty degeneration occurred. Liver lipid content was nearly twice the level of the controls and esterified cholesterol was five times that of the controls. For this exposure, phospholipid and neutral fat were not measured. Five male guinea pigs were exposed 133 times over 185 days and 5 female guinea pigs were exposed 93 times over 126 days. Symptoms included growth depression, liver weight

increase, increased plasma prothrombin clotting time, slight to moderate fatty degeneration, twice the level of the control total liver lipid, and five times the control level of esterified cholesterol. After 178 exposures to 25 ppm over 248 days, rabbits (2 per sex) showed increased liver weights and slight to moderate liver cirrhosis and fatty degeneration.

Twenty male and 20 female rats were exposed 136 times over a period of 192 days to 10 ppm CCl_4. These rats exhibited increase in liver weight, slight to moderate fatty degeneration and total lipid, neutral fat and esterified cholesterol levels that were twice the control levels. Guinea pigs (8 male and 8 female), who were exposed 139 times over 197 days, experienced liver weight increase, slight to moderate fatty degeneration without cirrhosis, and increased levels of total lipid, neutral fat, and esterified cholesterol. In an additional group of 18 male rats exposed 13 times to 10 ppm, slight fatty degeneration was seen as early as 17 days. Two male and two female rabbits tolerated the same regimen as the guinea pigs and showed no symptoms as a result of the exposure. Sixteen additional guinea pigs developed hepatic changes after 12 exposures in 16 days.

Twenty-five male and 23 female rats, exposed 145 times over 205 days to 5 ppm CCl_4, had no adverse effects. Nine male and nine female guinea pigs exposed 143 times over 203 days showed a statistically significant increase in the liver weights (females only), but only slightly higher liver lipid content. No additional histopathological effects were seen at this level of exposure.

Prendergast *et al.* (1967) exposed 15 Long-Evans or Sprague-Dawley rats, 15 guinea pigs, 3 rabbits, 2 dogs and 3 monkeys 30 times to a concentration of 515 $\pm$39 mg/m^3 (81.7 ppm) carbon tetrachloride (CCl_4) 8 hours a day, 5 days a week, for 6 weeks. Additionally, two 90 day continuous exposure studies were conducted. One study exposed 15 rats, 15 guinea pigs, 2 rabbits, 2 dogs and 3 monkeys to 61$\pm$5.2 mg/m^3 CCl_4 and the other exposed 15 rats, 3 rabbits, 2 dogs and 3 monkeys continuously to 6.1$\pm$0.3 mg/m^3 CCl_4 in inhalation chambers. Control groups consisted of 304 rats, 314 guinea pigs, 34 dogs, 48 rabbits and 57 monkeys. All the animals' weights were recorded prior to the study, at monthly intervals throughout the study, and at the conclusion of the study.

During the 6 week study, one monkey died following the 7th exposure, and 3 guinea pigs died following the 20th, 22nd and 30th exposures, respectively. Monkeys, guinea pigs, dogs and rabbits all exhibited weight loss. A high percentage of mottled livers was seen in all species except dogs. Histopathologic examination of the lungs and livers showed morphological changes in all the animals exposed to CCl_4 (most prominently the guinea pigs). The guinea pigs were the most sensitive species displaying discolored lungs, fatty livers, bile duct proliferation, fibrosis, focal inflammatory cell infiltration, hepatic cell degeneration and regeneration, early portal cirrhosis, and alteration of lobular structure. Hepatic lipid content in the guinea pigs was 35.4$\pm$10.7% compared to the control value of 11.0$\pm$3.6%. Alterations of liver lipid content were also observed, to a lesser extent, in the other four species; the most severe alteration occurred in the rats, less severe alteration in rabbits and dogs, and the least severe in the monkeys.

During the 61 mg/m^3 (9.7 ppm) CCl_4 continuous exposure study, 3 guinea pigs died (one each after 47, 63 and 71 days). All the monkeys were emaciated and experienced hair loss.

Depressed body weight increases were seen in all exposed animals compared to the controls. Autopsies showed enlarged and/or discolored livers in a high percentage (not given) of monkeys, guinea pigs, rabbits and rats. Rats and guinea pigs showed hepatic fatty acid changes, and a moderate reduction in succinic dehydrogenase activity was also evident in guinea pigs. Varying but lesser degrees of these changes were also seen in the other species tested.

The low concentration of 6.1 mg/m^3 (1 ppm) CCl_4 was attained by diluting the CCl_4 to 10% of the above concentration with *n*-octane, resulting in a solution of 6.1 mg/m^3 CCl_4 in 61 mg/m^3 of *n*-octane. The level of *n*-octane used was shown to be negligible by an *n*-octane control which yielded no effects. (The current TLV is 1400 mg/m^3 (ACGIH, 1992).) No animals died during this study, and no signs of toxicity were noted. All exposed animals except the rats showed reduced weight gain when compared to the controls, and all species exhibited nonspecific inflammatory lung changes. Guinea pig liver lipid contents and serum urea nitrogen concentrations were similar to the control values. In several animals there were some nonspecific inflammatory changes in the liver, kidney and heart, but the authors did not attribute these to the chemical exposure. There was no other observed hematologic or histopathologic toxicity at this level.

Shimizu *et al.* (1973) exposed groups of 4 female Sprague-Dawley rats to 10, 50 and 100 ppm of CCl_4 vapor for 3 hours a day, 6 days a week for up to 6-8 weeks. The rats were terminated two days after the last inhalation. Accumulation of CCl_4 occurred in the adipose tissue and was measured after 1 and 3 weeks of exposure. For the 10 ppm group, accumulation was gradual, reaching a level of 1/3 the amount found in the 50 ppm group after 6 weeks. A slight increase of triglycerides in the liver (6.2-6.4 mg/g) was observed in the 10 ppm group, but no control group was used for comparison.

The intermittent exposure caused a more pronounced and higher number of change indices to occur (34 as opposed to the 17 change indices of the monotonous regimen), indicating a greater intensity of liver damage. Changes included a significant decrease in hippuric acid synthesis, presence of mitochondrial enzymes (glutamate dehydrogenase and ornithine carbonyl transferase) in the blood (indicating severe damage to hepatocytes), significant increase in cytoplasmic enzyme activity, and a decrease in the level of cytochrome P-450 in liver tissue. The effects seen in the monotonous group were the same variety as those in the intermittent group, but were less intense. The content of CCl_4 in the blood was similar for both the intermittent and monotonous exposure groups. Another test was performed over a period of 27 days varying the regimen, and therefore the concentration, of intermittent exposure while keeping the TWA level of CCl_4 stable. Increasing the concentration threefold or fivefold with five 10 minute peaks did not potentiate the toxic effects. Varying the regimen tenfold to five 5-minute peaks (peak exposure 402 mg/m^3 (63.8 ppm)) with a time weighted average exposure of 6.5 ppm (41$\pm$1 mg/m^3) did, however, result in more severe liver damage.

Sakata *et al.* (1987) exposed 10-15 male Sprague-Dawley rats to <10 ppm CCl_4 vapor for 15 minutes a day, twice a week for 8 weeks. All the rats had chronic liver damage involving nodular liver surfaces and extensive fibrosis. Researchers also found similar results in rats after 8 weeks of subcutaneous injections of 0.1 mL of 50% CCl_4 solution in olive oil twice a week.

Ideura *et al.* (1993) exposed male Wistar rats to CCl_4 vapor for 7 minutes, 3 times a week for 6-10 weeks (concentration unspecified). Six experimental groups of 4-5 rats were used, two of which were exposed for 10 weeks, another two for 6 weeks, and two unexposed control groups. Following the last exposures, rats were injected with varying amounts of endotoxin (1.0 mL lipopolysaccharide (LPS)). The rats were sacrificed 24 hours after the injection and processed for histological examination. Examination of the rats' left kidneys and livers revealed liver cirrhosis with destruction of normal structure and massive ascites retention after 10 weeks of exposure as compared to the controls. Those exposed for 6 weeks exhibited an increase in fibrous tissue. The control groups displayed normal liver structure. Researchers found that rats previously resistant to endotoxin became susceptible following CCl_4 exposure, which were manifested as induced acute renal tubular necrosis in cirrhotic rats.

Yoshimura *et al.* (1993) performed a similar experiment to that of Ideura *et al.* (1992) by exposing male Wistar rats for 6 (5 rats) and 10 weeks (5 rats) to 99% CCl_4 vapor for 3 minutes a day. A control group of 5 rats was given phenobarbitone for 10 weeks. After 24 hours following the final exposure, rats were injected with endotoxin. Six weeks of CCl_4 exposure caused liver fibrosis with bridging fibrosis, while 10 weeks of exposure to CCl_4 caused liver cirrhosis and destruction of the normal liver architecture.

Pregnant rats were exposed to 0, 300, or 1000 ppm (0, 1938, or 6460 mg/m^3) carbon tetrachloride for 7 hours/day on days 6-15 of gestation (Schwetz *et al*., 1974). Significant fetal growth retardation, measured by decreased crown-rump length and body weight, was observed in the offspring of the exposed groups (n = 22 litters) compared with controls (n = 43 litters). Subcutaneous edema was observed in the 300 ppm group but not in the 1000 ppm group. Sternebral anomalies were observed in the 1000 ppm group.

Table 1. Effects of Chronic CCl_4 Exposure (Adams *et al.*, 1952)

Species	**Concentration (ppm)**	**Group size**	**Endpoint**	**Exposure scenario** (days exposed/ experiment length)
rats (male)	50 ppm	15	liver damage: fatty degeneration and cirrhosis; growth depression	134/187
rats (female)	50 ppm	15	same effects as males with the addition of increased kidney weight	134/187
guinea pigs	50 ppm	16	liver damage: fatty degeneration and cirrhosis; growth depression	143/200
rabbits	50 ppm	4	enlarged kidney; liver damage: fatty degeneration and cirrhosis; growth depression	155/216
monkeys	50 ppm	2	one experienced growth depression	198/277
rats	25 ppm	30	liver damage; early growth depression	137/191
guinea pigs (male)	25 ppm	5	liver damage: fatty degeneration; growth depression	133/185
guinea pigs (female)	25 ppm	5	liver damage: fatty degeneration; growth depression	93/126
rabbits	25 ppm	4	liver damage: fatty degeneration; and cirrhosis	178/248
rats	10 ppm	40	liver damage: fatty degeneration	136/192
guinea pigs	10 ppm	16	liver damage: fatty degeneration	139/197
rats	5 ppm	48	no adverse effects	145/205
guinea pigs (male)	5 ppm	9	no adverse effects	143/203
guinea pigs (female)	5 ppm	9	liver damage	143/203

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Adams *et al.* (1952)
Study population	9 male and 9 female guinea pigs
Exposure method	Discontinuous whole-body inhalation
Critical effects	Increase in liver weight and liver lipid content in females
LOAEL	5 ppm
NOAEL	Not observed
Exposure continuity	7 hours/day, 5 days/week
Average experimental exposure	1.0 ppm
Human equivalent concentration	1.7 ppm (gas with systemic effects, based on RGDR = 1.7 for lambda (a) : lambda (h) (Gargas *et al.* 1989))
Exposure duration	143 exposures over 203 days (7.3 months)
LOAEL uncertainty factor	10
Subchronic factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm; 6 ppb (40 $\mu g/m^3$; 0.04 mg/m^3)

Of the 2 adequate chronic inhalation studies available on CCl_4, the Adams *et al.* (1952) study was chosen over the Prendergast *et al.* (1967) study as the key reference for the carbon tetrachloride chronic REL. The Adams *et al.* (1952) experiment was conducted over a longer duration. In comparison, the Prendergast study was only conducted for a subchronic period of 6 weeks. In addition, the Adams study contained more specific endpoints of liver damage that were consistent with the mechanism of carbon tetrachloride toxicity. Both studies resulted in hepatic effects with exposed rats appearing less sensitive than the affected monkeys or guinea pigs.

The major strength of the REL is the use of a chronic exposure study. The major uncertainties are the lack of human data, the lack of a NOAEL observation, the small sample sizes used, and the lack of comprehensive multiple dose studies. For comparison, conversion of the oral U.S. EPA RfC value of 0.7 μg/kg/day to an equivalent inhalation value results in a concentration of 2.5 $\mu g/m^3$.

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CHRONIC TOXICITY SUMMARY

CHLORINE DIOXIDE

(anthium dioxcide; alcide; chlorine oxide; chlorine peroxide; chloryl radical; doxcide 50)

CAS Registry Number: 10049-04-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 μg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Vascular congestion and peribronchiolar edema; hemorrhagic alveoli and congested capillaries in the lung in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Yellow to red liquid or gas
Molecular formula	ClO_2
Molecular weight	67.64
Density	1.642 g/cm^3 @ 0°C (liquid)
Boiling point	11° C
Vapor pressure	Unknown
Solubility	Soluble in water, alkaline and sulfuric acid solutions
Conversion factor	1 ppm = 2.76 mg/m^3

III. Major Uses or Sources

Chlorine dioxide is used as a bleaching agent for cellulose, textiles, flour, leather, oils, and beeswax. It is also used in the purification of water and as a bactericide and antiseptic (HSDB, 1994).

IV. Effects of Human Exposures

Case reports of human occupational exposure to chlorine dioxide have shown that 19 ppm was fatal to one worker and 5 ppm was definitely irritating (Elkins, 1959). Seven out of 12 workers exposed regularly to chlorine dioxide at levels generally below 0.1 ppm (0.28 mg/m^3) reported symptoms of ocular and respiratory irritation leading to slight bronchitis (Gloemme and Lundgren, 1957). Concurrent exposure to chlorine and chlorine dioxide in pulp mill workers

resulted in an increase in the reporting of subjective symptoms of irritation (Ferris *et al.*, 1967). In this study, the chlorine dioxide concentrations ranged from trace levels to 0.25 ppm (0.69 mg/m^3). No differences were found between these workers and controls for pulmonary function tests.

V. Effects of Animal Exposures

Eight rats (sex unspecified) were exposed for 5 hours/day, 5 days/week, for 2 months to 0 or 1 ppm (2.8 mg/m^3) chlorine dioxide (Paulet and Debrousses, 1972). The number of control animals was not specified. Microscopic evaluation of the lungs revealed vascular congestion and peribronchiolar edema in all animals exposed to chlorine dioxide. The LOAEL for respiratory effects was therefore 1 ppm (2.8 mg/m^3). An earlier study by these researchers (Paulet and Debrousses, 1970) examined the effects of exposure to 2.5, 5, or 10 ppm chlorine dioxide for several hours/day for 30 days in rats and rabbits (n = 4-10 animals per group). Body weights, blood cell counts, and histopathological examination of the liver, lungs, and other tissues were measured in each group. At 10 ppm, nasal discharge, localized bronchopneumonia, and desquamated alveolar epithelium were observed. White and red blood cell counts were also increased with this exposure. Rats and rabbits exposed to 2.5 ppm for 7 hours/day for 30 days or for 4 hours/day for 45 days, respectively, showed significant respiratory effects, including hemorrhagic alveoli and inflammatory infiltration of the alveolar spaces.

Rats exposed to 5, 10, or 15 ppm (13.8, 27.6, or 41.4 mg/m^3) chlorine dioxide for 15 minutes, 2 or 4 times/day, for 1 month showed an increase in congested lungs, nasal discharge, and catarrhous lesions of the alveoli beginning at 10 ppm (Paulet and Debrousses, 1974). No significant changes in these parameters were seen at 5 ppm.

Dalhamn (1957) found that acute exposure to 260 ppm chlorine dioxide for 2 hours resulted in the death of 1 out of 4 rats. Five out of 5 rats died during exposures of 4 hours/day for 14 days. All exposed animals exhibited signs of respiratory distress and ocular discharge. No effects were seen in 5 rats exposed to 0.1 ppm for 5 hours/day, 7 days/week, for 10 weeks.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Paulet and Debrousses (1970, 1972); U.S. EPA (1995)
Study population	Wistar rats (8 per exposure concentration)
Exposure method	Discontinuous whole-body inhalation (0 or 1 ppm)
Critical effects	Vascular congestion; peribronchial edema; lung alveolar damage
LOAEL	1 ppm
NOAEL	Not observed
Exposure continuity	5 hours/day, 5 days/week
Exposure duration	2 months
Average experimental exposure	0.15 ppm for LOAEL group (1 x 5/24 x 5/7)
Human equivalent concentration	0.23 ppm for LOAEL group (gas with thoracic respiratory effects, RGDR = 1.57 based on MV = 0.17 m^3, SA(Th) = 3,460 cm^2)
LOAEL uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Subchronic factor	10
Modifying factor	3 (database deficiencies)
Cumulative uncertainty factor	3,000
Inhalation reference exposure level	0.00008 ppm (0.08 ppb, 0.0002 mg/m^3, 0.2 $\mu g/m^3$)

There were uncertainties in all areas of concern. Thus the best available study still was limited by lack of multiple exposure concentrations, the relatively short duration of exposures, the small number of animals examined, and the lack of adequate human health effects information. Other limitations were the lack of dose-response information and the lack of comprehensive multi-organ effects data.

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CHRONIC TOXICITY SUMMARY

CHLOROBENZENE

(monochlorobenzene; benzene chloride; benzene monochloride; chlorbenzene; chlorbenzol; phenyl chloride)

CAS Registry Number: 108-90-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1000 μg/m^3**
Critical effect(s)	Increased liver weights, hepatocellular hypertrophy, renal degeneration and inflammation, and testicular degeneration in rats
Hazard index target(s)	Alimentary system; kidney; reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Colorless, neutral liquid
Molecular formula	C_6H_5Cl
Molecular weight	112.56
Boiling point	132°C
Vapor pressure	11.8 mm Hg at 25°C
Solubility	Practically insoluble in water (0.049 g/100 ml); soluble in alcohol, benzene, chloroform, diethyl ether
Conversion factor	1 ppm = 4.60 mg/m^3 at 25 ^{o}C

III. Major Uses and Sources

As one of the most widely used chlorinated benzenes, mono-chlorobenzene has been a major chemical for at least 50 years. It was historically important in the manufacture of chlorinated pesticides, especially DDT, and in the production of phenol and aniline. Monochlorobenzene's principal current use is as a chemical intermediate in the production of chemicals such as nitrochlorobenzenes and diphenyl oxide. These chemicals are subsequently used in the production of herbicides, dyestuffs and rubber chemicals. Additionally, monochlorobenzene is used as a solvent in degreasing processes (e.g., in metal cleaning operations), paints, adhesives, waxes and polishes (HSDB, 1995; NIOSH, 1993).

IV. Effects of Human Exposure

Even though monochlorobenzene has been used industrially for many years, few epidemiologic and/or occupational studies have addressed the potential health status of workers chronically exposed to monochlorobenzene (NIOSH, 1993). A Russian occupational study (Rozenbaum *et al.*, 1947, as reported by the U.S. EPA, 1988) describes multiple central nervous system effects, including headache, numbness, dizziness, cyanosis, hyperesthesia, and muscle spasms, after intermittent exposure over 2 years to monochlorobenzene in a mixed chemical environment. No specific exposure levels or histopathologic data were reported.

Two small studies utilizing volunteers exposed to single doses of monochlorobenzene have reported central nervous system effects (Ogata *et al.*, 1991; Tarkhova, 1965). An exposure chamber study of five volunteers exposed up to 60 ppm monochlorobenzene (276 mg/m^3) for a single 7 hour exposure described acute subjective symptoms such as drowsiness, headache, eye irritation, and sore throat (Ogata *et al.*, 1991). One other human volunteer study described altered electrical activity of the cerebral cortex in four individuals exposed to 43.4 ppm monochlorobenzene vapors for 2.5 minutes (Tarkhova, 1965).

V. Effects of Animal Exposure

No chronic inhalation studies have evaluated the toxicity of monochlorobenzene. Only a single, oral chronic carcinogenicity study (NTP, 1985) has evaluated the long-term adverse affects of monochlorobenzene administration. However, a few subchronic inhalation studies have demonstrated adverse effects on the liver, the kidney, and, to a lesser extent, blood parameters following monochlorobenzene exposure over a period of weeks or months (Dilley, 1977; John *et al.*, 1984; Nair *et al.*, 1987).

One subchronic study evaluated Sprague-Dawley male rats and rabbits exposed to 0, 75, or 200 ppm of monochlorobenzene for 7 hr/day, 5 days/week, for up to 24 weeks (Dilley, 1977). In rats, monochlorobenzene-related toxicity included increased absolute and relative (to brain- or body-weight) organ weights (especially the liver) after 11 and 24 weeks of exposure (LOAEL 75 ppm). Male rabbits also demonstrated increases in liver weight after 24 weeks of exposure (LOAEL 75 ppm). Some hematological changes were reported in rats including differences in platelet and reticulocyte counts between control and exposed animals; however, some changes observed at 11 weeks were variable and comparable to controls at 24 weeks (red blood cell count, hemoglobin, hematocrit, and white blood cell count). Pathological changes were observed in rats, with occasional focal lesions in the adrenal cortex, tubular lesions in the kidneys, and congestion in the liver and kidneys.

Two other subchronic inhalation studies reported adverse organ effects following monochlorobenzene exposure in rats and rabbits (John *et al.*, 1984; Nair *et al.*, 1987). In the first study, John *et al.* (1984) reported increased liver weights in rats and rabbits following short-term (10 or 13 day, 6 hours/day) monochlorobenzene exposure (LOAEL = 590 ppm in rats and 210 ppm in rabbits). Nair *et al.* (1987) exposed male and female Sprague-Dawley rats to 0, 50, 150 or 450 ppm monochlorobenzene vapors daily for 6 hours over 10-11 weeks prior to mating, and

up to day 20 of gestation for 2 generations. Nair *et al*. found dose-related changes in the livers, kidneys, and testes in both generations of males (F_0 and F_1). Hepatotoxicity occurred as hepatocellular hypertrophy and increased liver weights (mean and absolute) at concentrations greater than 50 ppm (LOAEL = 150 ppm). At this concentration, renal changes included tubular dilation, interstitial nephritis, and foci of regenerative epithelium. Testicular degeneration of the germinal epithelium occurred in both generations of exposed males, but no chlorobenzene-induced adverse effects on reproductive performance or fertility were seen.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Nair *et al.* (1987)
Study population	Sprague-Dawley rats (30/sex/group)
Exposure method	Discontinuous inhalation exposures (0, 50, 150, and 450 ppm)
Critical Effects	Increases in absolute and relative liver weights (F_0 and F_1 both sexes), hepatocellular hypertrophy (F_0 and F_1 males), renal degeneration and inflammation (F_0 and F_1 both sexes), testicular degeneration (F_0 and F_1 males).
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hours/day, 7 days/week
Exposure duration	11 weeks
Average experimental exposure	13 ppm for NOAEL group (50 x 6/24)
Human equivalent concentration	26 ppm (gas with systemic effects, based on RGDR = 2.0 for lambda (a) : lambda (h)) (Gargas *et al*., 1989)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.3 ppm (300 ppb; 1.0 mg/m^3, 1000 µg/m^3)

Of the three inhalation studies available (Dilley, 1977; John *et al.*, 1984; Nair *et al.*, 1987), the Nair *et al.* (1987) two generational developmental study was selected for identifying a NOAEL and LOAEL. It best presented the histopathology of the adverse effects, and demonstrated a dose response relationship for these effects (statistically significant increases in mean liver weights, incidence of renal changes, and testicular degeneration).

Another subchronic inhalation study (Dilley, 1977) also observed increases in organ weights, including the liver, in rats after 11 and 24 weeks exposure to 75 and 250 ppm monochlorobenzene (LOAEL = 75 ppm), and, in rabbits at 24 weeks. Similar adverse liver and kidney effects were found in subchronic oral bioassays (Kluwe *et al.*, 1985; NTP, 1985). These

include increases in liver weight and hepatocellular degeneration in rats (LOAEL = 125 mg/kg/day) and mice (LOAEL = 250 mg/kg/day), and renal necrosis and degeneration in rats (LOAEL = 500 mg/kg/day) and mice (LOAEL = 250 mg/kg/day) after 13 weeks oral exposure to chlorobenzene.

Uncertainty factors are appropriate due to the lack of chronic studies, both animal bioassay and human, and the limited number of subchronic inhalation studies, thereby requiring estimation of the chronic REL from this shorter term, single species study. The magnitude of interspecies variation remains unknown, as few species have been tested and human data for comparison are lacking. However, metabolic studies have demonstrated species variation in the urinary elimination of chlorobenzene metabolites (Ogata and Shimada 1983; Ogata *et al.*, 1991; Yoshida *et al.*, 1986). Humans metabolize and excrete chlorobenzene predominately as free and conjugated forms of 4-chlorocatechol and chlorophenols, while the main rodent urinary metabolite, p-chlorophenylmercapturic acid, is found in minor amounts (<0.5%). No information exists which identifies human subpopulations possibly susceptible to monochlorobenzene exposure.

The strengths of the inhalation REL include the observation of a NOAEL, the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis, and the demonstration of a dose-response relationship. Major areas of uncertainty are the lack of adequate human exposure data and limited reproductive toxicity data.

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CHRONIC TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 µg/m^3**
Critical effect(s)	Increased mortality, increased lung weight, nasal rhinitis in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (from HSDB (1996) except as noted)

Description	Colorless to faint yellow liquid
Molecular formula	CCl_3NO_2
Molecular weight	164.4
Boiling point	112°C
Vapor pressure	5.7 mm Hg @ 0°C; 24 mm Hg @ 25°C (Fries and West, 1921)
Solubility	1.6 g/L water @ 25°C; 2.272 g/L water @ 0°C 1.9 g/L water @ 20°C; miscible with benzene, ethanol, carbon disulfide, ether, carbon tetrachloride, acetone, methanol, acetic acid
Conversion factor	6.72 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Chloropicrin is primarily used as a fumigant against insects and fungi in grain elevators and storage bins (HSDB, 1996). It has also been used in the fumigation of non-deciduous fruit trees and produce. Chloropicrin is used as an indicator chemical in other fumigants such as methyl bromide because of its potent irritational properties. Chloropicrin kills weed and grass seeds when applied to soil. Chloropicrin was used in World War I as a chemical warfare agent because of its potent activity as a lachrymator. Chloropicrin has a minor use in the chemical synthesis of methyl violet. Chloropicrin can also form in drinking water as a result of chlorination processes (Duguet *et al.*, 1985; Merlet *et al.*, 1985).

IV. Effects of Human Exposure

No studies are available which describe toxic effects to humans from chronic exposure to chloropicrin. Human exposures to concentrations less than 1 ppm for very short periods of time are extremely irritating (ACGIH, 1992; Fries and West, 1921). The threshold of odor detection in humans is approximately 1 ppm (ACGIH, 1992).

V. Effects of Animal Exposure

Burleigh-Flayer and Benson (1995) conducted a chronic inhalation bioassay with CD rats (60 per sex per dose) exposed discontinuously to 0, 0.1, 0.5 or 1.0 ppm 99.6% pure chloropicrin vapor 6 hours/day for 5 days/week over 107 weeks. Increased mortality was noted in males at 0.5 and 1 ppm and in females at 1 ppm. Absolute and relative increased lung and liver weights and increased nasal rhinitis were reported in both sexes at the 1 ppm level. However, no effects were seen at 0.1 ppm. Thus this study yielded a NOAEL of 0.1 ppm for chronic non-cancer effects in rats. A similar study carried out in mice for 78 weeks (Burleigh-Flayer et al., 1995) resulted in the same NOAEL.

Male Swiss-Webster mice (group numbers ranging from 16-24) were exposed by inhalation to a single level of different sensory irritants including chloropicrin for 6 hours/day for 5 days, with unexposed control groups of 8-10 mice (Buckley *et al.*, 1984). The exposure level for chloropicrin was 7.9 ppm, which approximated the level sufficient to cause a 50% decrease in respiratory rate in mice (RD50) (Kane *et al.*, 1979). Half the exposed mice and half the control animals were terminated immediately after the exposures and the other half 72 hours after the last exposure. All were examined for respiratory tract lesions. Body weights of chloropicrin exposed animals were reduced 10-25% below controls, but increased to normal levels during the recovery period. Nasal exudate and distention of the abdomen were observed. "Moderate" lesions characterized by exfoliation, erosion, ulceration, or necrosis were observed in the respiratory and olfactory epithelium and minimal inflammation and squamous metaplasia were observed in the respiratory epithelium alone. Moderate to severe damage to the lower respiratory tract was described as "fibrosing peribronchitis and peribronchiolitis". Exfoliation, hyperplasia, and squamous metaplasia were also noted.

Condie *et al.* (1994) conducted a study of the toxicity of chloropicrin by oral exposure in Sprague-Dawley rats. Ten and ninety-day studies were conducted by dosing animals daily with chloropicrin in vehicle (corn oil) at a volume of 1 ml/kg. Groups of 10 rats/sex/group were dosed with 0, 10, 20, 40, and 80 mg/kg for the 10-day study and with 0, 2, 8, and 32 mg/kg for the 90-day study. Parameters examined included mortality, body weight, food and water consumption, hematology, serum clinical chemistry, and gross pathology and histology of organs. Only the high-dose group and the control group animals from the 90-day study were examined histopathologically. In the 90-day study, 6 males and 2 females in the 32 mg/kg dose group and 1 male and 3 females in the 8 mg/kg dose group died before the scheduled termination time. The authors noted signs of pulmonary complications (inflammation and congestion) in the dead animals. Previously, the animals had shown signs of respiratory distress, including wheezing and dyspnea. The deaths were considered to be exposure related and most likely due

to aspiration of chloropicrin. Among the survivors, mean body weight, hemoglobin levels, and hematocrit were significantly reduced in males in the 32 mg/kg dose group. Absolute thymus weights were reduced in female rats at 32 mg/kg, and female rats in the 8 mg/kg dose group showed decreased white blood cell count. Most animals in the 32 mg/kg dose group (>60%) showed histopathological changes in the forestomach including chronic inflammation, acantholysis, and hyperkeratosis.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer and Benson (1995)
Study population	CD rats (60 per sex per dose)
Exposure method	Discontinuous inhalation (0, 0.1, 0.5 or 1.0 ppm)
Critical effects	Increased mortality, increased lung weight, nasal rhinitis
LOAEL	0.5 ppm
NOAEL	0.1 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	107 weeks
Average experimental exposure	0.018 ppm for NOAEL group (0.1 x 6/24 x 5/7)
Human equivalent concentration	0.004 ppm for NOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.25 based on MV = 0.33 m^3/day and SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.0002 ppm (0.2 ppb; 1 $\mu g/m^3$; 0.001 mg/m^3)

Significant strengths in the REL include the duration of exposure (lifetime) in the key study, the multiple dose study design with adequate sample sizes, and the demonstration of a NOAEL.

Major areas of uncertainty are the lack of adequate human exposure data and limited reproductive toxicity data.

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CHRONIC TOXICITY SUMMARY

HEXAVALENT CHROMIUM (SOLUBLE COMPOUNDS)

Molecular Formula	***Molecular Weight***	***Synonyms***	***CAS #***
CrO_3	99.99	Chromic trioxide, chromium oxide, chromium trioxide, chromium (VI) oxide	1333-82-0
K_2CrO_4	194.20	Potassium chromate, dipotassium chromate, potassium (VI) chromate, dipotassium monochromate, chromate of potash	7789-00-6
Li_2CrO_4	129.87	Lithium chromate, dilithium salt, chromium lithium oxide, chromic acid, lithium chromate (VI)	14307-35-8
Na_2CrO_4	161.97	Sodium chromate, chromic acid disodium salt, chromium disodium oxide, sodium chromate (VI), chromate of soda	7775-11-3
$K_2Cr_2O_7$	294.20 g/mol	Potassium dichromate, dichromic acid dipotassium salt, bichromate of potash	7778-50-9
$Na_2Cr_2O_7$	261.96	Sodium dichromate, bichromate of sodium, chromic acid disodium salt, chromium sodium oxide	10588-01-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.0008 µg/m^3 Cr(VI)**
Critical effect(s)	Respiratory effects (nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes) in human occupational study
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties of Chromic Acid (HSDB, 1994)

Description	Dark red or brown solid
Molecular formula	See above
Molecular weight	See above
Density	2.70 g/cm^3 @ 25°C
Boiling point	Not found
Melting point	197 °C
Vapor pressure	Not found
Solubility	Soluble in water, ethyl alcohol, ethyl ether, sulfuric and nitric acid
Conversion factor	Not applicable

III. Major Uses or Sources

Hexavalent chromium is more toxic than Cr (III), the form most commonly found naturally (ATSDR, 1993). While more information is available on the toxicity of soluble Cr (VI) compounds, information on insoluble Cr (VI) compounds has been included where applicable.

Chromates are used in paints and locomotives to inhibit metal corrosion due to recirculating water. Sources of chromium emissions include sewage sludge, municipal incineration, and chemical manufacture. Chromic acid, used to electroplate metal parts, is the most common hexavalent chromium compound produced (ATSDR, 1998).

IV. Effects of Human Exposure

Workers exposed to 2 µg/m^3 Cr(VI) as chromic acid for a mean of 2.5 years exhibited an increased incidence of nasal atrophy, nasal mucosal ulcerations, and nasal septal perforations as compared to controls (Lindberg and Hedenstierna, 1983). The same study reported statistically significant decreases in FEV_1, FVC, and FEF_{25-75} measurements taken on a Thursday afternoon as compared to those taken on a Monday morning in nonsmoking workers exposed to 2 µg/m^3 Cr(VI) or more. Similar changes were observed in the smokers although only the difference in the FVC measured on a Thursday was statistically significant. No significant differences were observed between pulmonary function measurements of exposed and unexposed workers taken on a Monday morning (prior to a work week of exposure). Thus the authors infer that the observed pulmonary function changes are transient.

Gastritis and duodenal ulcers, in addition to ulceration and perforation of the nasal septum, were observed in chrome platers exposed to a mean breathing zone concentration of 4 µg/m^3 chromic acid for an average of 7.5 years (Lucas and Kramkowski, 1975).

Male workers in the chromate and dichromate production industry, whose occupational exposures were 0.05-1.0 mg Cr(VI)/m^3 as chromium trioxide for a mean of 7 years, were reported to have elevated levels of low molecular weight proteins (retinol binding protein and

tubular antigens) in the urine (Franchini and Mutti, 1988). The authors suggest that the presence of such proteins in the urine is an early indicator of kidney damage.

V. Effects of Animal Exposure

Rats exposed to 200 µg/m^3 Cr(VI) as sodium dichromate by inhalation for 22 hours per day, for 42 days exhibited decreased alveolar macrophage phagocytic activity; the lung clearance of inert iron oxide was significantly reduced in exposed rats compared to controls (Glaser *et al.*, 1985). Increased alveolar macrophage activity and a significantly elevated antibody response to injected sheep red blood cells were observed in rats exposed to 25 or 50 µg/m^3 Cr(VI) for 22 hours per day for 28 days.

A later experiment exposed male rats to 0, 50, 100, 200, or 400 µg Cr/m^3 22 hours per day, 7 days per week for 90 days (Glaser *et al*., 1990). Bronchoalveolar lavage fluid contained elevated levels of albumin, LDH, and total protein in all exposed groups. Statistically significant elevations in these parameters were observed mainly in the 200 and 400 µg/m^3 exposure groups. At necropsy, a statistically significant increase in lung weight was observed in rats exposed to 100, 200, and 400 µg/m^3 as compared to controls. An analysis of the data (Malsch *et al.*, 1994) determined a benchmark dose (95% confidence interval with dose associated with a 10% elevation in the parameter) for each of these endpoints. The analysis also examined changes in lung and spleen weight reported in Glaser *et al.* (1985). The most sensitive endpoint was LDH in BALF.

Nasal septal perforation, hyperplastic and metaplastic changes in the larynx, trachea and bronchus, and emphysema were observed in mice exposed two days per week for 12 months to CrO_3 mist in concentrations of either 3.63 mg/m^3 for 30 minutes per day or 1.81 mg/m^3 for 120 minutes per day (Adachi, 1987; Adachi *et al.*, 1986).

VI. Derivation of Chronic Reference Exposure Level (REL)

Derivation of Chronic Inhalation Reference Exposure Level

Study	Lindberg and Hedenstierna, 1983
Study population	Human workers (100 exposed workers, 119 unexposed controls)
Exposure method	Occupational exposure
Critical effects	Nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes
LOAEL	Average occupational exposure of 1 µg/m^3 Cr(VI) as chromic acid, with a range between non-detectable concentrations (< 0.2 µg/m^3) and 2 µg/m^3
NOAEL	Not observed

Exposure continuity	8 hours per day, 5 days per week
Exposure duration	Mean of 2.5 years (range = 0.2 - 23.6 years)
Average exposure	0.24 µg/m^3 Cr(VI)
Human equivalent concentration	0.24 µg/m^3 Cr(VI)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0008 µg/m^3 Cr(VI)

The human exposure study of Lindberg and Hedenstierna (1983) was selected as the best available human study. The available animal studies had shortcomings that limited their usefulness. A 10-fold uncertainty factor was applied due to the lack of a NOAEL observation. The mean exposure duration (3% of lifetime) was less than the 8 to 12% of lifetime that has been used to differentiate chronic from subchronic studies. However, since exposure ranged up to 26 years, a factor of 3 was considered adequate.

The major strength of the REL is the use of adequate human data. The major uncertainties are the lack of controlled and quantified exposure data, the lack of an observation of a NOAEL, the lack of dose-response information, and the lack of comprehensive data on multi-organ effects.

***Derivation of Chronic Oral Reference Exposure Level* (U.S. EPA RfD)**

Study	Mackenzie *et al.*, 1958
Study population	8 male and 8 female Sprague-Dawley rats
Exposure method	Drinking water
Critical effects	No adverse effects seen
LOAEL	None
NOAEL	2.4 mg/kg-day (converted from 25 mg/L of chromium as K_2CrO_4)
Exposure continuity	Continuous
Exposure duration	1 year
Average experimental exposure	0.11 ppm chromium VI
LOAEL uncertainty factor	1
Subchronic uncertainty factor	5 (see below)
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	500
Oral reference exposure level	0.005 mg/kg bw-day

*Conversion Factors: Drinking water consumption = 0.097 L/kg/day (reported)

The oral REL is the U.S. EPA's oral Reference Dose (RfD) (U.S. EPA, 1996). Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0-11 ppm (0-11 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group (10/sex)

received distilled water. A second experiment involved three groups of 12 males and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (as K_2CrO_4); a second received 25 ppm chromium in the form of chromic chloride; and the controls received distilled water. No significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K_2CrO_4) showed an approximate 20% reduction in water consumption. This dose corresponds to 2.4 mg chromium (VI)/kg/day based on actual body weight and water consumption data.

For rats treated with 0-11 ppm (in the diet), blood was examined monthly, and tissues (livers, kidneys and femurs) were examined at 6 months and 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except that no animals were killed at 6 months. An abrupt rise in tissue chromium concentrations was noted in rats treated with greater than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group.

Similar no-effect levels have been observed in dogs and humans. Anwar *et al.* (1961) observed no significant effects in female dogs (2/dose group) given up to 11.2 ppm chromium(VI) (as K_2CrO_4) in drinking water for 4 years. The calculated doses were 0.012-0.30 mg/kg of chromium(VI). In humans, no adverse health effects were detected (by physical examination) in a family of four persons who drank for 3 years from a private well containing chromium(VI) at approximately 1 mg/L (0.03 mg/kg/day for a 70-kg human).

This RfD is limited to soluble salts of metallic chromium(VI). Examples of soluble salts include potassium dichromate ($K_2Cr_2O_7$), sodium dichromate ($Na_2Cr_2O_7$), potassium chromate (K_2CrO_4) and sodium chromate (Na_2CrO_4). Trivalent chromium is an essential nutrient. There is some evidence to indicate that hexavalent chromium is reduced in part to trivalent chromium in vivo (Petrilli and DeFlora, 1978; Gruber and Jennette, 1978). The literature available on possible fetal damage caused by chromium compounds is limited. No studies were located on teratogenic effects resulting from ingestion of chromium.

The uncertainty factor of 500 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 5 to compensate for the less-than-lifetime exposure duration of the principal study.

U.S. EPA stated its confidence in the RfD as: Study - Low; Data Base - Low; and RfD - Low. Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured, and the lack of toxic effect at the highest dose tested. Confidence in the database is low because the supporting studies are of equally low quality, and teratogenic and reproductive endpoints are not well studied. Low confidence in the RfD follows.

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CHRONIC TOXICITY SUMMARY

CRESOL MIXTURES

Compounds	*Synonyms*	*CAS Reg. No.*
cresols	cresylic acid; tricresol; hydroxytoluene; methylphenol	1319-77-3
o-cresol	1-hydroxy-2-methylbenzene; 2-hydroxytoluene; 2-methylphenol	95-48-7
m-cresol	1-hydroxy-3-methylbenzene; 3-hydroxytoluene; 3-methylphenol	108-39-4
p-cresol	1-hydroxy-4-methylbenzene; 4-hydroxytoluene; 4-methylphenol	106-44-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**180 µg/m^3**
Critical effect(s)	Neurotoxicity
Hazard index target(s)	Nervous system

II. Chemical Property Summary (HSDB, 1995, unless otherwise noted)

Description	Colorless in pure form; yellowish, brownish-yellow, or pinkish liquid
Molecular formula	C_7H_8O
Molecular weight	108.13
Boiling point	195.95°C (o-cresol) 202°C (m-cresol) 201.9°C (p-cresol)
Vapor pressure	0.299 mm Hg @ 25°C (o-cresol) 0.138 mm Hg @ 25°C (m-cresol) 0.11 mm Hg @ 25°C (p-cresol) (Chao *et al.*, 1983; Daubert and Danner, 1985) 1 mm Hg @ 38-53°C
Solubility	Soluble in 50 parts water; miscible with alcohol, benzene, ether, glycerol, petroleum ether; soluble in vegetable oils, glycol
Conversion factor	4.42 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Cresol compounds (mixtures of the ortho-, meta- and para-isomers) can be obtained from coal tar and petroleum or synthesized by sulfonation or oxidation of toluene (HSDB, 1995). Crude cresol (commercial grade) contains approximately 20% o-cresol, 40% m-cresol, and 30% p-cresol. Phenol and xylenols are present in small amounts as contaminants. Cresylic acid compounds are called cresol when the boiling point is below 204°C.

Cresols have a wide variety of uses including the manufacture of synthetic resins, tricresyl phosphate, salicylaldehyde, coumarin, and herbicides. Cresols also serve as components of degreasing compounds in textile scouring and paintbrush cleaners as well as fumigants in photographic developers and explosives. Cresols also function as antiseptics, disinfectants, and parasiticides in veterinary medicine. An approximate breakdown of cresol and cresylic acid use is 20% phenolic resins, 20% wire enamel solvents, 10% agricultural chemicals, 5% phosphate esters, 5% disinfectants and cleaning compounds, 5% ore flotation, and 25% miscellaneous and exports.

Any combustion process, which results in the generation of phenolic compounds (such as automobile exhaust or coal, wood or trash smoke), may be a potential source of exposure to cresols. However, under normal conditions low vapor pressure limits the inhalation hazard presented by cresols (HSDB, 1995).

IV. Effects of Exposures to Humans

Brief exposure to 6 mg cresol/m^3 resulted in irritation of the throat and nose, nasal constriction, and dryness in 8 of 10 subjects (Uzhdavini *et al.*, 1972).

Chemical burns may result from exposure to cresols (Pegg and Campbell, 1985). The lungs of humans exposed to cresols have shown signs of emphysema, edema, bronchopneumonia, and small hemorrhages (Clayton and Clayton, 1982). Skin contact has resulted in the development of white patches and blistering, eventually turning brown or black (Lefaux, 1968). Other reported effects include turbidity, inflammation, and fatty degeneration of the liver, nephritis, and hemorrhage of the epicardium and endocardium. An infant fatally exposed to ~20 ml of a 90% cresol solution dermally showed widespread edema of the internal organs, especially the brain and kidney (Green, 1975). The liver showed signs of centrilobular and midzonal necrosis.

Chronic systemic poisoning by any route of exposure may produce symptoms of vomiting, dysphagia, salivation, diarrhea, loss of appetite, headache, fainting, dizziness, and mental disturbances (Sittig, 1981). Skin rash and discoloration may also result from prolonged or repeated exposure of the skin. Death may result from severe damage to the liver and kidneys. Oral poisoning has resulted in kidney problems (likely from the direct action of cresol) and pancreatitis (from constriction of the pancreatic ducts) (Klimkiewicz *et al.*, 1974, as reported in HSDB, 1995).

V. Effects of Exposures to Animals

The effects of inhaled o-cresol were examined in several species (Uzhdavini *et al.*, 1972, as reported in ATSDR, 1992 and U.S. EPA, 1982). Cats exposed for 30 minutes to 5-9 mg o-cresol/m^3 showed signs of respiratory irritation as indicated by increased parotid gland secretions. Exposure of mice for 2 hrs/day for 1 month to 50 mg o-cresol/m^3 did not have an effect on mortality, however, heart muscle degeneration and degeneration of nerve cells and glial elements were observed.

Uzhdavini *et al.* (1972) exposed rats (both sexes, numbers not stated) by inhalation to 9.0 ± 0.9 mg o-cresol/m^3, first for 2 months (6 hours/day, 5 days/week), then for 2 more months (4 hours/day, 5 days/week). Endpoints examined in rats included elementary conditioned defensive reflex, white blood cell levels, bone marrow elements, and liver function (as indicated by increased susceptibility to hexobarbital narcosis). Both cresol-exposed and control animals showed some loss of the defensive reflex; the effect occurred in all exposed animals before the end of the second month and in control animals at later times. White blood cell counts were elevated in male animals, peaked at the end of the exposure period, and returned to normal one month after cessation of exposure. Exposed animals also showed a statistically significant change in the leukoid-to-erythroid ratio in the bone marrow. Liver toxicity was suggested by an extension in the duration of hexobarbital narcosis in treated animals. Although guinea pigs were similarly evaluated for changes in blood cell counts and ECG, scant reporting of experimental detail limits the usefulness of this portion of the study.

NR rats were exposed by inhalation to 0.0052 or 0.05 mg tricresol/m^3 for 3 months (Kurliandskii *et al.*, 1975; as described by U.S. EPA, 1982). The proportional composition of the compound was not specified. Effects observed in the high-dose group included decreased weight gain, increased central nervous system excitability, increased oxygen consumption, and histological changes in the lung and liver. Serum gamma-globulin levels were also reduced. No effects were observed in the low-dose group. Rats (6/group, sex unspecified) were also exposed for 24 hours to 0.01, 0.1, and 2.4 mg tricresol/m^3 with a control group of 6 rats for each exposure group. The absorption of neutral red dye by lung tissue was used as an indicator of protein denaturation in the tissue. Significantly increased dye absorption over control animals was observed at both 2.4 and 0.1 mg tricresol/m^3. The degree of dye absorption in the low-dose group was not significantly increased over controls.

In a 90-day subchronic toxicity study (U.S. EPA, 1986), 30 Sprague-Dawley rats/sex/dose were gavaged daily with 0, 50, 175, or 600 mg/kg/day p-cresol. Body and organ weights, food consumption, mortality, clinical signs of toxicity, and clinical pathology were evaluated. At 600 mg/kg/day, o-cresol showed 47% combined mortality (9/30 males, 19/30 females), and a 30% reduction in body weight at week 1 and 10% at final sacrifice. Kidney-to-body weight ratio was 13% higher than that of the control value at the end of the study. CNS effects such as lethargy, ataxia, coma, dyspnea, tremor, and convulsions were seen within 15 to 30 minutes after dosing; but recovery occurred within 1 hour post-gavage. At 450 mg/kg/day, combined mortality was 20% (1/10 male, 1/10 female). In the 175 mg/kg/day group, two animals exhibited tremors on day 1 of the study during the hour following gavage administration, and one of the two became comatose. At 50 mg/kg/day, no significant adverse effects were observed (USEPA, 1999a,b).

In a 90-day neurotoxicity study (U.S. EPA, 1987), 10 Sprague-Dawley rats/sex/dose were gavaged daily with o-cresol at 0, 50, 175, 450, or 600 mg/kg/day. In addition to the parameters evaluated above various signs of neurotoxicity were monitored. The lowest dose of o-cresol caused clinical signs of CNS-stimulation post-dosing, such as salivation, rapid respiration, and hypoactivity; however, these symptoms were low in incidence and sporadic in nature. Higher doses of o-cresol (greater than 450 mg/kg/day) produced significant neurological events, such as increased salivation, urination, tremors, lacrimation, palpebral closure, and rapid respiration. High dosed animals also showed abnormal patterns in the neurobehavioral tests. The NOAEL based on systemic toxicity was 50 mg/kg/day (USEPA, 1999a,b).

Dermal exposure of rats to 1.0-1.7 ml cresol/kg body weight for 1-2 hours resulted in skin discoloration and death of the animals (Campbell, 1941).

Exposure to high concentrations of toluene vapors, or to intravenous o-cresol, a toluene metabolite, at about 0.9 mg/min, caused excitation of the somatosensory evoked potential (SEP) and electroencephalograph (EEG) of Fischer 344 rats (Mattsson et al., 1989). Both substances induced an increase in EEG beta activity and caused a large increase in activity at 5 Hz. Toluene exposed rats were lightly anesthetized, while o-cresol rats were conscious but hyperreactive. When exposure was continued, both sets of rats had involuntary muscle movements and tremors. Neither benzoic acid and hippuric acid, also metabolites of toluene, caused neuroexcitation. The authors concluded that metabolically derived cresols are plausible candidates for the neuroexcitatory properties of toluene.

In rat liver slices at equimolar concentrations, p-cresol was 5- to 10-times as toxic as the o- or m-isomers for cell killing (Thompson *et al*., 1994). p-Cresol rapidly depleted intracellular glutathione levels, while the o- and m-isomers depleted it to a lesser extent. p-Cresol was metabolized to a reactive intermediate which bound covalently to protein. The reaction was inhibited by N-acetylcysteine.

The National Toxicology Program (NTP) sponsored reproductive toxicity tests of cresol isomers in Swiss CD-1 mice using the risk assessment by continuous breeding (RACB) protocol (Heindel *et al*., 1997a, 1997b). For o-cresol the exposure concentrations in the continuous cohabitation task were 0.05%, 0.2%, and 0.5% in feed (approximately 60, 220, and 550 mg/kg/day (Heindel *et al*., 1997a). At these doses o-cresol was not a reproductive toxicant. When a m-/p-cresol was used at concentrations of 0.25, 1.0 and 1.5% in feed (approximately 370, 1500, and 2100 mg/kg/day), the m/p mixture was a reproductive toxicant, since (1) fewer F_1 pups per litter were produced, (2) both generations showed reduced pup weights, and (3) reproductive organs showed weight reductions. Unfortunately the responses were not dose-dependent and the mixture was judged not to be a selective reproductive toxicant.

VI. Derivation of Inhalation Chronic Reference Exposure Level

Study	U.S. EPA, 1986, 1987, 1999a, 1999b
Study population	Sprague-Dawley rats
Exposure method	Gavage

Critical effects	Decreased body weights and neurotoxicity (tremors, salivation, lacrimation, etc.)
LOAEL	150 mg/kg-day
NOAEL	50 mg/kg-day
Exposure continuity	Daily gavage
Exposure duration	90 days
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
U.S. EPA Reference Dose (RfD)	0.05 mg/kg/day
Route-to-route extrapolation factor	3500 $\mu g/m^3$ per mg/kg/day
Inhalation REL	180 $\mu g/m^3$

The same RfD was derived by the USEPA for both o-cresol and m-cresol (USEPA 1998a, 1998b). The RfD for p-cresol was withdrawn by the USEPA.

The available literature on the observed toxicity of cresol compounds and cresol mixtures to humans by inhalation indicates that at high concentrations these compounds are initially toxic due to their ability to cause chemical burns and are therefore of concern at the site of contact. In humans occupationally exposed, inhalation exposure is reported to cause respiratory effects including the development of pneumonia, pulmonary edema, and hemorrhage (Clayton and Clayton, 1982). Other case reports of cresol toxicity to humans are confounded by the presence of other compounds, such as phenol, formaldehyde, and ammonia (Corcos, 1939; NIOSH, 1974). The only quantitative information from inhalation exposures to humans, however, comes from acute exposure studies showing irritation at 6 mg cresol/m^3 (Uzhdavini *et al.*, 1972, as reported in ATSDR, 1992). Toxic effects reported in animals include bone marrow and liver toxicity in rats from 4 month exposure to 9 mg cresol/m^3 (Uzhdavini *et al.*, 1972, as reported in U.S. EPA, 1982). Other animal studies have shown more systemic effects from inhalation exposure to cresols. Uzhdavini *et al.*, 1972 reported cardiac and nerve cell degeneration in mice exposed for 2 hour/day for 1 month to 50 mg o-cresol/m^3, Kurliandskii *et al.*, 1975, (as reported in HSDB, 1995) observed decreased weight gain with histological changes in the liver and lungs of rats exposed for 3 months to 0.05 mg tricresol/m^3. Although this study reports adverse effects at levels below those observed in the Uzhdavini *et al.* (1972) study, limited experimental detail precludes the use of these data in the development of the chronic REL.

The only useful inhalation data for the development of a chronic REL are those showing hematological toxicity to the bone marrow of rats exposed for 4 months to o-cresol (Uzhdavini *et al.*, 1972, as reported in U.S. EPA, 1982). These authors report a LOAEL of 9 mg tricresol/m^3. OEHHA staff decided not to use this study because: (1) a complete translation from the original Russian was not available so that only the interpretations of others were available; (2) some endpoints tested are not commonly used in toxicology; and (3) some of the results reported were unusual (e.g., elevation of white blood cells in male but not female rats).

As noted above, the inhalation study conducted by Kurliandskii *et al.* (1975) suggests that adverse health effects occur in experimental animals at exposure levels considerably below those reported by Uzhdavini *et al.* (1972) (9 mg/m^3 vs. 0.05 mg/m^3). The report from which the lower level is drawn has limitations. Human subjects exposed briefly to levels below the LOAEL have reported respiratory irritation.

The strengths of the REL include the use of measured exposure data of animals exposed over a significant fraction of their lifetime. Major areas of uncertainty are route-to-route extrapolation, the lack of chronic human data, and the paucity of reproductive and developmental toxicity studies. Additional inhalation studies of cresols will be useful.

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Response to Comments on the October 1997 Draft of the

Air Toxics Hot Spots Risk Assessment Guidelines Part III: Determination of Noncancer Chronic Reference Exposure Levels

Responses to Comments on the Second Set of 40 Chemicals

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Chemical Industry Institute of Toxicology (CIIT)

Comments on the chronic REL for **ethylene oxide** were received from Drs. Preston, Fennell and Janszen of the Chemical Industry Institute of Toxicology (CIIT). OEHHA developed a chronic REL of 5 $\mu g/m^3$ from a 1995 study of hospital workers by Schulte and coworkers.

Comment 1. In regard to exposure, major uncertainties exist in estimating ethylene oxide exposure to the workers and in interpreting the variability in exposure in the human study used to develop the cREL. The ethylene oxide analyses and calculations are not clearly explained. There may not be a significant association between individual exposure and hemoglobin adducts.

Source data for ethylene oxide assessment: The exposure response data used as the source for chronic exposure limits for ethylene oxide are those published by Schulte et al. *(Molecular, Cytogenetic, and Hematologic Effects of Ethylene Oxide on Female Hospital Workers*, Journal of Occupational and Environmental Medicine 37, 313-320, 1995). In order to adequately assess the data and conclusions drawn, it is necessary to also refer to a previous paper that presents much of the original exposure response data (Schulte, P.A. et al., *Biologic markers in hospital workers exposed to low levels of ethylene oxide*, Mutation Research 278, 237-251, 1992). The more significant differences between the two publications is that only female workers were considered in the analysis presented in the 1995 paper (see discussion below), and hematologic effects were analyzed in the 1995 paper. The relevance of the latter markers to risk assessment remains unclear, and for this and other reasons they are not considered further in this commentary.

Response: Staff have again reviewed both the papers by Schulte and coworkers (1992, 1995) to evaluate exposure issues. Based on these comments, those of the CMA, and OEHHA staff's re-evaluation, we decided not to use the study of Schulte et al. as the basis of the REL. Instead we have developed a revised chronic REL for ethylene oxide of 30 $\mu g/m^3$ based on the neurotoxicity study of Klees at al. (1990).

Comment 2. There are three broad areas of concern with the data as presented and these will be considered sequentially as exposure, statistical analyses and biological data. (a) Exposure: As noted in the draft Chronic Toxicity Summary on Ethylene Oxide, major uncertainties exist in estimating exposure, and in interpreting the variability in exposure concentration. In addition, Schulte et al. (1995) did not give adequate information on ethylene oxide analyses and calculations. More details of the exposure assessment and biomarker measurements were provided for this study population in Schulte et al. (1992). The data obtained on hemoglobin adducts may have the power to substantiate the assessment of exposure, since hemoglobin adducts represent a dose integrated over the lifespan of the erythrocyte. However, the uncorrected data were not presented in sufficient detail to enable this comparison to be made, and many of the important features of the data may not be readily apparent as a result of the particular nature of the presentation.

Response. The draft Chronic Toxicity Summary on Ethylene Oxide discussed the major uncertainties that exist in estimating exposure in the 1995 study by Schulte et al. Major areas of uncertainty are the usual uncertainty in estimating human exposure, the potential variability in exposure concentration, and the small number of subjects studied at each location. Schulte et al. also did not give adequate information on their EtO analyses and calculations in their report.

Comment 3. A critical question is whether there is a significant association between the calculated exposures for each individual and the hemoglobin adducts measured. The range observed for the adjusted hemoglobin adduct levels in the U.S. study participants in Figure 2 of Schulte et al. (1992) is extremely broad, and, as noted in the comments on the statistical analysis presented below, a horizontal line indicating a lack of correlation between hemoglobin adducts and the estimated exposure could equally well be valid. A hemoglobin adduct is a measure of the actual internal dose of ethylene oxide achieved in each individual, and is a more reliable estimate of exposure than those generated in Schulte et al. (1992). Unexpected variability of the data is demonstrated by the fact that for 7 individuals with the same log cumulative exposure of 3.4 (30 ppm.hr), the range of hemoglobin adducts was approximately 10 fold, from approximately 0.036 to 0.36 pmol/mg hemoglobin (calculated from the graph). Four of the participants from the >0-32 ppm.hr group had the same exposure assigned as individuals in the 0 ppm.hr category. These values were all plotted together with an exposure value corresponding to approximately 0.5 ppm.hr, and not 0 ppm.hr. No justification was provided for the choice of this value.

Response. Staff assume that the commentators believe that a 10-fold range is unexpectedly high variability of the data. Ten-fold is the common uncertainty factor used for intraspecies (human) variability by both OEHHA and USEPA. OEHHA staff are aware of only one instance in which USEPA has used a UF_H less than 10 when using the NOAEL/UF approach for an RfC. Recent studies by Hattis and coworkers indicate that for many chemicals the variability is more than 10-fold (e.g., Hattis D. 1996. Variability in susceptibility – how big, how often, for what responses to what agents? Environmental Toxicology and Pharmacology. 2:133-145; Hattis D et al. Distributions of individual susceptibility among humans for toxic effects – For what fraction of which kinds of chemicals and effects does the traditional 10-fold factor provide how much protection? Annals NY Academy of Sciences, submitted). As one example, in a study of DNA adducts from PAHs the interindividual variability was about 24-fold (Dickey C, Santella RM, Hattis D, Tang D, Hsu Y, Cooper T, Young TL, Perera FP. Variability in PAH-DNA adduct measurements in peripheral mononuclear cells: implications for quantitative cancer risk assessment. Risk Anal 1997;17(5):649-656).

The choice of 0.5 ppm-h as a cut-off is not an unreasonable choice based on the available data.

Comment 4. The shortcomings of the exposure measurements are discussed by Schulte et al. (1992). The estimates of exposure were based on 2-4 days of ethylene oxide measurements to model cumulative exposure. Exposure that occurred prior to the four-month period of the

exposure assessment may be more relevant for the generation of effects in lymphocytes. Given the uncertainty of the exposure assessment, and the potential utility of the hemoglobin adduct data as a dose measure, it is very surprising that an analysis of this data set has not been reported using hemoglobin adducts as the dose measure against the various measures of effect. Before using these studies (Schulte et al., 1995) as the basis of a risk assessment, it is important that the data stand up to reasonable scrutiny. Using hemoglobin adducts in place of an uncertain exposure measure would provide a means of reducing the uncertainty of a risk assessment.

Response. Exposure assessment is often a problem in epidemiologic studies and we can only use the data presented. If the pattern of exposure is fairly consistent, 2 to 4 days may be a representative sample. Sterilization is a routine procedure in hospitals and the study is published in a reputable journal. On the other hand, if the exposure is sporadic and variable, 2 to 4 days may be a poor sample. These uncertainties, coupled with the availability of Klees *et al*. (1990), were some of the reasons OEHHA is no longer using the studies of Schulte and coworkers.

Comment 5. The hemoglobin adduct measurements were made with an immunoassay method that can have considerable variability in specificity and in background levels of adduct between batches of antibody used (Tornqvist et al., *Ring test for low levels of (2-hydroxyethyl)valine in human hemoglobin*, Anal Biochem 203, 357-360). It is not clear whether a single batch of antibody was used in the Schulte et al. (1992) study. Failure to do so could affect the results and their interpretation.

Response. OEHHA staff appreciate the identification of this shortcoming. However, we use the data that are available in this peer-reviewed article, while aware of limitations.

Comment 6. (b) Statistical Analyses: The following issues raise questions of whether the statistical analyses for the Schulte et al. dataset were appropriate, and whether the results from a statistical viewpoint are soundly based or valid. (i) Use of same data set for model building and hypothesis testing: In epidemiological studies, one is frequently interested in two basic issues: 1) which factors are important for explaining the observed data; and 2) are the observed differences between groups, as defined by one or more categorical variables, statistically different with regard to a particular response variable. Frequently, as in the study performed by Schulte et al., the same data set is used to answer both questions, although it is not valid to do so. The reason is that this practice involves a type of circular reasoning.

Whenever any kind of stepwise regression is performed, one is interested in building a model of those factors that are deemed to be important for explaining the observed results. This process is designed to choose those factors out of many which significantly contribute to the response of interest. To use this data set to create a model is valid. But to create a model and then test to see if there are differences between groups which were determined by the data (via analysis of covariance) is not a valid exercise. Furthermore, the investigators are implying that the regression coefficients obtained from this small investigational study are

representative of the entire population. Unfortunately, a comparable second study group was not available to test this assumption. The investigators did decide to force certain variables into the model, which were occasionally significant.

A further example is given in the Schulte et al. (1992) article. The investigators arbitrarily decided where the breakpoint should be for creating a grouping variable for cumulative exposure to ethylene oxide. Then they tested to see if there was a difference between the two groups.

Response. OEHHA staff agree that the authors have attempted to make their study both exploratory and confirmatory. In addition to the theoretical undesirability of that approach, the authors' data are very variable. If the data had been more distinctively bimodal, the data might be more credible from a biological standpoint, if not from a statistical one. . These limitations constitute another reason for not using the studies of Schulte and coworkers.

Comment 7. Statistical analyses: (ii) Univariate versus multivariate analyses: Since three outcomes (hemoglobin adducts, SCE, and micronuclei) were measured on each subject, a multivariate analysis should have been performed, which would have taken into consideration the correlation between the responses. This is especially true and necessary for the hematologic effects analyses. A separate regression model for each biomarker response was created from the same data set. Because of the multiplicity of models being created from one data set, some sort of protection against over-significance should have been included, e.g., a p-value might need to be <0.005 for a particular variable to be declared significant. This is analogous to the multiple t-test problem.

Response. $p <0.005$ is an very stringent decision criterion. Another approach might be to modify $p < 0.05$ by the Bonferroni correction for multiple analyses, especially if one is hunting for differences. It might not be necessary in this instance. Hemoglobin adducts will have a biologically separate mechanism from that for micronuclei and SCEs. However hemoglobin adducts are a surrogate for DNA adducts. DNA adducts can lead to mispairing of DNA, and both SCE and micronuclei result from alterations in the DNA.

Comment 8. Statistical analyses: (iii) Significance of regression coefficients: For each biomarker or hematological response a multiple regression model was created. P-values for each variable in the model are given, and the implication is made that variables with small p-values are important for explaining the observed outcome. However, what is not stated and is true, is that the "significance" of a variable is totally *dependent* upon the presence in the model of the other variables. In other words, if there is a high degree of correlation between one independent variable and another (multicolinearity), this would explain the observed significance. Unfortunately, there is no statistical method to separate the dependence of one variable from another and still assess the importance of a given variable. However, in the Schulte et al. (1992) article, this assessment has been done graphically. In Figure 2, for example, the adjusted log hemoglobin adducts are plotted against log cumulative ethylene oxide exposure. The slope (from the multiple regression model) is 0.18, and the p-value is

given as 0.0006. This p-value is dependent on the model given in Table 4. This same argument applies to Figure 4, in which the adjusted SCE are plotted values against log cumulative ethylene oxide exposure. The true degree of significance can be determined as follows: if the regression line can be rotated about the point that represents the average value for each axis so that it is horizontal and between the 95% confidence intervals, then the relationship between the independent and dependent variable is not significant. Hence, in truth there appears to be no significant relationship between log cumulative ethylene oxide exposure and the adjusted log transformed biomarker responses. One might consider these p-values to be statistical "oddities" with no real interpretation. A similar argument can be presented for analysis of the hematological data. Although the data were not presented in detail in Schulte et al. (1995), it seems highly plausible that the reported statistically significant regression analysis for hematocrit, lymphocytes and neutrophils fall equally into the category of statistically uncertain.

Response. OEHHA staff do not agree that it is true that the "significance" of a variable is *totally* dependent upon the presence in the model of the other variables. The significance may be dependent on, and influenced by, the other variables but it is not totally dependent on them.

Staff also do not agree that the “if the regression line can be rotated about the point that represents the average value for each axis so that it is horizontal and between the 95% confidence intervals, then the relationship between the independent and dependent variable is not significant.” If the regression line as calculated is horizontal (b = 0), then one can say that there is no association. If the line has a slope, then the slope can be calculated and its significance assessed. The slope can be shallow and statistically significant. The rotation test is interesting but not the accepted method to test significant correlation.

The comment also implies that there is serious confounding. The study controlled for age, smoking and liquor. Smoking is a definite confounder; age and liquor probably less so. Unless identified, it is just a guess that there is another confounder.

The reference to “statistical "oddities" with no real interpretation” is confusing. Something is either statistically significant using the decision criterion specified, or it is not. Whether a statistically significant difference is biologically meaningful is a separate question.

Comment 9. Biological Data: (i) Controls: Population monitoring studies are basically small epidemiological studies that require that confounders of response be accounted for. As noted above, some attempt was made to do this through a statistical approach that has its own inherent problems, but this has to be considered as only a partial attempt to account for confounders. The selection of an appropriate and adequately sized control population can help diminish the influence of confounders. In the study of Schulte et al., the controls are woefully inadequate, being eight in number for the US hospital group and one for the Mexican hospital. Comparing responses from "high" and "low" exposure groups is not a substitute for a comparison between control and exposed, because this will be further complicated by the adequacy of the exposure assessment.

The inadequacy of the control selection is quite possibly the reason for the low mean SCE values presented for the US group (4.61 per cell). In other large control population studies, the mean SCE values are considerably higher, even though the methods used were the same or very similar. Bender et al. *(Chromosomal aberration and sister chromatid exchange frequencies in peripheral blood lymphocytes of a large human population sample,* Mutation Research 204, 425-433, 1988) reported a mean control SCE frequency of 8.29 ± 0.08 for 353 individuals, and Tucker et al. (*Variation in the human lymphocyte sister-chromatid exchange frequency: Results of a long-term longitudinal study,* Mutation Research 204, 435-444, 1988) one of 9.32 for 22 non-smoking individuals. Also of note, smoking was a considerable confounder, accounting for a mean of 1.85 extra SCE per cell. It *appears* to be less so in Schulte et al., but it is not possible to extract the actual data nor to establish the distribution of smokers among the different groups. Suffice it to say that the control data alone are sufficient to provide a very real concern about the validity of the conclusions.

Response. OEHHA staff agree that the number of controls in the Mexican hospital is problematic; as to the U.S. hospitals the adequacy of 8 controls depends on the tightness of the data. OEHHA is not aware of a widely accepted value for SCE in controls. All means in the Schulte study, both unexposed and exposed to ethylene oxide, are <7 which is less than the means of the 2 control groups cited by the commentator. The Bender et al. data seem surprisingly homogeneous while the commentators do not indicate the variability of the Tucker et al. data. Review of the Tucker paper indicated differences in SCE between smokers and non-smokers. Only the eight non-smokers studied by Tucker at al. can be considered controls. The commentators appear to have added the 8 nonsmokers, the 4 smoke-enders and the 10 variable smokers in Table 3 together to arrive at their sum of 22 non-smoking individuals, a questionable summation since the paper shows that smokers have higher levels of SCE and that it takes at least 12 months for SCE to return to normal levels. The Schulte et al. study also had 8 U.S. controls; their smoking status is not obvious.

A 1984 report (Laurent C, Frederic J, Leonard AY. Sister chromatid exchange frequency in workers exposed to high levels of ethylene oxide, in a hospital sterilization service. Int Arch Occup Environ Health 1984;54(1):33-43) found 7.52 ± 0.82 SCEs per cell in 15 non-smoking controls, a value lower than that quoted by the commentator. In the absence of an accepted standard for SCEs in controls, we judge the consistency and believability of the data itself as presented in the study.

Comment 10. Biological data: (ii) Micronuclei: Micronuclei can be formed from acentric chromosome fragments or whole chromosomes that failed to segregate at mitosis, and as such represent a mutagenic endpoint in contrast to SCE that are a genotoxic endpoint since they have not been associated directly with any cellular phenotype. In Schulte et al. (1992) the frequencies of micronuclei were not significantly different among the three sample groups (control, "high" exposure, "low" exposure) in the US sample. In Schulte et al. (1995), a significant difference between the high and low exposure group was reported. This was basically the same data set as that in Schulte et al. (1992) except that the analysis was only for female workers. However, there was no significant effect of gender on micronucleus frequency ($p = 0.57$) and so it is difficult to establish the reasons for the different conclusions

from the two analyses, absent a statistical quirk. There was no increase in micronucleus frequency in the Mexican hospital sample, but the single control individual makes this an unusable conclusion.

Response: OEHHA staff agree that the lack of SCE data for the one control is problematic.

Comment 11. Biological data: (iii) Relationship to risk assessment: As noted in Schulte et al. (1992) with regard to the interpretation of the analysis of responses (micronuclei, SCE and hemoglobin adducts) in peripheral lymphocytes, "It is not known whether these changes may be indicative of increased risk of disease; however, they do appear to reflect exposure to relatively low levels of ethylene oxide. The exact meaning of these changes is unknown." There has been a persistent concern on the utility of cytogenetic data, for example, collected in population monitoring studies. It is generally agreed that they can be used to demonstrate an exposure, but not absence of exposure. However, even in this mode, it can be argued that confounders could be of concern. The reason being that peripheral lymphocytes are terminally differentiated, non cycling cells. Chromosome alterations (micronuclei and SCE) produced by the great majority of chemicals, including ethylene oxide, require DNA replications for their formation. Thus, any cytogenetic alterations observed from the way the assays are conducted are produced as errors of DNA replication *in vitro* (i.e. in culture) from DNA damage that remains at the time of this *in vitro* replication. Given that DNA repair processes are operational in peripheral lymphocytes, most alterations will have been derived from recent exposure. This makes it very difficult to establish a relationship between exposure and response except in the case of rather high, accidental exposures. Thus, even as a measure of exposure, the assessment of cytogenetic alterations in peripheral lymphocytes has serious limitations.

Given that no risk can be assigned to genetic alterations that arise *in vitro,* following an in vivo exposure, it seems highly inappropriate to use such data in the development of chronic reference exposure levels for ethylene oxide, or indeed for a very broad range of chemicals that produce their biological responses by a similar mechanism.

Response: OEHHA appreciates the thoroughness of the comments. OEHHA staff used the Schulte studies because they were the best human data we could find. Indeed the results may be more applicable as an indicator of genotoxic damage and carcinogenic potential than of other types of toxicity. The commentators do not suggest an alternative, superior, human or animal study to use. OEHHA staff has recalculated a chronic REL for ethylene oxide using human and animal data on neurotoxicity, an endpoint reported in both. OEHHA is now proposing a chronic REL of 30 $\mu g/m^3$ based on human data reported by Klees et al. (1990).

Klees *et al.* (1990) observed cognitive impairment and personality dysfunction more frequently in hospital workers chronically exposed to EtO, compared to a control group. A group of 22 hospital workers who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years) were matched with 24 control subjects. Worker neuropsychological function was classified as normal or impaired on the basis of the questionnaires and neuropsychological tests by 2 clinical psychologists, who were unaware of

exposure status. (If the classification of the two clinicians did not agree, the subject was classified as "disagreement" which occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$).

Derivation of the revised chronic REL for ethylene oxide

Study population	22 hospital workers (and 24 controls)
Exposure method	Workplace exposure
Critical effects	Impaired neurological function
LOAEL	4.7 ppm
NOAEL	Not observed
Exposure continuity	8-hours/day (10 m^3 occupational inhalation rate), 5 days/week
Exposure duration	6.13 years (range 1-11 years)
Average experimental exposure	1.68 ppm (4.7 x 10/20 x 5/7)
Human equivalent concentration	1.68 ppm
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

Chemical Manufacturers Association - Ethylene Oxide Industry Council

Comments on the chronic REL for **ethylene oxide** were received from the Ethylene Oxide Industry Council (EOIC) of the Chemical Manufacturers Association (CMA) in a letter signed by Courtney M. Price dated January 29, 1998. OEHHA developed a chronic REL of 5 $\mu g/m^3$ from a 1995 study of hospital workers by Schulte and coworkers.

Comment 1. The OEHHA guidelines establish criteria for the determination of RELs. The 1995 Schulte study cited in the TSD, and the equally relevant 1992 study that is not cited, must be evaluated subject to Cal EPA guidelines on interpretation of human studies. Cal EPA OEHHA guidelines recognize that "[e]xposure measures frequently represent the greatest weakness of available epidemiological studies." Short-term exposure monitoring must frequently be used where long-term data are not available. "The degree to which air concentrations can be adequately measured is critical in determining the usefulness of an epidemiological study." "Covariables and confounding variables should be controlled or removed from the study." A limitation of controlled human exposure studies, in addition to their short duration, is that they usually involve small sample sizes. In evaluating evidence, OEHHA considers "strengths and uncertainties of each REL.... Issues such as observation of dose-response relationship, reproducibility of findings, and mechanism of action" are given weight in evaluating RELs. "Consistency of an association between chemical exposure and adverse effect is also evaluated. Relevant observations include similarity of effects noted in different studies and among different populations and/or species ...." When these guidelines are applied to the 1992 and 1995 Schulte studies, significant questions are raised concerning the validity of the findings.

Response. OEHHA acknowledges that human studies (including the 1992 and 1995 Schulte studies) often suffer from deficiencies in the assessment of exposure. The deficiencies were detailed by OEHHA in the TSD. We have since re-evaluated the utility of the Schulte et al. (1995) study in deriving the chronic REL and, as a result, are proposing to use a study by Klees et al. (1990) on neurotoxicity.

Comment 2. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the control population is too small. A valid epidemiologic study must have an adequate number of controls to yield reliable estimates of risk and permit adjustment for potential confounders that can bias results. The number of controls was much too small in the 1995 Schulte study - eight U.S. workers and one in the Mexican worker group. There is indication that the insufficient number of controls is not merely a formal deficiency, but undermines reliance on the TSD's conclusion that Schulte found a significant excess in SCE values and hernatocrit values. Taking SCE values, Schulte's U.S. control group shows SCE mean values of 4.61 per cell. Other larger studies report SCE values of 8.29 ± 0.08 for 353 individuals, and 9.32 for 22 non-smoking individuals. It is recognized that smoking is a considerable confounder and thus an adequate number of controls is especially important to a valid study. As a result of the small size of Schulte's control group and the anomalous level of SCEs reported in these controls, Schulte's findings lack the indicia of validity to be selected as the basis for the EO REL.

Response. The smaller the control group is, the more obvious the effect must be in the exposed group. The possibility that these controls have unusually low SCE values is important and may be a reason to doubt the small, purported increase in SCE in the EO exposed workers. As noted above, OEHHA is now proposing the use of a study on neurotoxicity as the basis for the chronic REL.

Comment 3. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the relevance of SCE data to risk assessment has not been demonstrated. Schulte et al. recognized in the 1992 paper a significant limitation not quoted by Cal EPA: micronuclei, SCE, and hemoglobin adducts appear to reflect exposure to relatively low levels of EO but it is not known whether they are indicative of increased risk of disease. Thus SCE data are biomarkers of EO exposure but it is not known whether they have any clinical significance or indicate any disease endpoint. Schulte himself recognizes that "the predictive value of SCEs and micronuclei to cancer is undetermined." Mutation Research, Vol. 278 at 239. Schulte states that "the significance of our findings [increased numbers of hemoglobin adducts and SCEs] for the long term health of workers is unknown." Id. at 248. Other investigators in addition to Schulte acknowledge that these cytogenetic changes have no known clinical significance. E.g., Stolley et al., "Sister-chromatid exchanges in association with occupational exposure to ethylene oxide," Mutation Research 129:89-102 (1984). It is unwarranted to treat these biomarkers of exposure as indices of health risk.

Response. Although the relevance of SCE data to risk assessment of ethylene oxide has not been demonstrated, the finding of increased SCE in Bloom's syndrome, in which the risk of cancer is increased several fold, indicates that SCE, a rearrangement of the genetic material, may be linked to cancer. However, OEHHA agrees that for noncancer, chronic risk assessment, the use of this endpoint is questionable. As such, OEHHA is proposing to use the Klees et al. (1990) study of neurotoxicity.

Comment 4. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the 1992 Schulte study does not indicate dose response for micronuclei. In the 1992 Schulte Study, frequencies of micronuclei were not significantly different in the U.S. population between controls, low and high exposure. Although the 1995 study overlapped the 1992 data set, an unexplained difference in results was observed which is not rationalized by the fact that the 1995 study was limited to female workers. When the 1992 data are considered, there is not an adequate dose-response to suggest causal association under OEHHA guidelines.

Response. In the U.S. data there is a statistically significant difference between the 0 exposure and the >32 category. The SCE are higher in the high exposure group in the 1995 report (Table 3). The p value is 0.02.

Comment 5. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the exposure assessment in the Schulte assessment was recognized by the author as a

weakness of the study. In the 1992 Schulte study, the estimate of four months of cumulative exposure was based on only two to four days of EO measurements. Schulte acknowledges as study "weaknesses" the fact that "the estimate of exposure was based on 2-4 days of EO measurements to model the cumulative exposure. The impact of peak exposures or other variations from the mean of those measurements could not be assessed." U.S. OSHA adopts a short term excursion limit of 5 ppm for EO given relevance of peaks of exposure. The Schulte data are flawed in their inability to adequately characterize exposure and to take intensity of exposure into account. The 1992 Schulte study simply does not account for the short term exposures (STEs) in conclusions or reporting. There is no indication of the magnitude or frequency of the exposures, even with multiple statements that the STEs are the primary source of exposure. Schulte simply takes all exposure measurements and calculates the ppm hour or cumulative time weighted exposure. Schulte then concludes from this number that effects are observed at exposure levels below the OSHA standard. This is a flawed conclusion because it ignores the implications of the OSHA excursion limit. OSHA has recognized the significance of STEs relative to health effects in the establishment of the EL. If an employer exceeds either the 8-hour limit or the 15 minute limit, the employer has violated the OSHA limits. It is unjustified to assume that health effects caused by exposures above an OSHA standard would apply below the standard. In addition, improper sampling techniques used by Schulte may have lead to inappropriate conclusions. In the study, results from different sampling techniques (personal monitoring, breathing zone, area samples) were used for the same study population and considered together, which would not be considered an appropriate method.

Response. OEHHA acknowledges the limitations of the exposure data in these 2 studies (and in many other human studies), the problems with measuring exposure to humans in such situations, and the problems associated with short-term excursions, especially with ethylene oxide in health care settings. OEHHA prefers to use human studies in developing RELs. We have revisited the use of this study as the basis of the chronic REL and have decided to use the study of Klees at al. (1990) instead.

Comment 6. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the complete blood count data are not significant given the small number of controls and the frequency of iron deficiency in a population of young women. Data on minor hematologic changes do not provide a sound basis for the REL, especially given inadequate sample size. The level of reduction in hemoglobin is well within the expected range for a population of female workers who may be iron-deficient for a variety of reasons.

Small differences were noted in hemoglobin and hematocrit between mid-dose and high-dose exposed workers but not between unexposed workers and either low-dose or high-dose groups. The differences between mid-dose and high-dose groups were not clinically significant. See attached report by Dr. Mark Udden, Baylor College of Medicine. None of the subjects' hemoglobin levels were below the range of normal women as reported in the authoritative reference, Williams' Hematology. Moreover, Schulte does not appear to have addressed some other potential causes for their hematologic status such as folate or other nutritional deficiency.

Schulte's claim that EO causes changes in the CBC data of a population are primarily based on granulocyte and lymphocyte changes. However, as Dr. Udden observes, it is not clear that these changes have biological significance given that there was no statistically significant effect on the total white cell count of EO-exposed women versus unexposed women. The shifts in granulocyte levels (10%) did not decrease to the low level associated with neutropenia, nor was there evidence of lymphocytosis. The study also lacks internal consistency. Although Mexican workers had higher average cumulative exposures than U.S. women, the Mexican workers did not show statistically significant percentage changes in lymphocytes or neutrophils as might be expected if there were a real biological effect. The findings, based on multiple linear regression (Table VII), do not indicate a statistically significant relationship with increasing cumulative exposure.

In addition, there is lack of external consistency or consistency across studies. Schulte identified in his 1995 paper three other studies that did not find the effects he reported. Thus there is not found a consistency of association between EO exposure and hematologic effects across studies. See TSD Guideline § 2.2.2,

A much larger number of women would need to be studied before any conclusion can be drawn that CBC data represent meaningful biological effects of EO exposure.

Response. The inconsistency of the data in the 2 Schulte reports with data in other reports in the literature is important. For this and other reasons OEHHA staff have reconsidered the basis of the chronic REL and are now proposing to use neurotoxicity data from Klees et al. (1990).

Comment 7. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the relevance of EO blood count data to worker health has been questioned. In June 1997 hearings at U.S. OSHA reviewing the current occupational standard on EO, Dr. Anthony LaMontagne appeared as the principal witness for the unions. In discussing recommended revisions to various ancillary requirements, Dr. LaMontagne stated that he questioned the usefulness of the complete blood count and differential in EO medical surveillance. See June 30, 1997 OSHA hearing transcript at 70-73 and exhibit to Dr. LaMontagne's testimony, "The Massachusetts Hospital Eto Health and Safety Study: A Summary Report for Study Participants and Supporters" (1996) at 37. Dr. LaMontagne recommended that the CBC count be eliminated from surveillance requirements, citing his publication, LaMontagne et al., "The utility of the complete blood count in routine medical surveillance for ethylene oxide exposure," Am. J. Ind. Med. 24:191-206 (1993). In this article, LaMontagne concludes that "a cross-sectional comparison of the CBC data from the EtO exposed workers to data from non-EtO exposed hospital workers showed no significant differences, ruling out an association of relative lymphocytosis with EtO exposure." The authors conclude that the CBC with lymphocyte differential is not useful in EO medical surveillance.

Response. Staff appreciate being apprised of Dr. LaMontagne's testimony. However, blood count was only one of the endpoints OEHHA considered. Also, as noted above, we have decided not to use the study by Schulte and coworkers as the basis of the chronic REL.

Comment 8. CONCLUSION: Individual epidemiologic studies addressing potential carcinogenicity of EO include hundreds or thousands of workers. It is inappropriate for Cal EPA to use the 1995 Schulte study with its small handful of workers in setting a REL for chronic effects given the significant limitations of the Schulte data.

Response. OEHHA appreciates the thoroughness of the comments. OEHHA staff used the Schulte studies because they were the best human data we could find. Indeed the results may be more applicable as an indicator of genotoxic damage and carcinogenic potential than of other types of toxicity. The commentators do not suggest an alternative, superior, human or animal study which OEHHA should use. OEHHA staff has recalculated the REL using human and animal data on neurotoxicity, an endpoint reported in both. OEHHA is now proposing a chronic REL of 30 $\mu g/m^3$ based on human data reported by Klees et al. (1990).

Klees *et al.* (1990) observed cognitive impairment and personality dysfunction more frequently in hospital workers chronically exposed to EtO, compared to a control group. A group of 22 hospital workers who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years) were matched with 24 control subjects. Worker neuropsychological function was classified as normal or impaired on the basis of the questionnaires and neuropsychological tests by 2 clinical psychologists unaware of exposure status. (If the classification of the two clinicians did not agree, the subject was classified as "disagreement" which occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$).

Derivation of the revised chronic REL for ethylene oxide

Study population	22 hospital workers (and 24 controls)
Exposure method	Workplace exposure
Critical effects	Impaired neurological function
LOAEL	4.7 ppm
NOAEL	Not observed
Exposure continuity	8-hours/day (10 m^3 occupational inhalation rate), 5 days/week
Exposure duration	6.13 years (range 1-11 years)
Average experimental exposure	1.68 ppm (4.7 x 10/20 x 5/7)
Human equivalent concentration	1.68 ppm
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

Chemical Manufacturers Association - Alkanolamines Panel

Comments on the chronic REL for diethanolamine were made by the Alkanolamines Panel (Panel) of the Chemical Manufacturers Association in a letter from Courtney M. Price dated January 29, 1998. The Panel is comprised of the major domestic producers of diethanolamine (The Dow Chemical Company, Huntsman Corporation, Union Carbide Corporation, and Occidental Chemical Corporation). The Panel urges OEHHA to withdraw its draft toxicity summary and proposed reference exposure level (REL) for diethanolamine. The Panel states that the study on which OEHHA has relied is inadequate to derive a REL, and the draft toxicity summary does not reflect accurately diethanolamine's toxicity database, particularly for reproductive and developmental effects. Also, the summary should be revised to characterize diethanolamine's vapor pressure accurately. In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including DEA. OEHHA developed a chronic REL for diethanolamine of 20 $\mu g/m^3$ based on hematologic changes in female rats exposed to the chemical in drinking water.

Comment 1. OEHHA should derive its REL for DEA from inhalation studies, not from a drinking water study. The California Toxic Air Contaminants Program provides that OEHHA shall evaluate the health effects of and prepare recommendations regarding ... toxic air contaminants. In conducting its evaluation, OEHHA must consider all available scientific data, including but not limited to, data provided by state and federal agencies, private industry, and public health and environmental organizations. The evaluation must include an assessment of the availability and quality of data on health effects, including potency, mode of action, and other biological factors. OEHHA has stated that, because it is required to develop chronic inhalation RELs, "[s]trong weight is given to inhalation exposure-based health effects data. Oral exposure data are used only if adequate inhalation data are unavailable.

In deriving its REL for DEA, OEHHA stated that no inhalation studies with diethanolamine were located. For this reason, OEHHA derived its REL for DEA from a subchronic drinking water study conducted in rats. As shown below, however, a substantial database exists on DEA's potential inhalation toxicity. None of these studies is referenced in the toxicity summary. These studies provide data that is far more relevant to DEA's potential inhalation effects than the drinking water study on which OEHHA has relied. OEHHA must review these studies to fulfill its obligations under the Toxic Air Contaminants Program, comply with its own Guidelines, and derive an up-to-date and scientifically defensible REL.

A substantial database exists on DEA's potential inhalation toxicity. According to OEHHA's chronic toxicity summary, the direct effects of DEA on the respiratory system are unknown since no subchronic or chronic inhalation studies have been conducted. A number of inhalation studies have been conducted with DEA, however. These studies include:

BG Chemie (1993): In this 14-day inhalation study, DEA was administered to rats in an aerosol. No effects were observed in response to the 0.2 mg/l dose. For the 0.4 mg/l dose, rats exhibited slightly decreased body weight and retarded body weight gain in the males, slightly decreased serum cholesterol in both sexes, and increased relative and absolute liver weight in the females. The study concludes that "[u]nder the conditions of the test the degree of toxic effects as reported in the literature after inhalation of *6* ppm, *25* ppm, and *200* ppm DEA-vapor could not be confirmed." It further finds that "[n]eurotoxic effects as reported after 13 week application in the drinking water were not found after 2-weeks inhalation."[BG Chemie (1993). Study on the inhalation Toxicity Including Neurotoxicological Examinations of Diethanolamine as a Liquid Aerosol in Rats (14 Day Test). Project No. 3610233/90008. A copy of this study is appended as Attachment 1.]

Gamer et al. (1996): In this 90-day liquid aerosol inhalation study, thirteen male and thirteen female Wistar rats were exposed head-nose to liquid aerosols of DEA for six hours per working day for 90 days. The target concentrations were 15, 150, and 400 mg/m^3. The study found no functional or morphological evidence of neurotoxicity. Retardation of body weight was observed in animals that received high concentrations. No systemic effects occurred at the low dose, but liver, kidney, male reproductive system and red blood systemic effects occurred in the high concentration dose group. In the mid dose group, mild liver and kidney effects were present. Local irritation of the larynx and trachea was found in the high and mid dose groups, with irritating laryngeal effects also detected in the low dose group. [Gamer, et al. (1996). Diethanolamine – 90-Day Liquid Aerosol - Inhalation Study in Wistar Rats. BASF Project No. 5010075/93011. A copy of this study is appended as Attachment 2.]

BASF (1966): In this study, rats were administered a saturated vapor of DEA for eight hours. No mortality was reported.

Foster (1972): In this study**,** rats administered 1,471 ppm of DEA via inhalation experienced lung edema and died less than two hours after exposure. [Foster, G. (1972) . "Studies of the Acute and Subacute Toxicologic Responses to Diethanolamine in the Rat." Dissert. Abst. B32:6549.]

Union Carbide Corp. (1950): Rats were administered a saturated vapor of DEA at 25°C for six hours. No deaths resulted. Rats were also administered DEA in a saturated mist for eight hours with no deaths resulting. [Union Carbide Corp. (1950). Bushy Run Research Center Report 13-67.]

Schaper and Detwiler-Okabayashi (1996): This three-hour inhalation study in mice compared the sensory and pulmonary irritating effects of amines found in metalworking fluids containing DEA. The RD50 (sensory irritation) for ethanolamines ranged from 500 to 1,500 mg/m^3. [Schaper, M. and Detwiler-Okabayashi, K. (1996). "Comparison of Sensory and Pulmonary Irritating Effects of Amines Found in Metal Working Fluids (MWF) . " Toxicologist 301:18 (abstract)] .

Knaak et al. (1997): The authors reported a study in which rats were administered 25 ppm. of DEA vapor for a period of nine days by continuous inhalation (23.5 hours/day). Increased

liver and kidney weights, elevated blood urea nitrogen, and serum glutamate oxaloacetate transferase reported. [Knaak J, et al. (1997) "Toxicology of Mono-, Di-, and Triethanolamine" in Ware, G (ed.). Reviews Environ. Contam. Toxicol.

Eastman Kodak Co. (1967): In this 90-day subchronic inhalation study, dogs, weanling rats**,** adult rats, and guinea pigs were administered saturated vapor concentrations of about 0.26 ppm DEA. Exposure did not produce any identifiable gross or microscopic alterations in organs that could be attributed to DEA in any species. [Eastman Kodak Company (1967). Health and Safety Studies for Diethanolamine, Laboratory Tests to Determine Effect of Inhalation of Two Ethanolamines - Diethanolamine (DEA), Methylaminoethanol (MAE), Formulation 485K - Histological Addendum to Final Report. TSCA 8d Submission 86-890000205, Microfiche Number OTS0516742. Washington, D.C.: OPPT, U.S. EPA.]

Eastman Kodak Co. (1967): As an extension of the study summarized above, rats, guinea pigs, and dogs were, for 45 days, administered atmospheric concentrations of approximately 0.5 ppm DEA. All animals survived the study, and their behavior and appearance appeared normal. No systematic toxic effects or irritation were observed. The clinical examination also revealed no abnormal response, except that a "slight retardation in growth rate in rats may have occurred." [Subacute - Inhalation Toxicity of Diethanolamine and Bimat Imbibant (485 K))

Hartung et al. (1970): The authors report a subchronic study in which inhalation of 6 ppm vapor by male rats on a workday schedule for 13 weeks caused depressed growth rates, increased lung and kidney weights, and some mortality. [Hartung, *R., et al. (1970).* "Acute and Chronic Toxicity of Diethanolamine." Toxicol. Appl. Pharmacol. 17:308]

The significance of the more recent studies conducted with DEA in predicting DEA's potential health effects was acknowledged recently during the deliberations of the Organization for Economic Cooperation and Development (OECD) Programme for the Investigation of High Production Volume Chemicals. This program, initiated in 1990, was established to gather data on chemicals produced in large quantities by member nations, provide for an initial screening of the potential risks to human health or the environment presented by these chemicals, and develop recommendations for further testing. The sponsor country for DEA, the United Kingdom, completed its Screening Information Data Set (SIDS) Dossier in 1993 [OECD, Screening - Information Data Set (SIDS) Dossier, OECD Am Chemicals Programme (June 1993) (prepared by the United Kingdom, Department of the Environment) (OECD SIDS Dossier)], and in 1995 submitted a SIDS Initial Assessment Report (SIAR). The SIAR, based on a comprehensive review of data, concluded that no further testing was necessary.

Some additional testing was nevertheless proposed at the SIDS Initial Assessment Meeting (SIAM) where the SIAR was discussed, although initially it was agreed at the SIAM that no further testing was necessary. In the OECD SIAR prepared to address the concerns raised at the SIAM, the National Centre for Ecotoxicity and Hazardous Substances of the United Kingdom's Environment Agency reiterated:

"Since SIAM 4 the results of good quality 2- and 13-week inhalation toxicity studies have been incorporated into the SIAR. These studies [OECD (1997). SIDS - Initial Assessment Report: Diethanolamine] included specific evaluations of subgroups for neurotoxicity. Also good quality developmental toxicity data has been incorporated. It is therefore concluded that further animal testing of diethanolamine is unnecessary."

The Panel believes that OEHHA must review and evaluate all available inhalation data including recent unpublished studies that OEHHA has characterized as being "of good quality," in order to reach sound conclusions about DEA's potential inhalation effects.

Response. OEHHA appreciates the suggestion of additional inhalation studies and the furnishing to OEHHA of some of the studies. However, many of the studies are acute or subacute studies:

- Foster (1972) - 2 hours;
- Schaper and Detwiler-Okabayashi (1996) – 3 hours;
- Union Carbide Corp. (1950) – 6 hours;
- BASF (1966) - 8 hours;
- Knaak et al. (1997) – 9 days;
- BG Chemie (1993) 14 days.

These studies are of little use for developing a chronic REL.

Of more relevance to the development of a chronic REL may be:

- the Gamer et al. (1996*)* 90-day liquid aerosol inhalation study in rats,
- the Hartung et al. (1970) 13 week (90 day) inhalation study of 6 ppm DEA in rats, and
- the Eastman Kodak Co. (1967*)* 90-day subchronic inhalation study in dogs, weanling rats**,** adult rats, and guinea pigs administered saturated DEA vapor concentrations of about 0.26 ppm.

The Gamer et al. study has not appeared in the peer-reviewed medical and toxicological literature as of March 1999. The Eastman Kodak study also has not appeared in the peer-reviewed literature; it provides a free-standing NOAEL for inhalation of 0.26 ppm. The Hartung et al. (1970) report on the effects of 6 ppm DEA is likely an abstract since it could not be located on Medline. Hartung and Cornish reported on the acute and short-term oral toxicity of 2-N-ethylaminoethanol in rats in 1969 (Food and Cosmetic Toxicology 7(6):595-602).

The Gamer et al. (1996) aerosol inhalation study can be used as a check against the chronic REL of 20 $\mu g/m^3$ proposed by OEHHA. The NOAEL from the Gamer et al. (1996) study was 15 mg/m^3 diethanolamine based on a 6 hour/day, 5 day/week exposure. The equivalent continuous exposure would be 2.7 mg/m^3. After dividing by 1,000 (10 each for subchronic to chronic, animal to human, and intraspecies uncertainty/variability), the REL would be 2.7 $\mu g/m^3$, one-seventh of the REL proposed. If this study is published in the peer-reviewed literature, OEHHA will consider lowering the REL to 2.7 $\mu g/m^3$.

As another check, the Hartung et al. (1970) free-standing LOAEL of 6 ppm (25.8 mg/m^3) for a 13 week exposure of male rats would require time adjustment for continuous exposure to 4.6 mg/m^3 and the maximum UF of 3,000 which results in a REL of 1.5 µg/m^3 (also below the proposed chronic REL).

Comment 2. OEHHA should derive its REL for DEA from the Gamer et al. (1996) inhalation study. The Panel believes that the recent Gamer et al. (1996) study provides adequate data on which to base a REL and should be used for that purpose instead of the Melnick et al. (1994) study. As OEHHA has acknowledged in its Guidelines, oral data are considered only where inhalation data are unavailable. Moreover by using a cumulative uncertainty factor of 3,000 to derive a REL for DEA from this study - the highest uncertainty factor used by OEHHA for any chemical - OEHHA also has acknowledged the relative weakness of this study for predicting DEA's potential toxicity.

OECD (1997) (Section Addressing Recommendations for Further Work) Recent studies reviewed in connection with the OECD SIAR include the BG Chemie (1993) and Gamer et al. (1996) studies.

In the Gamer et al. study, conducted in the Republic of Germany, male and female Wistar rats were exposed by head-nose to liquid aerosols of DEA for 6 hours per working day for 90 days. The target concentrations of treatment groups were 15, 150, and 400 mg/m^3. A complete necropsy and gross pathological examination was conducted on animals in the experimental and control groups.

The only clinically detectable effect was a reduction of body weight development among high dose (400 mg/m^3) males. No systemic effects occurred at the low dose, but liver, kidney, male reproductive system, and red blood systemic effects occurred in the high dose group. In the mid dose group, mild liver and kidney effects were observed. Local irritation of the larynx and trachea was found in the high and mid dose groups, with irritating laryngeal effects also detected in the low dose group.

The authors concluded that the liver, kidney, male reproductive system, and red blood were target organs for systemic effects at the high concentration tested, but that no systemic effects occurred in the low concentration. They concluded further that the no observed effect level (NOEL) for its systemic effects lies between 15 and 150 mg/m^3. The Panel believes that OEHHA should use the no observed adverse effect levels (NOAELs) from this study, together with the standard uncertainty factors set forth in the Guidelines, to compute a REL for DEA.

Response. OEHHA calculated a REL based on the Gamer et al. study in the response to the first comment. Systemic effects on the blood were seen in both the Melnick and Gamer studies, which indicates that DEA causes the same effects by both routes. The laryngeal irritation effects, detected in the low dose group, is of interest because it is an effect specific to the route of exposure.

Comment 3. OEHHA should revise its draft toxicity summary to describe accurately DEA's potential health effects and vapor pressure. The Panel also urges OEHHA to revise its draft chronic toxicity summary for DEA to characterize more accurately the chemical's potential chronic health effects. Although OEHHA states, for example, that there is a lack of reproductive and developmental toxicity studies on DEA, the database on these endpoints is robust. Among studies that provide data relevant to DEA's potential developmental toxicity are:

Bushy Run Research Center (1991): In this study, pregnant rats were dosed cutaneously with 150, 500, and 1,500 mg/kg/day of DEA in distilled water on gestation days 6-15. No mortality was observed during the study, and the pregnancy rate was equivalent for all groups. No evidence of embryotoxicity or malformations was observed; there were no decreases in the mean fetal body weight; and no treatment related differences in the incidence of external or visceral variations were seen. There was an increase in the incidence of fetal skeletal variations at 1,500 mg/kg/day. Maternal toxicity was observed primarily at 1,500 mg/kg/day. [Bushy Run Research Center. Definitive Developmental Toxicity Evaluation of Diethanolamine (DEA) Administered Cutaneously to Sprague Dawley Rats (Final Draft Report) (Unpublished) (Sept. 9, 1991)] .

BASF (1993): In this study, pregnant Wistar rats were dosed with DEA in an aerosol (nose-only on gestation days 6-15. The concentrations tested were 0.01, 0.05, and 0.2 mg/l (10, 50 and 200 mg/m^3). Maternal toxicity (vaginal hemorrhage) and embryo fetotoxicity (increased incidence of skeletal variations) were observed at the highest dose level. No teratogenic effects were seen at any dose level. NOAELs were computed as follows: maternal toxicity (50 mg/m^3); embryofetal effects (50 mg/m^3); and teratogenicity (greater than 200 mg/m^3). [BASF (1993). Study of the Prenatal Toxicity of Diethanolamin in Rats after Inhalation. Project No. 31RO233/90010].

*Neeper-Bradley and Kubena (1993)**:*** Pregnant rabbits were treated by occluded cutaneous application to three concentrations of DEA for 6 hours a day on gestation days 6-18. Maternal toxicity (severe skin irritation) was seen at the highest dose. No teratogenic or embryofetal toxic effects were seen at any dose tested. NOELs were computed as follows: maternal toxicity (100 mg/kg) ; embryofetal effects (350 mg/kg) ; and teratogenicity (greater than 350 mg/kg). [Neeper-Bradley, T. L. and Kubena, M. F. (1993) . Diethanolamine**:** Developmental Toxicity Study of Cutaneous Administration to New Zealand White Rabbits. Union Carbide Corp. Bushy Run Research Center Project Report 91NO136.]

Environmental Health Research and Testing, Inc. (1990): In a range–finding developmental toxicity study, Sprague-Dawley rats were administered aqueous solutions of DEA by gavage at levels of 0, 50, 200, 500, 800, or 1,200 mg/kg from gestation days 6-15. The dosing volume was held constant at 5 ml/kg. Fetuses were delivered by Cesarian section on day 20 of gestation. The number of implantation sites, resorptions, dead or live fetuses, and the gravid uterine weight were recorded. All animals at the 500 mg/kg or higher level died or were moribund and sacrificed. No maternal mortality was observed in the 50 or 200 mg/kg groups. Maternal body weight gain was significantly reduced in the 200 mg/kg group. At scheduled sacrifice, a litter was found to be completely resorbed in one dam in the 200 mg/kg

group. None of the recorded gestational parameters were significantly different between the treatment groups and controls, however. [Environmental Health Research and Testing, Inc. (1990) . Report: Range Finding Studies: Developmental Toxicity Diethanolamine When Administered Via Gavage in CD SpragueDawley Rats. NTP-89-RF/DT-002].

Burnett et al. (1976): No embryotoxic or teratogenic effects were produced by topical administration of 2 ml/kg semipermanent hair dye preparations containing 2 percent DEA (equivalent to about 40 mg/kg DEA) to the shaved backs of pregnant Charles River CD rats on gestation days, 1, 4, 7, 10, 13, 16, and 19. [Burnett, C. et al. (1976) "Teratology and percutaneous toxicity studies in hair dyes." J. Toxicol. Environ. Health 1:1027-1040.]

The Panel notes in this regard that the OECD SIAR reviewed these studies, particularly the BASF (1993) study, which it characterizes as "good quality developmental toxicity data," in repeating its recommendation that "further animal testing of diethanolamine is unnecessary. OEHHA should, therefore, assess and incorporate these studies into its chronic toxicity summary and also revise the text of its summary to reflect accurately the robust nature of DEA's toxicological database.

OEHHA similarly has failed to discuss or even reference reproductive studies conducted with DEA. These include:

Battelle Columbus (1989): Reproductive effects were reported in male rats administered DEA concentrations of 2.5 and 5 mg/ml in drinking water (233 mg/kg and 487 mg/kg body weights, respectively). " -Effects included atrophy of the seminal vesicle, hypospermia, and a decrease in sperm motility and sperm count. The doses at which adverse effects were seen, however, approximate toxic levels - evidenced by the fact that the rats exhibited a large depression in their group mean body weight. Body weight gains relative to controls were significantly depressed in all male and female treatment groups. Weight depressions ranged from 66 percent in male rats administered 5 mg/ml DEA, to 11 percent in females administered the lowest dose (0.16 mg/ml). The authors acknowledged that "these doses are much too high for a chronic study," and recommended that doses for a chronic study should not exceed 0.16 mg/ml (the lowest dose used in the Battelle Columbus study). As noted in a toxicology review recently conducted in connection with the OECD's Programme on the Cooperative Investigation of High Production Volume Chemicals, the results observed in this study for DEA are "unlikely to be indicative of specific reproductive toxicity," and "further reproductive effects toxicity studies in animals cannot be justified. [Battelle Columbus (1989). Diethanolamine: Subchronic Dosed Water and Dermal Studies in F344 Rats and B6C3Fl Mice - Final Report for Prechronic Dosed Water Study for Diethanolamine in Fischer 344 Rats. TSCA FYI Submission FYI-OTS-1189-0721, Microfiche Number OTS0000721. Washington, D.C.: OPPT, U.S. EPA.]

Battelle Columbus (1989): In a 14-day oral dosed water study, for example, DEA was administered to mice at concentrations ranging from 0.63 to10 mg/ml of water. Exposure to the test solutions resulted in a calculated intake of 110 to 1,362 mg/kg/day for male mice and 197 to 2,169 mg/kg/day for female mice. No effects on the reproductive system were

detected in either gross necropsy or during histopathologic examination of high dose mice of both sexes. Battelle Columbus (1989) at 4 and Tables 5 and 6.

Hejtmancik et al. (1988): In a follow-up 13-week subchronic oral dosed water study, B6C3F1 mice were administered DEA concentrations of up to 10 mg/ml. As in the 14-day screening study, reproductive effects were found following gross necropsy or histologic examination. [Hejtmancik, M, et al. (1988a) . Prechronic Dosed Water Studv of Diethanolamine (CAS 111-42-2) in B6C3F1 Mice (Report prepared by Battelle, Columbus, Ohio)].

Response. OEHHA appreciates the additional information on the effects of DEA on development. As much as possible OEHHA based its chronic RELs on articles appearing in the peer-reviewed toxicologic and medical literature. Published reports on the reproductive/developmental effects of DEA are lacking. The studies cited by the commentator are nearly all unpublished, in-house reports. They also are either by the cutaneous (skin) or oral (gavage, drinking water) routes. An exception to these routes is the unpublished BASF (1993) study of inhalation of aerosolized DEA, which resulted in NOAELs of 50 mg/m^3 both for embryofetal effects and for maternal toxicity. However, OEHHA would prefer to use data other than a 10 day study for developing a chronic REL.

Comment 4. OEHHA should also ensure that the draft toxicity summary adequately characterizes DEA's physical characteristics. OEHHA's draft summary states, for example, that DEA's vapor pressure is less than 0.01 mm Hg at 20 degrees Celsius. DEA’s vapor pressure is, however, much lower - less than 0.00015 mm Hg at that temperature. OEHHA should revise the summary to correct this error. The public must be provided with accurate information regarding DEA's vapor pressure because it ensures that ambient air concentrations of DEA are extremely low.

Response. The commentator requests that we be more accurate in reporting the vapor pressure of DEA. Indeed HSDB (1997) reports the value of 0.00014 mm Hg at 25°C, which is found in Dow Chemical’s Alkanolamine Handbook (1980). OEHHA will revise the value.

Chemical Manufacturers Association – Arsenic

Comments on the chronic REL for **arsenic** were made by the Arsenic Acid Task Force of the Chemical Manufacturers Association Biocides Panel in a letter from Courtney M. Price dated January 28, 1998. The members of the Chemical Manufacturers Association Biocides Panel Arsenic Acid Task Force are: American Chrome & Chemicals; Chemical Specialties, Inc.; Hickson Corporation; J.H. Baxter & Company; Osmose Wood Preserving, Inc.; Occidental Chemical Corporation; Peninsula Copper Company; and Phibro-Tech, Inc. OEHHA proposed a chronic REL of 0.03 $\mu g/m^3$ based on reduced fetal body weight in mice exposed to arsenic during days 9-12 of gestation.

Comment 1. The Task Force has reviewed the OEHHA draft chronic inhalation and oral Reference Exposure Level (REL) for arsenic. With regard to the chronic inhalation REL, the Task Force is concerned that OEHHA's analysis relies primarily on one study and fails to account for the well-known differences in toxicity among arsenic compounds based on the chemical oxidation state and the differences in animal metabolism of arsenic. Similarly, the Task Force is concerned about the development of an REL under the "Hot Spots" program that is dependent on oral exposure, as wells as the primary reliance in the chronic oral REL on the Taiwanese drinking water studies, especially in light of questions raised about those studies. The Task Force's concerns about each of these points is discussed in more detail below. The Task Force asks that OEHHA carefully consider these comments and make the appropriate revisions to the chronic REL for arsenic.

Response. OEHHA staff recognize that there are differences in toxicity among arsenic compounds based on the chemical oxidation state. However, in the Hot Spots program industries do not speciate their arsenic emissions. Also there are differences in animal metabolism of arsenic. A PBPK model is needed to address this but only one has appeared in the peer-reviewed literature. OEHHA staff address the more detailed comments below.

Comment 2. OEHHA's chronic inhalation REL for arsenic is based primarily on a single publication by Nagymajtenyi et al. that describes the results of an inhalation developmental toxicity study in mice exposed to arsenic trioxide (As_2O_3). In this study, pregnant mice were exposed to trivalent inorganic arsenic (As,O) at concentrations of 28.5, 2.9 or 0.26 mg/m^3, which equates to total arsenic concentrations of 21.6, 2.2 or 0.2 mg/m^3 as arsenic. Even if one discounts maternal toxicity and considers delayed ossification as a fetal malformation, adverse effects were seen at the highest dose level only:

As_2O_3, mg/m^3 Exposure	As mg/m^3 Exposure	Fetal effect reported
28.5	21.6	29% (fetal body weight; delayed ossification)
2.9	2.2	9% (fetal body weight)
0.6	0.2	3% (fetal body weight)

Only the effects observed at the highest dose have biological significance and of those, only reduced fetal body weight can be viewed as meaningful because the recoverability of the delay in bone maturation was not assessed in the study. Weight decrements of 9% and certainly 3% are not biologically meaningful.

OEHHA interpreted the Nagymajtenyi data as demonstrative of an adverse effect at each dose level; accordingly, a No-Observed-Adverse-Effect-Level (NOAEL) was not considered in the interpretation of the study data. Also, well-known differences in toxicity among arsenic compounds based on the chemical oxidation state and differences in animal metabolism of arsenic were not taken into account by OEHHA in the proposed arsenic chronic inhalation REL.

Response. The weight decrements of 9.9% and 3% were both statistically significant. A weight difference of 9.9% may be biologically meaningful in a very small, developing animal. The weight decrement of 3% might not be biologically significant if the loss is generally distributed. If it were specific, it could be. In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. (Hogue CJ, Buehler JW, Strauss LT, Smith JC. Overview of the National Infant Mortality Surveillance (NIMS) project--design, methods, results. Public Health Rep 1987 Mar-Apr;102(2):126-138; Rees DC, Hattis D. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third Edition. AW Hayes, editor. New York: Raven, 1994). In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant.

In order to investigate the effects of environmental arsenic on human reproduction, Ihrig et al. (1998) conducted a hospital-based case-control study of stillbirths in a central Texas community. (Ihrig MM, Shalat SL, Baynes C. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiology 1998 May;9(3):290-294). The community included a facility with a more than 60 year history of producing arsenic-based agricultural products. Data were collected on 119 stillbirth cases and 267 controls (randomly selected from healthy live births at the hospital, matched for year of birth). Arsenic exposure levels were estimated from airborne emission estimates and an atmospheric dispersion model; the results were linked to a geographical information system (GIS) database. Exposure was linked to residence address at time of delivery. A conditional logistic regression model was fit to the data including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. The prevalence odds ratio (OR) for stillbirths observed for Hispanics in the high-exposure group (>0.1 $\mu g/m^3$ As) was 8.4 (95% confidence interval = 1.4-50.1). Based on these statistically significant results in people, the proposed REL of 0.03 $\mu g/m^3$ for arsenic does not appear to be too conservative

since LOAEL/NOAEL and intraspecies UFs would need to be applied to the human data to develop a chronic REL.

Comment 3. According to Garcia-Vargas and Cebrian (in Toxicology of Metals, 1996) and the US EPA (EPA, 1984), inorganic trivalent arsenic is generally regarded as being more acutely toxic than inorganic pentavalent arsenic. According to Marie Vahter (in Arsenic Exposure and Health, 1994), a prominent and perhaps leading authority on arsenic metabolism: The methylation of inorganic arsenic in mammals functions as a detoxification mechanism. The methylated metabolites are less acutely toxic than inorganic arsenic. They are also less reactive with tissue components and faster excreted in urine than is inorganic arsenic.

The inorganic arsenic, especially As(III), is the main form of arsenic interacting with tissue constituents. This means that factors influencing the methylation (of arsenic) may influence arsenic toxicity.

Vahter presents comparative metabolism data that show mice methylate inorganic arsenite (trivalent arsenic) about 3.6 times more efficiently than humans for a given dose of arsenic (Vahter, 1994).

Response. Comment noted. OEHHA acknowledges that there are differences in metabolism and in toxicity between trivalent and pentavalent arsenic. However, arsenic emissions are not speciated in the Hot Spots program. Thus we prefer to use data on the more toxic species.

Comment 4. OEHHA should have considered these facts in proposing a chronic REL for arsenic. Using these facts, the derivation of a chronic inhalation REL for arsenic would be:

LOAEL	2.2 mg/m^3 as arsenic (Nagymajtenyi, 1985)
NOAEL	0.2 mg/m^3 as arsenic (Nagymaitenyi, 1985)
LOAEL Uncertainty Factor	1
Interspecies Uncertainty Factor	3.6
Intraspecies Uncertainty Factor	10
Cumulative Uncertainty Factor	36

Inhalation Reference Exposure Level 0.2 mg/m^3 x 36 = 7.2 mg/m^3

OEHHA should revise the chronic inhalation REL for arsenic to take into account the points presented above and repropose a chronic inhalation REL of 7.2 mg/m^3 total arsenic. An REL of 7.2 mg/m^3 takes into account relevant inhalation toxicity data for arsenic compounds and contains a safety factor in addition to those listed by California. In OEHHA's calculations, the REL is based on trivalent inorganic arsenic toxicity data and assumes that all exposure to arsenic is to the trivalent form - the most toxic form of inorganic arsenic. Real-world exposures are not limited exclusively to trivalent arsenic, but include exposure to the less toxic forms as well. Thus, calculating the chronic inhalation REL using the

above-referenced conservative assumptions will protect against adverse effects from trivalent arsenic, which also overprotects against exposure to all other forms of arsenic.

Response. The commentator appears to have confused calculation of a REL with calculation of a Margin of Exposure. The chronic REL of 7.2 mg/m^3 proposed in the comment is 720 times the ACGIH TLV for arsenic of 0.01 mg/m^3. The 50 minute LC_{50} for arsenic in mice (acute lethality) is 99 mg/m^3, only 12x the chronic REL proposed by the commentator. If the suggested NOAEL of 0.22 mg/m^3 is divided by the suggested cumulative UF of 36, a tentative REL of 5.5 $\mu g/m^3$ is estimated. However, OEHHA staff do not agree with the choice of the NOAEL for the study. In addition the suggested interspecies UF would require special consideration.

In the absence of a superior study in the peer-reviewed literature on which to base a REL, the chronic inhalation REL proposed for arsenic is still 0.03 $\mu g/m^3$

Comment 5. OEHHA has reestablished, in addition to an inhalation REL, an oral REL for arsenic. As a threshold matter, the Task Force objects to the inclusion of a chronic oral REL in the guidelines at all, since the purpose of the guidelines is to derive risk levels for airborne toxic contaminants. These risk levels, in turn, will be used to characterize the hazards associated with routine industrial releases of chemicals to the atmosphere. Nothing in the "Hot Spots" program requires or authorizes OEHHA to develop oral RELs. Even if OEHHA was otherwise authorized to develop oral RELs, the chronic oral REL for arsenic is based exclusively on the US EPA Oral Reference Dose (RfD) for arsenic in drinking water. The US EPA RfD for arsenic is based on the Taiwanese drinking water studies published by Tseng (1968,1977). These studies have been the subject of much scientific review and are not without criticism as to methodology (analytical chemistry and epidemiology) and applicability to US populations. This criticism is presented by Brown (1994, 1996) and suggests that reliance on the Taiwanese studies to establish US regulatory limits for arsenic exposure is not appropriate because of the necessity to extrapolate from high-dose exposures to low-dose exposures and across cultural lines.

Specifically, Brown has stated that a more detailed exposure classification than previously used is needed for reliable descriptions of cancer mortality in Taiwanese villagers and arsenic concentrations in drinking water. Brown also states that the cancer mortality dose-response curve for the Taiwanese cohorts is nonlinear at the low-dose end (arsenic drinking water concentrations of <0.05mg/L) suggesting that there may be a low-dose threshold for the observation of human cancer. US EPA surveys of US drinking water have shown that 95% of the samples collected and analyzed have arsenic levels of less than 0.005mg/L; the highest value recorded was 0.082mg/L (Borum and Abernathy, 1994). Finally, Brown has pointed out evidence that arsenic may be adequately methylated and detoxified at drinking water concentrations below 0.05mg/L. The adverse health risks, particularly cancer, ascribed to ingestion of arsenic in drinking water may be inaccurately stated for US populations when based on the Taiwanese studies. Accordingly, OEHHA's reliance on the Tseng studies (via US EPA) is inappropriate for establishing a chronic oral REL, even if oral RELs were authorized under the "Hot Spots" program.

Response. The Air Toxics Hot Spots risk assessments of facilities include an analysis of all potential pathways of exposure. Oral RELs are needed in the Hot Spots program to do multipathway analysis of chemicals that are emitted as particulates. Not only are these materials inhaled but they also are deposited on and ingested from home-grown crops and from soil, and can be absorbed following dermal contact with contaminated surfaces. Multipathway analyses have been part of the Hot Spots program since its inception. Proper parameters to use are discussed in the 1993 CAPCOA Guidelines and in the draft Exposure Assessment and Stochastic Analysis Technical Support Document. USEPA RfDs are being used as oral RELs. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfDs as oral RELs was one action that OEHHA took to address the RAAC recommendations and to implement the Executive Order.

Comments on the deficiencies in the RfD for arsenic should be directed to USEPA.

Chemical Manufacturers Association (CMA) - Carbon Disulfide Panel

Comments on the chronic REL for **carbon disulfide** were made by the CMA Carbon Disulfide Panel. OEHHA proposes use of the US EPA Reference Concentration of 700 $\mu g/m^3$, based on effects on the nervous system

Comment 1. These comments address the chronic toxicity summary and proposed reference exposure level (REL) for carbon disulfide presented in the "Air Toxics Hot Spots Program Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels" (Guidelines). In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including carbon disulfide.

OEHHA should not characterize the database supporting the REL as "limited." The carbon disulfide database is robust, as other agencies reviewing it have found. In its toxicity summary, OEHHA states that one major uncertainty in the REL is the "limited nature of health effects studies conducted. The database supporting the REL cannot fairly be characterized as "limited," however, given the numerous epidemiological and animal studies of carbon disulfide‘s inhalation effects. The findings of other agencies that have reviewed this substantial body of data support this conclusion. For example, in proposing a test rule under Section 4 of the Toxic Substances Control Act (TSCA) for chemicals listed as hazardous air pollutants (HAPs) under the federal Clean Air Act (CAA), EPA decided not to pursue toxicity testing for carbon disulfide. EPA stated unequivocally that carbon disulfide has "a large inhalation toxicology database." As another example, the Toxicological Profile prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) reviewed the numerous animal and human studies conducted with carbon disulfide. With respect to neurological effects, for example, the Toxicological Profile discussed occupational epidemiological studies in a variety of settings and summarized a number of animal studies. With respect to other endpoints, the Toxicological Profile stated that human data provide information on acute and chronic effects from inhalation exposure to carbon disulfide, as well as immunologic, neurologic, developmental, and reproductive effects. Animal inhalation data are available on intermediate systemic, neurologic, developmental, and reproductive effects.

Moreover, the key epidemiological study underlying the proposed REL, conducted by Johnson et al. (1983), has been subject to both external and internal peer review, and EPA concluded in its Integrated Risk Information System (IRIS) that it is "well designed and conducted, uses adequate numbers of subjects, and is well supported by other occupational studies examining the same effect. Because of its greater confidence in human data, ATSDR relied on this study to establish a minimum risk level (MRL) for carbon disulfide. In light of the large body of human and animal data on carbon disulfide's inhalation effects, and given the review of and reliance on by other agencies of the key study on which the REL is based, OEHHA should delete the reference to the "limited nature" of health effects studies conducted.

Response. OEHHA has reexamined the description of the quality of the health effects database and agrees with the commentator that the term "limited" is not warranted. The text has been changed to reflect this. However, the database for this chemical also can not be viewed as exhaustive. As noted by US EPA, significant areas of uncertainty include the exposure histories of workers examined in the key study and the possibility of developmental effects in humans.

Comment 2. OEHHA should eliminate the use of the modifying factor of 3. This factor is not needed, given carbon disulfide's extensive database. The Panel also believes that no uncertainty or modifying factor should be applied to address any purported deficiencies in the toxicological database for carbon disulfide. OEHHA does not discuss why it has accepted EPA's 3-fold modifying factor for database deficiencies, or why any modifying factor at all is appropriate. Indeed, OEHHA itself has expressed skepticism about the propriety of any modifying factor to address purported database deficiencies. When deriving chronic RELs using its own Guidelines, OEHHA does not employ a modifying factor to address database weaknesses. Given the extensive toxicological database on carbon disulfide's inhalation effects, such an uncertainty factor is particularly inappropriate here.

Response. As a result of both scientific judgement and legislative mandate, OEHHA considers US EPA an authoritative scientific body whose prior scientific assessments carry great weight. Furthermore, OEHHA has been directed to harmonize with US EPA as regards guidance levels for exposure of the general public to chemicals by both the Risk Assessment Advisory Committee (RAAC) and Governor's Executive Order W-137-96. Minor differences in scientific conclusions between two agencies such as OEHHA and US EPA are likely to arise, but such differences add a burden to those attempting to address two differing sets of recommendations. Thus, unless the difference of opinion is substantial, OEHHA will incorporate US EPA guidance into its programs. This does lead to the result that risk assessment recommendations for two different chemicals may be based on slightly different assumptions, as noted by the commentator.

Comment 3. OEHHA should revise the chronic toxicity summary for carbon disulfide to provide a more balanced and accurate summary of the scientific database on carbon disulfide's chronic health effects. The Panel believes that the toxicity summary provided in EPA's recent Sector Notebook for the Plastic, Resin and Manmade Fiber Industry provides such a summary and urges OEHHA to adopt that discussion.

Response. The health effects reviews presented in the chronic reference exposure level document are not intended to be exhaustive but rather to highlight the most important scientific data. Information on health effects of and risk assessment guidelines for more than 100 chemicals are presented in the document, which totals more than 700 pages in length. In addition, for chemicals such as carbon disulfide which have previously been addressed by USEPA in its Reference Concentration (RfC) program, OEHHA gives considerable weight to

US EPA's position as a recognized authoritative body and in most cases has proposed adopting the USEPA RfC.

Comment 4. OEHHA's summary of "effects of human exposure from carbon disulfide" is inaccurate and misleading. OEHHA's chronic toxicity summary for carbon disulfide fails to provide a balanced or accurate summary of the scientific database on carbon disulfide's chronic health effects. For example, the summary of the section entitled "Effects of Human Exposure" states:

"[A] primary target of carbon disulfide (CS_2) toxicity is the nervous system. The major neurotoxic action of carbon disulfide is the development of mental disturbances, such as change of personality, irritability, and forgetfulness, often with accompanying neurophysiological and neuropathology changes after prolonged exposure. Alterations in behavioral indices have been historically associated with high levels of CS_2, often in the excess of 20 ppm."

OEHHA's summary is misleading in not stating clearly that it is only high levels of exposure, well in excess of current regulatory levels, that may result in such effects. EPA's recent Sector Notebook for the Plastic, Resin and Manmade Fiber Industry (Sector Notebook) more accurately states that long-term (chronic) exposure to high levels [of carbon disulfide] in excess of regulatory standards may result in peripheral nerve damage (involving the nerves that control feet, legs, hands, and arms) and cardiovascular effects. The Panel thus urges OEHHA to revise the summary, and in this regard, the Panel urges OEHHA to consider adopting the Sector Notebook summary.

Response. The examples cited do not indicate the OEHHA summary was inaccurate. The current TLV is 10 mg/m^3. However, the sections have been reviewed in light of the comment and changes made in the presentation to better clarify the type of exposures that have been associated with observable adverse health effects.

Comment 5. OEHHA's summary of carbon disulfide's reproductive toxicity is similarly misleading and inaccurate. With respect to this end-point, OEHHA says simply that "carbon disulfide causes reproductive toxicity in both males and females. This statement fails, however, to reflect accurately the robust database on carbon disulfide's potential reproductive toxicity and the scientific uncertainty regarding the no effect level that should be used based on these studies. Although there are substantial data bearing on carbon disulfide's potential reproductive effects, as discussed above, there remains substantial uncertainty about the significance of these effects and the no effect level that can be derived from these studies. This uncertainty should be reflected in any statements regarding carbon disulfide's potential reproductive toxicity.

Similarly, the EPA Sector Notebook notes that "[A] few studies contend that chronic exposure may also result in potential reproductive effects. The Panel urges OEHHA to revise its summary and in this regard to consider adopting the Sector Notebook summary,

which accurately reflects the scientific uncertainty underlying carbon disulfide's potential reproduction effects.

Response. Again, the examples cited do not demonstrate that the OEHHA summary was inaccurate. Similarly, however, the sections have been reviewed in response to the comment and changes made in the chapter to better clarify the evidence for reproductive toxicity from carbon disulfide exposures.

Comment 6. The Panel additionally urges OEHHA to review and rely on the following two recent publications on carbon disulfide's potential toxicity, which are appended as Attachments 1 and 2:

Price, B., *et al.* (1996). A Benchmark Concentration for Carbon Disulfide: Analysis of the NIOSH Carbon Disulfide Exposure Database. *Regulatory Toxicol. Pharmacol.* 24:171-176.

Price, B., *et al.* (1997). A Review of Carbon Disulfide Exposure Data and the Association between Carbon Disulfide Exposure and Ischemic Heart Disease Mortality. *Regulatory Toxicol. Pharmacol.* 26:119-128.

Response. The two papers cited have been reviewed and their findings have been summarized in the revised toxicity summary for carbon disulfide.

Chemical Manufacturers Association – Cresols Panel

Comments on the chronic REL for **cresols** were made by the Cresols Panel of the CMA in a letter from Courtney M. Price dated January 29, 1998. The members of the Cresols Panel are Concord Chemical Company, CRI Fine Chemicals, Dakota Gasification Company, General Electric Company, Merichem Company, Mitsui Petrochemicals (America) Ltd., PMC Specialties Group, Inc., and Sumitomo Chemical Americas, Inc. In the draft TSD OEHHA proposed a chronic REL of 4 $\mu g/m^3$ based on the Uzhdavini et al. (1972) discontinuous, 4 month inhalation study in rats which resulted in alterations in bone marrow cellularity.

Comment 1. As discussed in the appended comments, the Panel urges OEHHA to withdraw its draft toxicity summary and proposed reference exposure level (REL for cresol mixtures (cresols). The studies on which OEHHA has relied cannot support a REL, and cresols do not merit priority attention for evaluation or regulation. These comments address the chronic toxicity summary and proposed inhalation reference exposure level (REL) of 4 $\mu g/m^3$ for cresol mixtures (cresols) presented in the Guidelines. In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including cresols.

The Panel urges OEHHA to withdraw its draft toxicity summary and proposed REL for cresols for the following reasons:

- The proposed REL for cresols is based on a single, poorly reported study that does not comply with Good Laboratory Practices, and other data do not support the findings of that study or the proposed REL.

- In any event, cresols do not merit priority attention for assessment or regulation because they are present in the ambient air only in very small concentrations. Available data show very low workplace and general population exposure concentrations - well below those that implicate health concerns.

Response. The detailed comments are individually addressed below.

Comment 2. The Uzhdavini et al. and Kurliandskii et al. studies are of insufficient quality to derive or support a REL. OEHHA derived its REL for cresols from a Russian inhalation study conducted with rats in 1972. OEHHA refers to a second Russian study of the same era as providing support for the REL. Neither study, however, is of sufficient quality to derive or support a REL and OEHHA should, therefore, withdraw the proposed REL.

The Uzhdavini et. al (1972) study is of insufficient quality to support a REL. OEHHA's proposed chronic toxicity REL for cresols is based on the Uzhdavini et al. (1972) observations regarding o-cresol exposure in rats. Uzhdavini et al. reported that rats exposed to 9 mg/m^3 o-cresol by inhalation showed an increase in white blood cells, and a statistically

significant change in the leuko-to-erythmo ratio in the bone marrow. The authors also reported an extension of hexobarbital narcosis duration in treated animals. The Uzhdavini et al. study - which was performed more than 25 years ago in the then Soviet Union under conditions that do not approximate current scientific methods and standards - cannot be used to support a REL. The study findings are difficult to interpret for a variety of reasons. The study parameters reported are vague; the specific data are not included (only summary statements) and the conclusions relate only to imprecisely measured concentrations of "vapor/ aerosol." Additionally, the published study report does not describe chamber generation methods, precise analytical methods, exposure details, animal characteristics (weight, age, sex, strain), observational information (times, frequency, duration, specific conditions examined), or specific experimental conditions. From the summary nature of the information presented and the absence of information about the study design, a dose-response relationship cannot be determined. This study would be judged inadequate under GLP requirements for use in determining potential risk to humans. Relying on the study clearly contravenes OEHHA's own Guidelines, which state unequivocally that any animal data supporting a REL "should have a clear rationale and protocol, use [GLP] Standards, and use appropriate analysis methods.

With respect to the specific findings at issue, the results - even if credited - do not indicate adverse effects from exposure to cresols. For example, while white blood cell counts reportedly were elevated in some treated animals, these effects were observed in male animals only, and blood counts returned to normal after cessation of exposure. The reversibility of the effects, and the fact that effects were seen in male animals only, suggests that they were neither serious nor clearly associated with exposure to cresols. Moreover, the authors report with respect to this study that no changes were found in the leuko-erythmo ratio in the second species tested - guinea pigs. Additionally, Uzhdavini reported that:

- the vapor pressure of cresols was so low that acute inhalation toxicity could not be induced with vapor alone, only with a mixed vapor aerosol of cresols could adverse effects be produced;
- nonspecific irritation was produced in the respiratory tract by high concentrations of cresols aerosols;
- in repeated exposure experiments, cresols did not exhibit cumulative toxicity; and
- in rats, where recovery studies were made, recovery from cresols effects (blood parameters) was seen.

Thus, the Uzhdavini et al. findings simply cannot support OEHHA's proposed REL. Indeed, other agencies have discounted the Uzhdavini et al. (1972) study observations regarding o-cresol exposure in rats, as well as the additional limited information reported in the Uzhdavini study regarding effects from inhalation exposure to o-cresol in several species, including humans. [For example, the study reported a human threshold for respiratory irritation (dryness, constriction in the nose, irritation of the throat, a taste in the mouth) of 6 mg/m^3 (1.4 ppm) Uzhdavini et al. (1972).] The American Conference of Governmental Industrial Hygienists (ACGIH) considered the Uzhdavini et al. study, but elected not to rely on it to establish its 8-hour threshold limit value (TLV) for exposure to cresols of 22 mg/m^3 (5 ppm). Similarly, the National Institute for Occupational Safety and Health (NIOSH) rejected

the Uzhdavini data when it recommended an "immediately dangerous to life or health" (IDLH) population exposure limit of 1,123 mg/m^3 (250 ppm), and a number of countries, in addition to the United States, have established inhalation exposure levels for cresols at 22 mg/m^3.

ACGIH (1991) (Documentation of the Threshold Limit Values and Biological Exposure Indices (1991) at 341) noted that eight of ten human subjects exposed to 1.4 ppm of o-cresol in the Uzhdavini et al. study complained of upper respiratory tract irritation, but criticized the study because the minimal exposure levels and duration associated with the irritation had not been reliably documented. The U.S. Occupational Safety and Health Administration (OSHA) also has established a time-weighted average (TWA) for all cresol isomers of 5 ppm (29 C.F.R. Part 1910).

Moreover, the U.S. Environmental Protection Agency's (EPA) Health Effects Assessment for Cresols, on which OEHHA also relied in drafting the toxicity summary, has criticized the two Russian studies. Because of the absence of detail regarding the severity or type of changes reported, EPA concluded that "it would be imprudent to use either of these studies to derive a value for an AIS [Acceptable Intake Subchronic] without further information. EPA also noted that NIOSH had concluded that the two Russian studies "were considered inadequate as a result of the incomplete presentation of experimental design and the confusing presentation of results.

Given the many defects and omissions in the Uzhdavini et al. study discussed above, the results cannot be deemed reliable for predicting the chronic health effects potentially associated with exposure to cresols. It is not surprising that the study has been accorded little weight in decision-making by regulatory agencies in the United States and elsewhere. OEHHA likewise should not rely on the results obtained in the Uzhdavini et al. study to reach conclusions about cresols, potential chronic effects, or to derive a REL.

Response. OEHHA originally selected the Uzhdavini et al. (1972) study in order to base as many chronic RELs as possible on inhalation data. The study reports unusual endpoints by today's standards. However, the study had been reported on by both NIOSH and ATSDR in their documents. Therefore the study was selected as the basis for the REL despite its shortcomings. On reconsideration we have decided to base the chronic REL on the USEPA RfD. The U.S. EPA RfD was based on 90 day animal toxicity studies done by USEPA and reported in 1986.

The commentator states: "The reversibility of the effects, and the fact that effects were seen in male animals only, suggests that they were neither serious nor clearly associated with exposure to cresols. Moreover, the authors report with respect to this study that no changes were found in the leuko-erythmo ratio in the second species tested - guinea pigs." OEHHA staff do not agree that these are useful criteria for addressing toxicity results. Elevated carboxyhemoglobin levels are both potentially adverse and reversible. Certain chemicals have the propensity to be more toxic to, or only toxic to, one sex versus the other. Limonene and dichlorobenzene cause kidney tumors only in rats and only in male rats. Other agents may cause adverse effects in only one species or strain or not cause adverse effects in

only one species. Benzo(a)pyrene is highly carcinogenic in all species and strains except DBA2 mice. Thalidomide is teratogenic except in rabbits. Even the lethal level of a chemical can vary among species. The LD_{50} of TCDD varies widely (guinea pig = 0.001-0.002 mg/kg; male rat = 0.022 mg/kg; female rat = 0.045 mg/kg; mouse = 0.114 mg/kg; hamster = 1.157 mg/kg).

Comment 3. The Kurliandskii et al. (1975) study is of insufficient quality to support a REL. Although OEHHA did not rely on the Kurliandskii et al. (1975) study to derive the REL, it cited the study as further support for the REL and as evidence that chronic adverse health effects may occur in animals exposed to cresols at levels lower than those reported by Uzhdavini et al.

The Kurliandskii et al. study, however, suffers from the same inadequacies that plague the Uzhdavini et al. study. Among other methodological defects, the study lacks information necessary to interpret the findings; fails to report how many hours per day animals were exposed; and fails to report whether the exposure was daily. NIOSH found the findings difficult to assess "because of unexplained differences in the experimental results" and "unanswered questions concerning the procedures used to measure central nervous system function." Like the Uzhdavini et al. study discussed above, the Kurliandskii study also fails to comply with fundamental GLPs and, pursuant to the OEHHA Guidelines, is thus inadequate to derive or support a REL.

Response. OEHHA agrees that the Kurliandskii et al. study also has shortcomings. In addition it indicates that 0.05 mg/m^3 is a LOAEL and 0.0052 mg/m^3 is a NOAEL for some endpoints, whereas 9 mg/m^3 was considered a LOAEL in the Uzhdavini et al. study.

Comment 4. Other data show no adverse effects from exposure to cresols. Not only do the Uzhdavini et al. and Kurliandskii et al. studies not support a REL, but other data show no adverse effects following inhalation exposure to cresols. These include:

- Mellon Institute of Industrial Research (1949): In this acute toxicity study conducted with rats, animals were exposed to a saturated vapor of m-cresol on a single day for eight hours (saturated vapor concentration of m-cresol at room temperature is estimated to be 0.3 mg/L (300 mg/m^3 or 68.2 ppm)). No effects were observed, except that one rat failed to gain weight.

- CONOCO (1975): Rats exposed to a single 6-hour exposure of o-cresol vapor by inhalation at doses up to 4,500 ppm (19,800 mg/m^3 or 19,800,000 mg/L) did not experience mortality or clinical signs of toxicity other than eye irritation, which cleared up within 24 hours after exposure.

Similarly, a number of oral studies conducted with cresols show none of the blood chemistry changes reported in the Uzhdavini et al. (1972) study. These studies include:

- Hornshaw et al. (1986) Spleen weight and white blood cell (WBC) count were unaffected when o-cresol was administered in feed at doses up to 400-720 mg/kg/day in ferrets and 320-480 mg/kg/day in mink. Similarly, no effect was seen on spleen weight or WBC count in a reproduction study where mink were administered 105-190 mg/kg/day of o-cresol in feed for six months.

- Microbiological Associates, Inc. (1988a, b, c): No mortality or illness due to infections were seen in mice or rats receiving either o-cresol or m/p-cresol mixture in feed for 90 days at concentrations up to 20,000 ppm or 30,000 ppm (for mice and rats, respectively). Hematology parameters including WBCs, lymphocytes, monocytes, and eosinophils were unremarkable at all dose concentrations. In mice, changes in spleen or thymus were observed at 15,000 and 30,000 ppm, but there were no changes observed following gross or microscopic examination.

- Bushy Run Research Center (BRRC) (1989a, b, c). Two-generation reproduction studies were conducted by oral gavage in rats with each cresol isomer. The dose levels used achieved systemic toxicity in adult animals (lethality). First and second generation parents were necropsied, and selected organs, tissues, and all gross lesions were examined. The adrenal gland, spleen, mandibular and mesenteric lymph nodes, pituitary, thyroid, and thymus region were among the tissues examined. The study pathologist reported no compound-related effects in any of these tissues for any of the cresol isomers. [BRRC (1989a). Two-generation reproduction study of o-cresol (CAS No. 95-48-7) administered by gavage to Sprague-Dawley (CD) rats. Project Report 51-614. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D.C.; BRRC (1989b). Two-generation reproduction study of p-cresol (CAS No. 106-44-5) administered by gavage to Sprague-Dawley (CD) rats. Project Report 52-512. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D.C.; BRRC (1989c). Two-generation reproduction study of m-cresol (CAS No. 108-39-4) administered by gavage to Sprague-Dawley (CD) rats. Project Report 51-634. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D. C. These data were submitted to EPA by Union Carbide. See Union Carbide Corporation, "Two-generation reproduction studies on ortho-, meta-, and para-cresols administered by gavage to Sprague-Dawley (CD) rats (final reports) with attachments and cover letter dated 12-06-89." TSCA 4 submission 40-8960311, microfiche number OTS0529224. Washington, D.C. OPPT, U.S. EPA (Nov. 9, 1989).]

- U.S. National Toxicology Program (NTP) (1992): In these studies, groups of mice and rats were administered oral doses of cresol isomers and mixture for 13 weeks. A full battery of hematology parameters were evaluated. No blood alterations were seen in rats exposed to o-cresol or a m/p-cresol mixture up to 30,000 ppm. Mice exposed to 20,000 ppm of o-cresol also displayed no hematological changes. Mice exposed to up to 10,000 ppm m/p-cresol showed a mild decrease in hemoglobin at study termination, but no blood changes similar to those reported by Uzhdavini. The author of the NTP study report concluded that the hematology changes observed in mice following exposure to m/p cresol were "largely unremarkable."

Response. The commentator presents 2 acute inhalation studies of 8 and 6 hours (Mellon and CONOCO, respectively), which showed no adverse effects, and several oral studies that indicate that cresols do not affect hematology parameters, which the Uzhdavini et al. study (1972) claimed cresols affect. As stated above, due to the shortcomings in the Russian studies OEHHA has decided to base the chronic REL on the U.S. EPA RfD.

Comment 5. Cresols are present in the ambient air at very low concentrations, and do not merit priority consideration for evaluation or regulation. The California Toxic Air Contaminants Program (Program) provides that, in evaluating the health effects of toxic air contaminants, OEHHA "shall give priority to the evaluation and regulation of substances based on factors related to the risk of harm to public health, amount or potential amount of emissions, manner of, and exposure to, usage of the substance in California, persistence in the atmosphere, and ambient concentrations in the community." Because cresols concentrations in the ambient air are very low - well below those that implicate health concerns -cresols merit neither evaluation nor regulatory action under the Program.

Response. ARB estimates that at least 12,000 pounds of cresols are released annually into California air. While statewide ambient concentrations are probably low overall, the Hot Spots program addresses ambient concentrations around facilities that are potential "Hot Spots" for emissions of cresols.

Comment 6. Available monitoring data show very low cresols ambient air concentrations Available data show very low cresols concentrations in the atmosphere, even near manufacturing facilities. Monitoring data include:

- EPA 1982 Survey: In a survey of volatile organic compounds (VOCS) found in the atmosphere commissioned by EPA, cresols were found near source-dominated sites (adjacent to chemical plants) at levels ranging from 0.1 to 30 parts per billion (ppb), with a median of 1.6 ppb. [Brodzinsky, R. and Singh H. (1982). Volatile organic Compounds in the Atmosphere: An Assessment of Available Data, EPA Office of Research and Development. Research Triangle Park, North Carolina]

- EPA's Hazardous Substances Databank Entries: Entries for cresols note that o-cresol was detected near a phenolic resin factory in Japan at a maximum concentration of 40 ppba8 ~ and that m-cresol and p-cresol were not detected at all in air samples taken in both urban and rural areas of western Colorado and Utah.

- Gordon (1976): On behalf of EPA, Gordon (1976) estimated cresols air concentrations at a hypothetical facility producing 80 million pounds of cresols annually and emitting 160,000 pounds of cresols per year - an amount greater than actual emissions reported by any one facility for 1994. The estimated air concentration 500 meters downwind of the hypothetical plant was 0.163 mg/m3 or 37 ppb - an amount well below the OSHA, ACGIH, and NIOSH limits for full day occupational exposures. Thus, the population

living near a major source is at a very low risk of exposure from industrial cresols emissions.

- Merichem Data: Merichem Company modeled cresols concentrations at its Houston facility in 1991. At 2,000 feet from the facility, at the fenceline, the concentration of cresol isomers was 38 pg/m^3. This is far below the OSHA, ACGIH, and NIOSH worker exposure limits (10,000 - 22,000 pg/m^3).

- ATSDR Toxicological Profile: In its 1992 Toxicological Profile discussion of general population exposure to cresols, the Agency for Toxic Substances and Disease Registry (ATSDR) concluded that "[m]onitoring data have not shown cresols to be widely occurring. .The median air concentration of o-cresol at source-dominated sites is 0.359 ppb for 32 samples."

The Program requires consideration of exposure data (including emissions data and data on estimated actual exposure) when selecting chemical substances for priority for evaluation and regulation. In light of their low documented emissions and exposure potential, cresols do not merit priority consideration for evaluation or regulation.

Response. It is encouraging that cresols are not wide-spread toxic air contaminants like benzene or butadiene. However, as stated above, the Hot Spots program addresses ambient concentrations around facilities that may be Hot Spots for emissions of cresols. Also cresols are not being given priority consideration.

Comment 7. Modeling data show that even under extreme conditions, highly unlikely to occur, exposure levels are very low. Accidental release modeling shows that even under extreme conditions, cresol vapors would quickly disperse to levels below regulatory levels of concern. Dakota Gasification Company modeled two accident scenarios using the ARCHIE computer program and assuming EPA's worst-case weather conditions of 68° F and 3.4 miles per hour wind speed. The first scenario modeled was a 100,000 gallon tank rupturing and 879,452 pounds of cresols spilling out within one minute. The cresols product temperature was modeled at 68°F. The model predicted that peak cresols concentrations at 1,536 feet (468 meters) from the tank would be 4 ppm (18 mg/m^3), which is below the previously established OSHA and ACGIH 8-hour average limit of 22 mg/m^3. At 2,333 feet (711 meters), the concentration would be only 2.1 ppm (9.3 mg/m^3), less than the NIOSH recommended 10-hour average limit of 10 mg/m^3.

The second scenario assumed that a distillation column failed instantaneously, releasing 75,762 pounds of cresols at 365°F. Modeled concentrations from this extreme scenario were 9.6 ppm (42 mg/m^3) at 2,194 feet (669 meters), which is well below the NIOSH IDLH of 250 ppm. By 3,450 feet (1,052 meters), the concentration is less than 5 ppm, and by 5,962 feet (1,817 meters), the modeled concentration is 2 ppm (8.8 mg/m^3), which is below the NIOSH recommended limit.

These modeled accidental release scenarios represent conditions under which the highest air concentrations of cresols could reasonably be expected (that is, large amounts released within a short interval of time during worst-case weather conditions) . Even under these extreme conditions, the modeled air concentrations of cresols in the near vicinity of the facility - concentrations which would persist for only a brief period of time - are on the order of concentrations which are considered acceptable for occupational exposure, i.e., acceptable for 40 hours per week.

The amount of cresols modeled to be released in the second scenario - 75,762 pounds - is more than the amount reported by most facilities as their annual emission quantity. The amount modeled as released in the first scenario - 879,452 pounds far exceeds the total reported cresols air emissions for all cresols manufacturing facilities for 1994. Clearly, then, cresols air concentrations in the vicinity of emitting facilities due to normal operations - that is, concentrations due to emissions of much smaller quantities over an extended period of time - are low, demonstrating that cresols should not be given priority consideration for evaluation or regulation under the Act.

Response. Comment noted. Again cresols are listed as listed Hot Spots chemicals. OEHHA staff attempted to develop as many health guidance values for Hot Spots chemicals as it could find data for. Since the industrial emissions of cresols are low, the ground level concentrations should be well below the chronic REL.

Comment 8. Cresols' physical characteristics ensure low concentrations in the ambient air. The physical characteristics of cresols help explain the very low concentrations found in the ambient air. Cresols air concentrations are limited by the short lifetime of cresols in the atmosphere. During the day, cresols are removed by reaction with hydroxyl radicals. At night, nitrate radical reactions predominate. ATSDR reports cresols half-lives (calculated from kinetic data) as being less than ten minutes at night and less than ten hours during the day. As ATSDR summarized, "cresols have a short residence time in both day- and night-time air; despite continual releases of cresols to the atmosphere, levels are probably low."

Because cresols air concentrations are so low and cresols so rapidly degrade when emitted, the Panel does not believe that cresols in the air present general population exposure concerns. Indeed, EPA stated that it "has also determined that cresols released to the atmosphere are not expected to create an exposure problem." EPA further stated: "Cresols are not expected to persist in the atmosphere because (1) cresols have low estimated half-lives of less than 1 day; (2) they are sensitive to photolysis; and (3) the water solubility of cresols may be expected to cause transport from the atmosphere to the soil or aqueous environment."

Accordingly, the available data show that exposure to cresols is uniformly low, that cresols have a low potential for "persistence in the atmosphere" within the meaning of the Act, and that cresols should not, therefore, be considered a priority for evaluation and regulation.

Response. OEHHA staff attempted to develop as many health guidance values for listed Hot Spots chemicals as it could find data for. Some chemicals will be of more concern than others. Cresols may well be of lesser concern than most listed compounds. Otherwise the commentator encourages OEHHA not to develop a chronic inhalation REL for cresols because there is not a problem. But OEHHA's way of addressing the situation is to develop a chronic inhalation REL and then compare it with ambient levels and with modeled levels around Hot Spots facilities to determine if the levels are above or below the REL.

Comment 9. A majority of the general population exposure is not the result of manufacturing operations, but naturally occurring and other sources. Cresols are ubiquitous in the environment. The vast majority of cresols found in the environment are derived from natural sources. Cresols are formed as metabolites of microbial activity and are excreted in the urine of mammals, including humans. They are present in the lipids of a number of different plant species and are found in foods such as tomatoes, cooked asparagus, cheese, butter, oil, red wine, coffee, and black tea. The Panel has estimated that releases from naturally-occurring sources of cresols are at least 15 million pounds a year - nearly an order of magnitude greater than the 1.7 million pounds reported on EPA's Toxics Release Inventory (TRI) in 1995.

Cresols also are products of combustion both from natural and anthropogenic sources. Cresols are released to the air from fires associated with lightning and volcanic activity.

According to a study performed on behalf of EPA, the "major ambient source [of cresols] is automotive emissions. Cresols also have been detected in stack emissions from municipal waste incinerators, in emissions from vegetable material incineration, in fly ash from coal combustion, in emissions from wood combustion, and in cigarette smoke.

Thus, there are numerous and diverse sources of cresols air emissions. A significant portion of cresols air emissions is due to natural sources -- which are not a concern of California's laws governing toxic air contaminants. Indeed, releases from natural sources dwarf those from manufacturing operations and further confirm that cresols emissions from industrial facilities should not be given priority for evaluation and regulation under the Program.

Response. Since the chronic REL will be compared to off-site, annual ground level concentrations based on modeled facility emissions and not on monitoring data, the background concentrations should not interfere with use of the REL. On the other hand, if cresols are monitored, facility contributions to the outdoor concentration could be detected based on comparison of upwind and downwind concentrations of cresols. Many other compounds emitted by facilities also have measurable natural emissions.

Comment 10. New NESHAPS will further reduce the potential for exposure to cresols. Concentrations of cresols would be expected to be greatest in the vicinity of a facility that emits relatively large quantities of cresols to the air. A review of the TRI database for cresols indicates that, of the facilities which individually have relatively high emissions of cresols,

nearly all are or will be subject to NESHAPs pursuant to the 1990 Clean Air Act (CAA) Amendments. Implementation of these NESHAPs will reduce even further potential exposure to cresols. (These attachments are based on data received from the EPA TRI User Support Library and the National Library of Medicine's ToxNet database.)

Attachments 2, 3, and 4 summarize the top twenty emitters of cresol isomers and mixed cresols in 1993, 1994, and 1995, as reported to the TRI. Only one facility in California was among the top twenty emitters in 1993 and 1994 and no California facility is among the top twenty emitters in 1995 - the latest year for which TRI data is available. In each year, the top twenty emitters represented nearly 100 percent of all reported cresol isomers emissions and between 60 to 94 percent of mixed cresols emissions. Review of the Standard Industrial Classification (SIC) codes associated with each of these facilities indicates that they already are, or soon will be, subject to maximum achievable control technology (MACT) standards under various NESHAPs.

Attachment 5 lists the twenty SIC codes with the highest reported TRI emissions of cresol isomers and mixed cresols in 1995. These SIC codes include primarily pulp and paper operations, chemical manufacturers, surface coating operations, and other sources that are or will be subject to MACT standards established by forthcoming NESHAPs. These include the following:

- The HON: Many manufacturers of cresols themselves are subject to the hazardous organic NESHAP (HON) for the Synthetic organic Chemical Manufacturing Industry. For individual isomers, between 33 percent and 81 percent of emissions are associated with facilities in SIC Code 2865 for Cyclic Crudes and Intermediates or SIC Code 2869 for Industrial Organic Chemicals, both of which are subject to the HON. Cresols emissions will be reduced even further because many of the principal uses of cresols are as chemical intermediates in the manufacture of other chemicals that also are subject to the HON.

- Metal Coil (Surface Coating) Source Category: In 1995, approximately 60 percent of emissions of m-cresol and 28 percent of p-cresol and mixed cresols air releases are reported by facilities in SIC Code 3357 - Nonferrous Wire Drawing and Insulating. Cresols are used at these facilities as a solvent for wire enamel. MACT standards for the Metal Coil (Surface Coating) source category are scheduled for promulgation by the year 2000.L3-1 This category will address hazardous air pollutants (HAP) emissions from facilities that engage in the surface coating of continuous metal strips that are packaged in a roll or coil, such as wire.

- Amino and phenolic resin production: O-cresol is used in the production of epoxy-o-cresol resins and other resins. A presumptive MACT standard has been issued for amino and phenolic resin production that will require controls for cresols emissions.

- Pulp and paper mills: Over 55 percent of releases of mixed cresols isomers in 1995 were produced as a byproduct of pulp, paper, paperboard, and related manufacturing operations. Air emissions from pulp mills, paper mills, and paperboard mills are now subject to a NESHAP. This NESHAP is expected to reduce VOC emissions, including cresols, by

716,000 megagrams (Mg) annually. Existing mills became subject to the NESHAP in December 1996 and reductions in emissions will be reflected in future TRI reports.

- Petroleum refining: Cresols are produced as a byproduct of petroleum distillation. A NESHAP for petroleum operations has been promulgated and is expected to reduce total air emissions by 59 percent.

- Agricultural chemical production: Cresols are used in the production of agricultural chemicals such as 4,6-dinitro-o-cresol, which are subject to MACT controls.

- 4-chlor-2-methyl phenoxyacetic acid production: Cresols are used in the production of 4-chlor-2-methyl phenoxyacetic acid, for which MACT standards will be issued.

- Anthropogenic sources of cresols: Cresols also are produced as a byproduct of various combination operations. These sources of cresols will be reduced by MACT standards for hazardous waste boilers and incinerators; and off-site waste recovery operations.

In summary, most of the individual sources of cresols emissions will be regulated under a NESHAP within the next few years. The Panel believes that cresols emissions also will be reduced significantly in the near future as a result of voluntary efforts undertaken by industry. Panel members who are CMA member companies, for example, are committed to CMA's Responsible Care program, pursuant to which they have agreed to reduce emissions continually. All of these efforts will reduce concentrations of cresols in the ambient air and the need for evaluation or regulatory action under either the Program or the Act.

Response. OEHHA acknowledges that many individual emission sources of cresols will be regulated under various NESHAPs. A chronic REL will still be useful to gauge how far below the health benchmark the ambient concentration of cresols actually falls. In addition there are other environmental sources of cresol, such as cigarette smoke, for which a chronic REL will be useful as a health benchmark.

Comment 11. Measures implemented to reduce ozone levels will reduce emissions that include cresols from mobile and stationary sources. During the past several years, EPA has implemented an aggressive set of programs for achieving the National Ambient Air Quality Standard (NAAQS) for ozone, driven in large part by the new nonattainment provisions enacted by the 1990 CAA Amendments. These programs address ozone precursor emissions from both stationary and mobile sources, and thus are directed toward the reduction of smog levels in affected areas. The very low environmental concentrations of cresols will fall even lower as EPA makes continuing progress toward attaining the NAAQS for ozone, thus further reducing smog exposure levels in current "nonattainment" areas. EPA recently issued a final rule that has tightened the NAAQS for ozone, for example.

These programs will reduce cresols emissions, to which the general population is exposed, from automobile and diesel exhaust, coal-fired power plants, and other operations. These measures will reduce the levels of VOCs, such as cresols, and their contribution to

ozone formation and to urban smog. Since actual emissions inventory data (and TRI data) must be considered in selecting chemical substances for priority evaluation and regulation, these current and future reductions in cresols emissions further demonstrate the inappropriateness of according priority treatment to cresols.

Response. Cresols are not being given priority treatment. OEHHA staff developed health guidance values for as many chemicals as possible listed under the Hot Spots program, which includes cresols. OEHHA has decided to base the chronic REL, not on the Uzhdavini et al. (1972) study, but on the USEPA RfD. The U.S. EPA RfD was based on 90 day toxicity studies done by USEPA and reported in 1986. The RfD is 0.05 mg/kg/day and the equivalent chronic REL is 180 $\mu g/m^3$. The critical effects are decreased body weight and neurotoxicity and the target organ is the nervous system.

Chemical Manufacturers Association – Diisocyanates Panel

Comments on the Proposed Toxicity Summaries and Reference Exposure Levels for **methylene diphenyl isocyanate (MDI) polymer** and **2,4- and 2,6-toluene diisocyanate (TDI)** were made by the Chemical Manufacturers Association Diisocyanates Panel. The Dissocyanates Panel represents the major domestic producers of methylene diphenyl isocyanate ("MDI") and toluene diisocyanate ("TDI"). Members of the Panel are: ARCO Chemical Company; BASF Corporation; Bayer Corporation; The Dow Chemical Company; and ICI Americas, Inc. OEHHA used the original USEPA RfC of 0.02 $\mu g/m^3$ based on hyperplasia of the olfactory epithelium in rats as the chronic REL for MDI polymer. For TDI OEHHA used the original USEPA RfC of 0.07 $\mu g/m^3$ based on decreased lung function in occupationally exposed workers as the chronic REL.

Comment 1: CALCULATION OF THE REL FOR POLYMERIC MDI. OEHHA's proposed Chronic Toxicity Summary and REL for polymeric MDI are based on the U.S. EPA's IRIS Summary and inhalation RfC. In April 1996, U.S. EPA announced a Pilot Program to update the IRIS database entries for eleven chemicals, including MDI. Pursuant to this program, U.S. EPA currently is reviewing and revising the IRIS summary and RfC for MDI. U.S. EPA expects to finalize the IRIS entry for MDI in February 1998. The Diisocyanates Panel urges OEHHA to defer its recommendation of an REL for MDI pending completion of the updated IRIS assessment and revised RfC.

In connection with the IRIS Pilot Program, U.S. EPA has circulated, for peer review, a draft Toxicological Review for MDI. The Draft Toxicological Review provides an updated summary of the available data for 4.4'-MDI ("monomeric MDI") and polymeric MDI. Based on this review, U.S. EPA proposed a revised RfC of 2×10^{-4} mg/m^3 for MDI. The proposed RfC was based on the adjusted NOAEL of 0.036 mg/m^3 for nasal effects reported by Reuzel *et al.* (1994). EPA recalculated the human equivalent concentration for the NOAEL group ("NOAEL HEC") in the Reuzel Study based on a revised Regional Deposited Dose Ratio (RDDR) for MDI of 0.453. U.S. EPA's revised NOAEL HEC for MDI is 0.016 mg/m^3. In calculating its revised RfC, EPA applied three uncertainty factors to the NOAEL HEC: (1) a factor of 10 was applied for intraindividual variation; (2) a factor of 3 was applied for database deficiencies; and (3) a factor of 3 was applied for intraspecies variation. Thus, U.S. EPA proposed an RfC for polymeric and monomeric MDI of 2×10^{-4} mg/m^3, rather than the value of 2×10^{-5} mg/m^3 that was previously calculated by EPA and on which OEHHA has relied for its proposed REL

The CMA Dissocyanates Panel met with U.S. EPA and submitted comments on the IRIS assessment for MDI. The Panel presented a benchmark analysis of the Reuzel data developed by Drs. Bruce Allen and Melvin Andersen of ICF Kaiser. Based on this analysis, the Panel calculated an RfC for MDI of 9.64×10^{-4} mg/m^3. The Panel urged U.S. EPA to adopt the benchmark methodology in calculating the RfC for MDI. The benchmark approach has received broad scientific support and U.S. EPA and others have recognized the advantages of the benchmark analysis as an alternative to relying on the NOAEL for non-cancer risk assessment. Advantages of the benchmark approach include reduced dependency on dose selection and spacing, more appropriate reflection of sample size, and better inclusion

of dose-response information. The Panel's comments to EPA presenting its proposed RfC calculation based on the benchmark approach are included in Attachment I (Allen and Andersen (1997) is appended thereto).

EPA has not yet finalized the Toxicological Review and RfC for MDI. However, EPA staff have informed Panel representatives that the Agency intends to use the benchmark analysis in deriving the RfC. The Panel recommends that the State of California similarly adopt the benchmark approach in establishing its REL for MDI. For the reasons presented in the Panel's comments to EPA, the Panel believes that the REL for MDI should be 9.6×10^{-4} mg/m^3.

Response: All USEPA Reference Concentrations (RfCs), available when the draft Technical Support Document (TSD) on chronic Reference Exposure Levels was released in October 1997, are being used as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program. Staff plan to review the scientific basis of each revised RfC when it becomes available and determine whether the scientific literature cited in the RfC is current. Appropriate RfCs will be submitted to the SRP for review and possible endorsement. OEHHA has reviewed the updated IRIS value for this chemical but it was released after October 1997 and OEHHA has not automatically accepted new RfCs. The new RfC for MDI is based on a benchmark dose approach, specifically a BMC10. OEHHA staff believe that consensus has not been reached on benchmark dose methodology. Both BMC10 and BMC05 approaches have their advantages and their proponents. The BMC10 is usually in the linear range of most models while the BMC05 more closely resembles a NOAEL than the BMC10 does. We will continue to review the updated RfC and present it to the SRP in our first update of chronic RELs. In the interim we have revised our proposed chronic REL from 0.02 $\mu g/m^3$ to 0.5 $\mu g/m^3$. (See next response.)

Comment 2: APPLICATION OF THE REL TO 4,4'-MDI MONOMER. OEHHA has stated that the "major limitation" of the proposed REL for MDI *"is* that it is based on data on exposures to MDI polymers." OEHHA states that, because "monomers frequently are much more toxic than polymers, ... OEHHA considers the value is only predictive of adverse effects of polymeric *MDI*. Effects of monomeric MDI may occur at concentrations several orders of magnitude lower than in the reported study on MDI polymer." This conclusion is not supported by the available data. The study by Reuzel *et al.* (1994) was conducted using the substance described commercially as polymeric MDI. This substance is not, however, a true

MDI polymer. Rather, it is more accurately characterized as MDI oligomer and is comprised of approximately 40 to 60% monomeric MDI and diminishing proportions of MDI dimer and other low-order MD1 oligomers. Polymeric MDI also is the more commercially relevant *NMI* product and accounts for greater than 90% of MDI sold domestically.

In addition, the pulmonary effects reported by Reuzel *et al.* (1994) are generally consistent with those reported in the whole body inhalation study of monomeric MDI in rats by Hoymann *et al.* (1995) (abstract only) which reported effects, which were related primarily to the impairment of *MDI* clearance, only in the highest dose group. The International Isocyanate Institute ("III") currently is sponsoring a comparison of the Hoymann data with the Reuzel (1994) data. Pathologists are reviewing the salient slides from the respiratory tract and the lung to assess the toxicology and also to understand the likely origin of the lesions observed in the two studies. Thus, it appears that monomeric *MDI* has a toxicity that is approximately the same as that of the polymeric MDI evaluated by Reuzel, and monomeric MDI does not have an effect level that is several orders of magnitude lower.

Further evidence of a lack of significant difference between polymeric and monomeric *MDI* is in parallel teratology studies performed by Garner *et* al. (1995) and Buschmann *et al*. (1996), respectively. In similar exposure scenarios, the no embryotoxic effect level was observed at 3 mg/m^3 for monomeric MD, and 4 mg/m^3 polymeric *MDI*. Maternal effects also were comparable between the polymeric MDI used in the Gainer study and the monomeric MDI in the Buschmann study. This further supports the conclusion that the toxicity of monomeric and polymeric MDI is similar.

Response: OEHHA has revised the text to account for the fact that nearly half the airborne material was monomer. OEHHA has also removed the database modifying factor of 10 since new studies on teratology have been published by Buschmann and others. The HEC calculation has also been revised. OEHHA has recalculated the chronic REL to be 0.5 $\mu g/m^3$.

Comment 3: 2,6- AND 2,4-TOLUENE DIISOCYANATE: ON-GOING EPIDEMIOLOGY STUDIES OF TDI-EXPOSED WORKERS. OEHHA also relied on the IRIS RfC in proposing an REL for 2,4- and 2,6-TDI. The RfC for TDI is based on a 1982 epidemiology study by Diem *et* al. showing lung function decrement in workers occupationally exposed to TDI. ARCO Chemical Company is looking into the feasibility of updating the Diem study. In addition, efforts currently are underway to complete several other epidemiology studies of TDI-exposed workers. Studies of workers in TDI production facilities are being conducted by Dow Chemical Company and BASF. These studies are expected to be completed in 1998. These additional studies will expand and improve the available epidemiology database related to the human health effects of TDI exposure. Thus, the Panel urges OEHHA to await the results of these studies before finalizing its REL for TDI.

Response: The adoption of USEPA RfCs by OEHHA was described above. OEHHA is pleased that better data may become available and will review the studies when they are finished. We assume that USEPA will do the same. As of April 1999 OEHHA had not

received the updated studies. The current chronic REL is based on the data currently available.

Comment 4: CALCULATION OF THE RfC FOR TDI. U.S. EPA based the RfC for TDI on the epidemiology study of occupationally exposed workers by Diem *et al.* (1982). In calculating the RfC, U.S. EPA relied on the analysis of the data from the Diem study by Hasselblad (1993) to derive a NOAEL of 0.006 mg/m (0.9 ppb) for TDI.

The Diisocyanates Panel does not agree with Hasselblad's conclusion that the Diem study supports a NOAEL of 0.006 mg/m^3. As explained in the attached letter by Dr. Gerald Ott of BASF Corporation (copy enclosed as Attachment 1), the statistical analysis of the epidemiology data conducted by Hasselblad is flawed in several respects. First, it selectively applies the data from Diem *et al.* and the other available epidemiology studies (in particular, by failing to consider the findings within the "former smoker" subpopulation). It also employs questionable procedures to estimate TDI concentrations consistent with the reported decline in forced expiratory volume (FEV1) and overlooks important biological parameters in deriving the NOAEL.

Moreover, the Diem Study was not designed to support the derivation of an overall NOAEL for TDI. The study evaluates cumulative exposure categories, which limits examination of exposure intensities. According to Garabrant and Levine (1994), the lung function decrement observed in the study was more likely related to episodic exposure to TDI at 6 levels above 20 ppb than to exposures in the 5 to 10 ppb range. Although the Diem *et al.* study does not permit the examination of exposure intensities, we believe that it is consistent with an overall NOAEL for TDI of 5 ppb.

The Panel further believes that U.S. EPA's use of the Diem Study to derive a NOAEL of 0.9 ppb for TDI is inconsistent with the TDI epidemiological database as a whole. The results reported by Diem *et al.* have not been replicated in larger and more recent studies of TDI-exposed workers, which rely on more precise methods for estimating exposures below 5 ppb. *see* Bulger *et al.* (1991); Jones *et al.* (1992); *see* also Allport *et al.* (1993). Overall, eight studies have failed to demonstrate lung function decrement from exposure to TDI at concentrations below 5 ppb. Thus, the overwhelming epidemiological evidence supports the conclusion that 5 ppb (0.036 mg/m^3) is the no-effect-level for exposure to TDI with decreased living function being the most sensitive endpoint.

Response: These concerns should be addressed to the USEPA for possible reevaluation of the RfC.

Comment 5: The Diisocyanates Panel believes that the additional studies currently being conducted will strengthen the TDI database and provide a better data set from which to derive a NOAEL for TDI. For this additional reason, the Panel suggests that OEHHA await the results of these studies before finalizing its REL for TDI.

Response: USEPA last updated the RfC for TDI on IRIS in September 1995. OEHHA is proceeding with the finalizing of the chronic REL based on information currently available but will review the new data when made available.

Chemical Manufacturers Association (CMA) - Ethylene Glycol Ethers Panel

Comments on the chronic REL for **ethylene glycol butyl ether** (EGBE) were received from the Ethylene Glycol Ethers Panel of the Chemical Manufacturers Association (CMA). The Chemical Manufacturers Association (CMA) Ethylene Glycol Ethers Panel is made up of the Dow Chemical Company, Eastman Chemical Company, Occidental Chemical Corporation, Shell Chemical Company, and Union Carbide Corporation. In the original TSD OEHHA derived a chronic REL of 200 $\mu g/m^3$ for EGBE based on a 1983 study by Dodd *et al*. showing decreased red blood cells in female rats. (The chronic REL has been revised to 700 $\mu g/m^3$ as described below.)

Comment 1: Significant new information should be employed in the calculation for EGBE**.** The TSD (pp. A-274 to A-278) proposes an REL for EGBE of 0.04 ppm (200 $\mu g/m^3$). This REL is derived by applying a cumulative uncertainty factor of 100 to an average experimental exposure No Observed Adverse Effect Level (NOAEL) of 4.5 ppm, which is equated to a Human Equivalent Concentration (HEC) based on default assumptions. The NOAEL is obtained from the Dodd (1983) 90-day inhalation study in rats that found a NOAEL of 25 ppm with 30 hour/week exposures (converted to continuous exposure by multiplying by 6/24 x 5/7). The cumulative uncertainty factor represents uncertainty factors of 10 each for (a) absence of a chronic study (the subchronic uncertainty factor) and (b) potential intraspecies differences.

A more appropriate REL for EGBE can be established by taking into account significant data on EGBE developed in recent years. These data, described below, should be employed to determine the HEC more accurately and to diminish the need for ten-fold uncertainty factors for intraspecies differences and for the absence of chronic data.

First, a validated physiologically-based pharmacokinetic (PBPK) model has been developed for EGBE. This PBPK model makes EGBE a compound for which "[c]omparison of human and animal pharmacokinetics and metabolism may be useful in selecting the relevant animal model for predicting human health effects" (TSD, at p. 17). As the enclosed publication describing the model (Corley et al.) shows, a more accurate determination of the HEC can be achieved by use of the PBPK model than is obtained by the standard default calculations employed in the TSD to convert discontinuous to continuous exposures (TSD, at p. 23).

Response: According to the Summary, Corley et al developed a PBPK model to describe the disposition of EGBE and its major metabolite, EGBEA (2-butoxyacetic acid), in rats and humans (Corley RA, Bormett GA, Ghanayem BI. Physiologically based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans. Toxicol Appl Pharmacol 1994;129(1):61-79). The model predicts that rats metabolize EGBE and eliminate the EGBEA faster per kg body weight than humans do. The balance of these two processes plus physiological differences between species result in higher predicted peak blood concentrations as well as total areas under the blood concentration time curves for EGBEA for rats versus humans. These species differences (and the fact that human blood is significantly less susceptible than rat blood to the hemolytic effects of EGBEA) indicate that

there is considerably less risk for hemolysis in humans from exposure to EGBE than predicted solely from standard toxicity studies with rats. In the original REL, instead of the interspecies UF default value of 10, OEHHA used an interspecies UF of 1, which indicates no likely interspecies differences. There is presently no guidance for using a factor of less than 1. To use a factor of less than 1, there would need to be reproducible data showing that the AUC of BAA in animals was a specific multiple of the AUC of BAA in humans.

Comment 2: Second, research conducted by Dr. Mark M. Udden at Baylor College of Medicine has demonstrated that blood from the elderly and from patients with hemolytic disorders does not show an increased sensitivity to the hemolytic effects of EGBE (which, as the TSD finds, are the critical toxicologic effects for establishment of an REL for EGBE). Enclosed are Dr. Udden's 1994 publications, which demonstrate that an uncertainty factor of ten for intraspecies differences is unwarranted.

Response: The demonstration that blood from the elderly and from patients with hemolytic disorders does not show an increased sensitivity to the hemolytic effects of EGBE is reason to depart from the intraspecies UF default value of 10. Since there may still be other sources of intraspecies uncertainty or variability, OEHHA staff have changed the intraspecies UF to 3. The cumulative UF is then 30 and the revised chronic REL is 0.15 ppm (724.5 $\mu g/m^3$, which rounds to 700 $\mu g/m^3$).

Comment 3: The PBPK and Udden work are both described in more detail and employed in the enclosed Draft IRIS Support Document developed jointly by U.S. EPA scientists (Drs. Jeff Gift, Annie Jarabek, and Vicki Dellarco) and scientists from Panel member companies. Although the Support Document is not yet final and EPA's scientists have not yet reviewed all sections of it, the Panel believes its recommendations for an IRIS Reference Concentration (RfC) for EGBE are consistent with the views of all the scientists working on the IRIS Document. We anticipate working with EPA in 1998 to complete the Document and establish an RfC for EGBE.

We call to your attention, particularly, the derivation of an RfC in Chapter 6 of the IRIS Draft Document. The Draft calculates RfC's by several methods: (1) the standard IRIS RfC method, which is quite similar to California's REL methodology; (2) a methodology that incorporates information from the PBPK model; (3) a benchmark dose methodology; and (4) a methodology incorporating both the PBPK model and the benchmark dose methodology.

The Draft IRIS Support Document recommends adoption of the fourth method because it most fully employs the complete database. That methodology yields an RfC (or REL) of 15 ppm (73 mg/m^3). We urge California to do the same. At a minimum, the State should take advantage of the PBPK model to adopt an REL of 6 ppm (27 mg/m^3); such an REL would represent a more refined determination of the HEC based on the PBPK model and an acknowledgment that the Udden data shows an intraspecies uncertainty factor of 3 is fully sufficient.

The Panel urges CalEPA to make use of the significant information we enclose in adopting an REL for EGBE. Alternatively, the State may wish to await EPA's adoption of an IRIS RfC. EPA announced this month that it intends to complete its IRIS review of EGBE in 1998 (63 Fed. Reg. 74, 75, Jan. 2, 1998). By waiting for a short period, CalEPA could also take advantage of the results of chronic bioassays with EGBE in mice and rats to be announced soon by the National Toxicology Program.

Response: The draft TSD was released in October 1997. As of June 1999 IRIS has no listing for EGBE or butoxyethanol. If and when it is finalized, OEHHA will review it, consider whether or not OEHHA should adopt the USEPA RfC, and forward its findings to the Scientific Review Panel for its consideration. We are not willing to wait for the USEPA RfC since there is no date certain for its completion. For now we are proposing a revised chronic REL of 0.15 ppm (700 $\mu g/m^3$).

Chemical Manufacturers Association - Hydrazine Panel

Comments on the chronic REL for hydrazine were made by the Hydrazine Panel of the Chemical Manufacturers Association in a letter dated January 29, 1998. OEHHA developed a chronic REL of 0.2 $\mu g/m^3$ based on the critical effects of amyloidosis of the liver and thyroid in hamsters (Vernot at al., 1985). OEHHA considered the lowest dose used (0.25 ppm) in hamsters to be a LOAEL since at this level the authors noted weight depression, mineralization of the kidney, and amyloidosis of the thyroid.

Comment 1: The Panel agrees that Vernot et al. is the appropriate study for derivation of the hydrazine chronic REL, but disagrees with OEHHA's interpretation of that study. The Panel believes that the 0.25 ppm dose level should be considered a NOAEL, not a LOAEL. Although the frequency of amyloidosis in hamsters exposed at this level was increased compared to controls, the frequency levels nonetheless were within the range reported in the literature for control animals.

Response: Controls reported in the same study are more relevant than historical controls for several reasons. Same study controls were exposed to the same environmental and dietary conditions and potential pathogen exposures as the exposed group. Also, the study control and exposed groups use the same strain of animal, whereas historical controls may have significant genetic differences from the test group. In addition to amyloidosis of the liver, thyroid and adrenal glands, male hamsters exposed to 0.25 ppm hydrazine showed other statistically significant increases over controls in liver hemosiderosis, bile duct hyperplasia, lymphadenitis of the lymph nodes, and mineralization of the kidney.

Comment 2: Even if the 0.25 ppm dose level is considered a LOAEL, an uncertainty factor often is overly conservative to extrapolate from a LOAEL to a NOAEL for these effects. The reported amyloidosis was at most an acceleration of a natural aging process, the incidence of the effect was within the levels normally seen in control populations, and hamster amyloidosis is an effect that may have questionable relevance for human health hazard assessment. For these reasons, an uncertainty factor of no more than three is appropriate to extrapolate from a LOAEL to a NOAEL.

Response: The relevance of historical controls was discussed in response to Comment 1. The basis for the statement that amyloidosis is not relevant to human health hazard assessment is unclear. A diverse array of human medical disorders, both neurologic and systemic, are associated with extensive amyloidosis. Human amyloidosis can be severe, with some forms associated with a median survival duration after diagnosis of as low as 25 months (Raikumar SV, Gertz MA, Kyle RA. Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. Am J Med 1998 Mar;104(3):232-7). Amyloid deposits may cause direct harm or may be markers for an underlying metabolic disorder. Thus amyloidosis does not fit the mild effect category described in the OEHHA chronic REL document.

Comment 3. Alternatively, it may be advantageous to calculate the hydrazine REL using a benchmark concentration approach. Such an approach uses all of the available study data and avoids the difficulties associated with determining whether a NOAEL has been identified in a given study.

Response. The potential use of benchmark concentration (BMC) modeling was extensively evaluated. Dose-response modeling of the data of Vernot and associates (1985) illustrates some of the complexities of using BMCs. Several mathematical models (probit, Wibull, quantal quadratic, quantal linear, and gamma models using USEPA BMDS software) were fit to the data. None of the models fit well the unusual dose-response relationship where all three concentrations, covering a 20-fold range, were associated with a significantly increased incidence of liver amyloidosis relative to controls, but where the dose-response slope appears very shallow over this range. The models able to converge on a solution tended to project a BMC_{10} of 1 to 3 ppm. However, all the fits are questionable since they are based on assuming (1) that the true control and low dose incidence are both 30-35%, when the observed incidences were 23% and 42% respectively, and (2) that the dose-response slopes are modeled to be much steeper than actually observed. This represents one possible explanation: that the true dose-response relationship is steeper than observed due to sampling error. However, alternative explanations, more consistent with the observed data, can not be ruled out. One explanation would be that the dose-response relationship is not unimodal; there may be a susceptible subgroup at increased risk of amyloidosis at relatively low concentrations and a second more resistant subgroup. Secondly, caution against using poorly modeled BMCs or those exceeding a LOAEL has been emphasized (Gaylor et al., 1998, Procedures for calculating benchmark doses for health risk assessment, Regul. Toxicol. Pharmacol. 28, 150-164). For the above reasons a BMC can not substitute for the experimental observations in this case.

Comment 4: OEHHA should remove the reference to endocrine effects from its chronic toxicity summary for hydrazine. Although amyloidosis was seen in the thyroid of hamsters, no effects on the endocrine system were noted even at the highest doses studied. Nor have any other studies reported adverse effects on the endocrine system from exposure to hydrazine.

Response: The categorization of adverse health effects is intended to denote only the general category of organ system affected. Thus, as thyroid amyloidosis was observed and the thyroid is an endocrine gland, the effect is noted as “endocrine,” and is only meant to imply an endocrine gland was affected, and not to imply that abnormalities in hormone production are anticipated.

Comment 5: The chronic toxicity summary gives undue weight to the poorly-reported findings in the Sotaniemi case report. Other epidemiological studies that are not discussed by OEHHA do not corroborate the findings of Sotaniemi. The Panel therefore requests that OEHHA revise its discussion on the effects of human exposure to hydrazine to provide a more balanced presentation of the available data.

Response: The Sotaniemi paper is not an epidemiological study but rather a case report. Both this paper and the description of this case report as presented in the draft chronic REL document were reviewed. The case was well presented in the original report and the chronic REL review was found to be accurate. Some additional text is being added to clarify some aspects of the case: (1) a cause and effect relationship between the hydrazine exposures and the sudden death of the worker is strongly suggested but not proven; (2) the worker was 59 years old and healthy prior to hydrazine exposure; and (3) the worker's once per week exposure was reported to be routinely followed by 1-2 days of conjunctivitis and tremor.

Only a single epidemiological study of human hydrazine exposures was found and a description is being added to the OEHHA document. This study (Wald, 1984, *IARC Scientific Publication* 65:75-80; Wald et al., 1984, *British Journal of Industrial Medicine* 41:31-34) was based on a review of medical records of 406 of 427 male workers at a single chemical factory. Only 78 of these workers were believed to have had more than incidental exposure to hydrazine. Only cumulative mortality was reviewed. Health effects reported during or after hydrazine exposure were not examined. No increase in mortality was noted for lung cancer, other cancers, or causes other than cancer. However, this small study has little power to detect increased mortality, and age of death was not examined.

Chemical Manufacturers Association (CMA) - Hydrogen Fluoride Panel

The Chemical Manufacturers Association Hydrogen Fluoride Panel (Panel) on January 29, 1998 submitted comments on the October 1997 draft OEHHA chronic inhalation reference exposure level (REL) for fluorides, including hydrogen fluoride (HF). The Hydrogen Fluoride Panel includes 3M Company, Allied Signal Inc., Aluminum Company of America, Chemtech Products, Inc., Daikin America Inc., DuPont, Elf Atochem, NA, Inc., General Chemical, Industrial Quimica de Mexico, S.A. de C.V., LaRoche Industries Inc., LCI/Norfluor, Occidental Chemical Corp., OSRAM Sylvania Inc., and Quimica Fluor S.A.

Comment 1. In general, the Panel believes the chronic toxic summary for fluorides prepared by OEHHA is well-written. However, for reasons set forth below, the Panel believes the REL should be higher by a factor of three. In the case of hydrogen fluoride and other fluorides, an uncertainty factor of three should be sufficient to protect sensitive individuals.

The Technical Support Document discusses the application of an uncertainty factor to account for "the potential for greater susceptibility in subpopulations, including infants and children (p. 29-30). OEHHA indicates it generally will use an uncertainty factor of ten to protect sensitive individuals (p. 30). In the presentation at the OEHHA Workshop held in Long Beach, California on December 4, 1997, however, OEHHA staff presented a slide showing the possibility of using uncertainty factors of one, three or ten for "sensitive subgroups" when justified. The Panel believes a factor of three is scientifically appropriate in the case of fluorides.

As noted in the Technical Support Document, the steepness of the dose-response relationship affects the adequacy of the uncertainty factor for sensitive individuals. The Panel believes that the abundant information available on fluorides, with studies of large and varied human populations, documents a dose-response which would justify an uncertainty factor of three, rather than ten. Much of this information is summarized in a recent National Research Council (NRC) publication ("Health Effects of Ingested Fluoride," National Research Council, National Academy Press, 1993). The NRC publication addresses oral data, and the Panel recognizes that OEHHA typically would prefer to base an inhalation REL on inhalation studies. Nevertheless, it is generally recognized that oral exposure data can provide valuable information (Technical Support Document, p. 30-31) and, specifically in the case of fluorides, it is known that 75 to 90 percent of ingested fluoride is absorbed (Ekstrand, J., Boreus, A.L.O. and Norlin A., 1977, Pharmacokinetics of Fluoride in Man after Single and Multiple Oral Doses, Eur. J. Clin. Pharmacol. 12:311-317). The level of absorption is certainly equivalent to the amount absorbed via inhalation (approximately 99%) (Morris, J.B. and Smith, F.A., 1982, Regional Deposition and Absorption of Inhaled Hydrogen Fluoride in the Rat, Toxicol. Appl. Pharmacol. 62:91-99). Thus, the Panel believes the extensive oral data provide a scientifically sound basis for evaluating the appropriate uncertainty factor for protecting sensitive individuals. Further, since fluoride elimination is primarily via renal clearance, people with impaired renal function or nutritional deficiencies, e.g., Vitamin C or calcium, may be expected to have a greater susceptibility to fluoride toxicity. However, data from Spencer et al. (Spencer, H., Kramer, L., Gatza, C.A., 1980, Fluoride Metabolism in Patients with Chronic Renal Failure. Arch. Intern. Med. 140:1331-35) indicate that retention is not

more than about three-fold between those with normal renal clearance and those with impaired clearance. Therefore, these data would support the use of a less conservative uncertainty factor.

As a scientific "reality check," one can compare OEHHA's proposed REL of 0.03 mg/m^3 with the oral reference dose (RfD) of 0.06 mg/kg/day published by U.S. EPA in its Integrated Risk Information System (IRIS) database. Assuming a person breathes 20 cubic meters of air per day and the air contains HF at a concentration equal to the proposed REL, that person would inhale (but not absorb) 0.6 mg fluoride per day. By comparison, ingesting fluoride at the level of the oral RfD, a 50 kg adult would ingest 3.0 mg per day. One could also use for comparison California's Drinking Water Standard of 1400-2400 µg/L fluoride ion (compared to USEPA's 4000-8000 µg/L, under which an adult could safely ingest at least 2.8 mg (2 liters x 1400 µg) fluoride ion per day. These comparisons show that the proposed chronic inhalation REL for fluorides is approximately five-fold more conservative than USEPA's RfD or the State of California's existing drinking water standard. Using an uncertainty factor of three to account for potential human variability would produce an REL that is consistent with these other regulatory standards.

Response. The intent of the OEHHA reference exposure levels is to provide health-based guidance. Thus regulatory standards, which consider other issues in addition to health effects, were not considered in the development of the RELs. OEHHA RELs are intended to protect the general public, including potentially sensitive groups such as children, the elderly, and those with chronic illness. Chronic RELs, similar to USEPA RfC values, are meant to be protective to the general public rather than predictive of risk. Thus, exposure to a REL concentration may or may not be associated with adverse effects. But because of uncertainties in available data, RELs are calculated at some lower concentration than that at which adverse effects have been observed. The cumulative uncertainty factor of 10 for HF is one of the lowest used among more than 100 OEHHA chronic RELs and USEPA RfCs.

Comment 2. In summarizing the article by Derryberry et al. (1963), the chronic toxicity summary overstates the extent to which bone density increases were observed in workers. The chronic toxicity summary characterizes bone density for several workers as "high" (Table 1). However, the actual Derryberry et al. article simply notes with an asterisk those individuals who had "bone density changes." The study originally planned to include three categories of osseous changes: 1) normal skeletal density; 2) minimal or questionable bone changes indicative of increased bone density; and 3) positive characteristics of increased bone density. Derryberry reported no individuals in the latter category. According to the radiologist, none of the x-rays showed sufficient increase in bone density to be recognized as such in routine radiological practice. Thus, the authors did not express the opinion that "[t]he increased bone density observed was considered as indicating adverse effects had occurred" (Chronic Toxicity Summary, p. A-315). The study by Riggs et al. (1990), which also is cited in the chronic toxicity summary, employed pharmacologic doses of fluorides at levels almost four times those known to result in crippling fluorosis (USEPA, National Primary Drinking Water Regulations; Fluoride; 50 Fed. Reg. 47,142, Nov. 14, 1985). While it may be reasonable to use such questionable radiologic changes as the endpoint for determining a

lowest observed effect level (LOEL) or no observed effect level (NOEL), OEHHA has provided insufficient justification to show that the levels chosen represent a lowest observed adverse effect level or a no observed adverse effect level.

Response. Changes are being made in response to this comment. Text modifications will better clarify the minimal changes in bone density reported by Derryberry and associates. However, the minimal extent of the findings do not mean they are not relevant to developing RELs to protect the general public. In general, it is necessary to consider studies where statistically significant changes of questionable biological significance are consistent with frank adverse effects at higher exposures in other studies. A similar situation would be where high exposures to a chemical were established as causing clear liver toxicity and lower exposures in another study caused minimal effects such as increased liver weight without other observable effects. In these cases it is a reasonable public health goal to avoid exposures which begin going down the path from minimal to frank adverse effects, especially as subgroups in the populations may have preexisting conditions that render them especially susceptible to changes in a particular organ.

Comment 3. Section IV of the chronic toxicity summary ("Effects of Human Exposure") summarizes the few, and mostly older, reports of the effects of human inhalation exposure to generally very high levels of hydrofluoric acid. There is no mention of the abundant literature on human exposure to fluorides by the oral route, nor is there any indication that a certain level of fluoride intake is recommended by public health authorities for the prevention of dental caries (NRC publication, supra, n.6). This information should be included so that readers will be aware that fluoride is among those substances, which have beneficial effects at certain levels, with harmful effects only at higher levels.

The study on which OEHHA is relying to set the REL (Derryberry et al.) reports airborne exposures to fluorides. However, the authors note, "The principal routes through which these compounds are introduced into the human system are by ingestion or swallowing of dust containing fluorides and by inhalation of fluoride compounds." Thus, ingestion of fluorides was a major source of fluoride exposure even for those workers studied by Derryberry et al.

Response. *Text is being added to review normal dietary exposures* to fluorides and the use of fluoride supplements and to augment generally the health effects of fluorides other than hydrogen fluoride.

Comment 4. The document should be revised to state more clearly that the REL applies to all fluorides, not just to hydrogen fluoride. The title of the chronic toxicity summary is "FLUORIDES including HYDROGEN FLUORIDE, " with subtitles referencing hydrofluoric acid (aqueous solution) and hydrogen fluoride (as a gas). The only substance discussed under "Major Sources and Uses" is hydrogen fluoride, and the literature review also mostly addresses hydrogen fluoride. The article by Derryberry et al., however, is based on exposures to fluorides, not exposure to HF. Fluoride from HF and fluoride from other sources are

essentially indistinguishable by the human body (as well as by air sampling methods). There are many sources of fluoride other than HF. The Panel agrees that it is appropriate to recommend an REL for all fluorides, not just hydrogen fluoride. The Panel recommends that an additional statement be added to the introduction to the chronic toxicity summary to make clear that the REL applies to all fluorides, not just to hydrogen fluoride, even though much of the underlying data is derived from HF studies.

Response. Changes have been made in response to this comment. As noted in the comment, OEHHA relied primarily on health effects data on hydrogen fluoride because most of the available fluoride inhalation data are for this chemical.

Chemical Manufacturers Association (CMA) - Maleic Anhydride Panel

The Chemical Manufacturers Association (CMA) Maleic Anhydride Panel (Amoco Chemical Company, Ashland Chemical Company, Bayer Corporation, Huntsman Corporation) submitted comments on the OEHHA proposed chronic Reference Exposure Level for **maleic anhydride** on January 29, 1998. In the draft TSD OEHHA developed a chronic REL of 0.2 $\mu g/m^3$ based on respiratory tract effects in rats, hamsters, and monkeys. (The chronic REL has been revised as described below in the Responses to Comments 4 and 5.)

Comment 1. As we detail below, the strongest basis for a REL is the monkey data by Short et al., which leads to an inhalation REL of 0.06 mg/m^3 (60 $\mu g/m^3$). This is the preferred approach for maleic anhydride, which is highly reactive in nasal tissues, because of the strength of the Short monkey data and because the monkey respiratory system is more like that of humans than are rats or hamsters.

Response. In light of these comments, OEHHA has undertaken a reevaluation of the proposed maleic anhydride chronic REL, as presented below. However, as noted below in the response to Comment 2, OEHHA staff do not believe that the monkey data should be used to develop the REL.

Comment 2. California proposes an REL for maleic anhydride of 0.0002 mg/m^3 (0.2 $\mu g/m^3$, 0.05 ppb) based on the 1.1 mg/m^3 Lowest Observed Adverse Effect Level (LOAEL) it found for rats, hamsters and monkeys in the Short, et al., six-month inhalation studies (R.D. Short, et al., 1988, A six-month multispecies inhalation study with maleic anhydride, Fundamen. Appl. Toxicol. 10:517-524). The State says the study did not find a No Observed Adverse Effect Level (NOAEL) and cites as the critical effects hyperplastic change and neutrophilic infiltration of the nasal epithelium and respiratory irritation. It proposes converting the 6-hour/day, 5 days/week LOAEL exposures of 1.1 mg/m^3 to an average experimental exposure of 0.20 mg/m^3 and converting that value to a human equivalent concentration (HEC), using standard default values for gases, of 0.019 mg/m^3. To calculate the REL, the HEC is divided by 100 to account for uncertainty factors of 3 for use of a LOAEL rather than a NOAEL, 3 for interspecies variability, and 10 for intraspecies variability.

In developing its REL, California relied on highly conservative assumptions that do not present an accurate and balanced assessment of the human health risks from exposure to maleic anhydride. As we explain below, the REL should be based on the Short monkey data that are more relevant to humans. Maleic anhydride is highly irritating to nasal tissue. The Short studies of inhalation exposure for six months resulted in histological changes to nasal tissue that were indicative of such irritation.

In rats and hamsters, the histological changes observed by Short consisted of nasal epithelial hyperplasia (trace to mild) and/or metaplasia and inflammation (neutrophilic infiltration). Such lesions occurring as a result of inhalation exposure to a known strong irritant such as maleic anhydride are considered a reversible and adaptive response rather than

an adverse effect. (Monticello, T.M., K.T. Morgan, L. Uriah, 1990, Nonneoplastic lesions in rats and mice, Environ. Health Perspect, 85:249-274; Reuben, Z. and C.G. Rousseaux, 1991, The limitations of toxicologic pathology, In Handbook of Toxicologic Pathology, pp. 131-142, San Diego, Academic Press). Considerations of the adversity of hyperplastic and metaplastic lesions in rodent nasal cavities have been evaluated in the context of determining a critical effect for setting an EPA RfC (Foureman, G.L., M.M. Greenberg, G.K. Sangha, B.P. Stuart, R.N. Shiotsuka and J.H. Thyssen, 1994, Evaluation of nasal tract lesions in derivation of the inhalation reference concentration for hexamethylene diisocyanate, Inhalation Toxicology, 6(suppl): 341-355) and have been adopted by EPA for an RfC (Greenberg, M.M. and G.L. Foureman, 1995, Derivation of the inhalation reference concentration for hexamethylene diisocyanate, Toxic Substances Mechanisms, 14: 151-167).

By contrast, only slight inflammation, consisting of an infiltration of neutrophils, was observed by Short in the nasal tissues of monkeys. Pulmonary function tests in monkeys revealed no compound-related effects.

California chose the hamster data from the Short study as the basis for the REL, but the hamster data provides an inappropriate model for human health risk assessment and significantly overstates potential risks. The Panel recommends use of the monkey data because these results would provide a better estimate of the possible effect of maleic anhydride on the human nasal airway. Both monkeys and humans are nose and mouth breathers, whereas rodents are obligate nose breathers (Proctor, D.E., and Chang, J.C.F., 1983, Comparative anatomy and physiology of the nasal cavity, In: Nasal Tumors in Animals and Man, Vol. III, pp. 1-33 (G. Reznik and S.F. Stinson, Eds.), CRC Press, Boca Raton, FL; Bridger, M.W., and van Nostrand, A.W., 1978, The nose and paranasal sinuses - applied surgical anatomy, J Otolaryngol. 7 (suppl. 6): 1-33; Morgan, K.T., and Monticello, T.M., 1990, Airflow, gas deposition, and lesion distribution in the nasal passages. Environ. Health Persp. 88: 209-218; Harkema, JR., 1991, Comparative aspects of nasal airway.) Further, the anatomical structure of the nasal cavity of the monkey is more like the human nasal cavity compared to rodents (Harkema, JR., 1990, Comparative pathology of the nasal mucosa in laboratory animals exposed to inhaled irritants. Environ. Health Perspect. 85: 231-238). Thus, for a highly reactive chemical such as maleic anhydride, which produces nasal irritation with no systemic toxicity, human risk assessment should use the monkey data.

Response. The observation by Short and colleagues that monkeys, unlike rats and hamsters, did not develop hyperplastic changes of the nasal epithelium was discussed in the presentation of the proposed chronic REL. The difficulties in adopting the primate data as the sole basis for deriving a REL are: (1) neutrophilic infiltration of the nasal epithelium and irritation were observed in primates at all dose levels, and (2) only 3 monkeys per sex per dose were studied by Short et al. (1988) thus giving little evidence whether such changes might occur in a significant minority of monkeys. With only 3 animals per group there are only 16 possible outcomes of the experiment and, on chance alone, each one would occur with a probability of 0.0625. Thus no outcome has a $p < 0.05$. In addition, as noted in the document, challenge with particulate maleic anhydride at an average concentration of 0.83 mg/m^3 has resulted in acute asthmatic response in a sensitized worker.

Comment 3. The Short study finds a NOAEL for monkeys of 9.8 mg/m^3. Monkeys exhibited mucosal and/or submucosal infiltration of neutrophils into the nasal tissues at all exposure levels, but no morphological changes such as hyperplasia were observed. Since maleic anhydride is known to be very irritating to nasal tissue, this slight inflammatory response in monkeys is considered to result from the acute irritating properties of maleic anhydride.

Response. The common situation where the primary adverse effect observed for a chemical is an *acute* irritation response presents a special difficulty in developing an appropriate *chronic* REL. The chronic REL must still be protective against such effects that can be repeatedly or chronically induced as a result of long-term exposures to acutely irritating substances. The scenario in which a subset of sensitized individuals develop an atopic response to lower levels than might be a concern for non-sensitized individuals is an additional complication. Both of these issues apply to maleic anhydride.

Comment 4. The Panel thus proposes that the REL be based on the monkey data as follows:

NOAEL	9.8 mg/m^3
Average experimental exposure:	1.75 mg/m^3 for NOAEL group
Human equivalent concentration:	1.75 mg/m^3 for NOAEL group (monkeys considered equal to humans based on similar anatomy of the nasal cavity and similar surface area to volume ratio)
Subchronic uncertainty factor:	1
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10
Cumulative uncertainty factor:	30
Inhalation REL:	0.06 mg/m^3 (60 µg/m^3)

This monkey data-derived REL is both based on the best animal model for human risk assessment of maleic anhydride and within an order of magnitude of the REL values that would apply if the Short rat or hamster data were used, as shown below. Because the only systemic effects found in rodents in the Short studies are the weight losses at the highest doses in male and female rats, a REL derived from that data would be:

NOAEL	3.3 mg/m^3
Exposure continuity:	6 h/day, 5 days/week
Average experimental exposure:	0.6 mg/m^3 for NOAEL group
RGDR:	(0.395 m^3 /15 cm^2)/(20 m^3/200 cm^2)=0.263
Human equivalent concentration:	0.6 mg/m^3 x 0.263 = 0.16 mg/m^3
Exposure duration:	6 months
Subchronic uncertainty factor:	1
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10

Cumulative uncertainty factor: 30
Inhalation reference exposure level: 0.005 mg/m^3 or 5 µg/m^3

Similarly, a hamster-based REL would be based on a NOAEL as described below. The mild to trace hyperplasia and metaplasia observed in hamsters are not considered to be adverse effects for the reasons described above at page 2. The incidence of these lesions appears to be slightly lower in hamsters than in rats. As there were no compound-related effects observed for body weight in hamsters, the concentration of 9.8 mg/m^3 is a NOAEL for hamsters. Thus, the REL would be calculated as follows:

NOAEL: 9.8 mg/m^3
Exposure Continuity: 6 hr/day, 5 days/week
Average experimental exposure: 1.75 mg/m^3
RGDR 0.096 (hamster)
Human equivalent concentration: 1.75 mg/m^3 x 0.096 = 0.168 mg/m^3
Exposure duration: 6 months
Subchronic uncertainty factor 1
Interspecies uncertainty factor 3
Intraspecies uncertainty factor 10
Cumulative uncertainty factor 30
Inhalation reference exposure level 0.006 mg/m^3 or 6 µg/m^3

Response. The derivation of the chronic REL for maleic anhydride was reexamined in light of these comments. The results of three alternative analyses are presented in the following tables.

A. Alternative analysis for the repeated acute effects of irritation and inflammatory responses among the larger experimental group size rodent study.

Study	Short *et al.*, 1988
Study population	Rats (15/sex/group), hamsters (15/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium, respiratory irritation in all species
LOAEL	1.1 mg/m^3
NOAEL	Not observed
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	Relevant exposure assumed to be 1.1 mg/m^3 for repetitive acute exposures
Human equivalent concentration	0.100 mg/m^3 for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.096, based on hamster data)
Exposure duration	6 months
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1

Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.001 mg/m^3 (1 µg/m^3, 0.0002 ppm, 0.2 ppb)

B. Alternative analysis for repeated acute irritation and inflammatory responses in the smaller experimental group size monkey study

Study	Short *et al.*, 1988
Study population	Monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium, respiratory irritation in all species
LOAEL	1.1 mg/m^3
NOAEL	Not observed
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	Relevant exposure assumed to be 1.1 mg/m^3 for repetitive acute exposures
Human equivalent concentration	Not determined (inadequate data for monkeys)
Exposure duration	6 months
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1 (due to acute inflammatory character of response)
Interspecies uncertainty factor	10 (default since HEC could not be calculated)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.004 mg/m^3 (4 µg/m^3, 0.001 ppm, 1 ppb)

C. Alternative analysis for chronic effects in the smaller group size monkey study

Study	Short *et al.*, 1988
Study population	Monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Hyperplastic changes of the nasal epithelium
LOAEL	Not observed (1.1 mg/m^3 in rats and hamsters)
NOAEL	9.8 mg/m^3
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	1.75 mg/m^3 for NOAEL group
Human equivalent concentration	Not determined (inadequate data for monkeys)
Exposure duration	6 months
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10 (less than 8% of lifetime)

Interspecies uncertainty factor	10 (default since HEC could not be calculated)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Inhalation reference exposure level	0.002 mg/m^3 (2 µg/m^3, 0.0005 ppm, 0.5 ppb)

Comment 5. In sum, the strongest basis for a REL is the monkey data by Short et al., which leads to an inhalation REL of 0.06 mg/m^3 (60 µg/m^3). This is the preferred approach for maleic anhydride, which is highly reactive in nasal tissues, because of the strength of the Short monkey data and because the monkey respiratory system is more like that of humans than are rats or hamsters. RELs based on rats (5 µg/m^3) or hamsters (6 µg/m^3) are consistent between these two species and within an order of magnitude of the REL based on the monkey data. The rat and hamster values are lower primarily because they are nasal breathers and have a more tortuous architecture in their nasal cavities that tends to enhance the retention of reactive vapors and gases, factors not applicable to humans.

Response. The response to Comment 4 presented a reassessment by OEHHA with 3 alternative analyses that incorporate consideration of the lack of evidence of cumulative chronic effects or systemic toxicity differing substantially from acute irritative effects. These analyses using guidelines developed by USEPA and OEHHA resulted in possible chronic REL values of 1, 2, and 4 µg/m^3. Because of the small size of the monkey group studied and several reports implicating maleic anhydride in asthmatic responses in sensitized individuals, OEHHA recommends the first reanalysis (*A.* Alternative analysis for the repeated acute effects of irritation and inflammatory responses among the larger experimental group size rodent study). This reanalysis resulted in a chronic REL for maleic anhydride of 1 µg/m^3 to protect against both chronic and repetitively induced acute adverse effects.

Chemical Manufacturers Association - Olefins Panel

Comments on the chronic RELs for **ethylene** and **1,3-butadiene** were received from Courtney M. Price, on behalf of the Olefins Panel of the Chemical Manufacturers Association (CMA), in a letter dated January 29, 1998. (Comments on propylene were dealt with previously.)

In addition to the comments below, the commentator provided a list of the references cited. This list is available upon request. The commentator also provided two slides of data in an appendix. These slides were presented by Dr. James Swenberg of CMA in March of 1996 regarding ethylene and ethylene oxide research. The appendix is also available upon request.

I. Comments regarding the ethylene REL. OEHHA developed a chronic inhalation REL of 100 $\mu g/m^3$ for ethylene based on the chronic REL of ethylene oxide, to which ethylene is metabolized.

Comment 1. OEHHA should not use an ethylene oxide study to establish the REL for ethylene. It is fundamental to sound science that, when sufficient data are available, the risk assessment for a chemical should be based on studies of the chemical itself. To do otherwise is scientifically unjustified and introduces unnecessary uncertainties into the risk assessment. Use of surrogates (e.g., structural analogue relationships or metabolite studies) may be appropriate if there is insufficient data on the chemical itself, but, even then, such approaches should be used with caution.

Although sufficient data exist to conduct a risk assessment for ethylene [discussed in more detail below], OEHHA has used data for ethylene oxide. Such an approach - using data on a metabolic product when data on the chemical are available - is highly unusual and is unprecedented in U.S. EPA and other agency evaluations of ethylene. The Panel strongly objects to this approach.

Response. OEHHA staff agree that such approaches are unusual and should be used with caution. However, when the chronic REL was developed, OEHHA staff wanted to base as many RELs as possible on human data. Since ethylene is metabolized to ethylene oxide, we originally decided to base the REL for ethylene on the REL for ethylene oxide, which was based on human data. However, based partly on critiques of the Schulte et al. by the Chemical Industry Institute of Toxicology (CIIT) and the Ethylene Oxide Industry Council of the CMA, we are revising the chronic REL for ethylene oxide and basing it on the report of neurotoxicity in EtO exposed workers by Klees at al. (1990).

Comment 2. The data do not support OEHHA's use of an ethylene oxide study to establish the ethylene REL. OEHHA's rationale for using the ethylene oxide data is that 1) ethylene is metabolized to ethylene oxide and 2) humans may be more sensitive to effects from ethylene oxide inhalation than are animals in experimental studies. The OEHHA summary states that, at the maximum rate of metabolism of ethylene in the rat, the theoretical ethylene oxide exposure is 5.6 ppm, which is below observed NOAEL levels in the rat of 10-50 ppm

ethylene oxide. OEHHA then speculates that humans may be more sensitive to ethylene oxide exposure than experimental animals, because "[n]on-cancer adverse effects (LOAELs) have been found at concentrations of 10 to 0.17 ppm (Zampollo *et al.*, 1984; Estrin *et al.*, 1987; Schulte *et al.*, 1995)." A comprehensive review of these studies shows they do not support this contention.

The 0.17 ppm value is taken from Schulte *et al.* (1995), which OEHHA also used as the basis for the ethylene oxide REL. The Schulte *et al.*, study is discussed extensively in comments which are being submitted separately by the Ethylene Oxide Industry Council, which are incorporated herein by reference. Those comments show: 1) the Schulte study is of questionable validity because of its small control population; 2) the effects noted by Schulte *et al.*, have not been demonstrated to have clinical significance -- that is, they are not adverse effects; and 3) the exposure assessment, which was acknowledged by the study authors to be a weakness of the study, did not account for peak exposures. Schulte *et al.* state in their paper that their results are not conclusive and may merely reflect chance physiological variation. Therefore, the Schulte *et al.*, study does not support 0.17 ppm as an adverse effect level in humans.

Zampollo *et al.* (1984) reported two cases of peripheral neuropathy in twelve nurses who removed objects from an ethylene oxide sterilizer and sorted the objects on a tray. The paper provides very little information on the collection of ethylene oxide concentration data, but does clearly state that values were 30 to 400 ppm in the vicinity of the sorting tray while a nurse sorted sterilized objects. Thus, this study does not support a human LOAEL of 10 ppm or less.

Estrin *et al.* (1987) measured nervous system function in 8 hospital workers that worked in proximity to ethylene oxide sterilizers and in 8 nonexposed controls. The authors report that, "Six exposed subjects reported olfactory detection of the gas on repeated occasions indicating exposures near or above the odor threshold of 700 ppm." In addition, industrial hygiene sampling records showed peak exposures in the employees' breathing zones in excess of the upper detection limit of 200 ppm. Estrin *et al.* (1987) note that, "Exposure to EtO [ethylene oxide] in hospitals generally occurs in predictable, relatively high, short-term peaks." Thus, although the average exposure may be low, the observed effects in studies of hospital workers quite possibly are due to the high peak concentrations and are not indicative of potential effects from chronic exposure to low levels of ethylene oxide. Thus, this study does not support a LOAEL of 10 ppm or less for human exposure to ethylene oxide.

Response. Because of the difficulties with the use of the study of Schulte et al. (1995) in the development of a REL for ethylene oxide (see CIIT and CMA comments and responses on the ethylene oxide REL), OEHHA has decided not to base the chronic inhalation REL for ethylene on that report.

Comment 3. In contrast to the Zampollo *et al.* and Estrin *et al.* case studies of workers exposed to high peak concentrations, Joyner (1964) conducted a retrospective morbidity study of 37 workers with 5 to 16 years of occupational exposure to ethylene oxide at 5 to 10 ppm.

There was no statistically significant increase in the incidence of neurological disorders compared to controls. After a review of the data for ethylene oxide, Golberg (1986) concluded that neurological effects were unlikely to occur at ethylene oxide exposures up to 100 ppm. Thus, the weight of evidence does not support OEHHA's proposition that humans are more sensitive to ethylene oxide exposure than are experimental animals.

Response. Other studies have been reported since Golberg made his conclusion in 1986. OEHHA staff believe that neurological effects may occur in workers due to chronic exposures to ethylene oxide below 100 ppm. Such studies are described in the ethylene oxide summary under effects of human exposure and include Estrin *et al*. (1987, 1990) and Klees *et al*. (1990). OEHHA is now proposing a revised chronic REL for ethylene oxide of 30 $\mu g/m^3$ based on nervous system effects in humans as reported by Klees et al. (1990).

Comment 4. Furthermore, even if there were evidence that humans are more sensitive than rodents to inhaled ethylene oxide, it would not follow that humans are most sensitive to effects from inhaled ethylene. The metabolism of a compound to a toxic metabolite occurs within the cells of metabolically-active tissues such as the liver. The effects of directly inhaling ethylene oxide, therefore, are not necessarily the same as the effects of ethylene oxide generated by metabolism of inhaled ethylene.

There are a number of endogenous sources of ethylene in the human organism: lipid peroxidation, oxidation of free methionine, oxidation of hemin in hemoglobin, and metabolism of intestinal bacteria (Filser *et al.*, 1992). In addition, natural exogenous sources of ethylene exist. It is a natural product of vegetation of all types and acts as an endogenous plant growth regulator. Sawada and Totsuka (1986) estimate that approximately 74 percent of ethylene emissions are from natural sources. Thus, humans evolved in the presence of both exogenous and endogenous sources of ethylene.

Studies being conducted by Dr. James Swenberg of the University of North Carolina demonstrate that humans have endogenous levels of significant quantities of ethylene oxide adducts. Dr. Swenberg has found that endogenous levels of the ethylene oxide-DNA adduct in the human liver are equivalent to levels produced in rats exposed to 10 ppm ethylene oxide or mice exposed to 33 ppm ethylene oxide. [Note: The level of 7-hydroxyethylguanine (7-HEG) in DNA from liver of nonexposed humans was 1.4 to 4.5 pmol/μmol Guanine, with a mean value of 3.0 pmol/μmol G. The mean level of 7-HEG in the liver of rats exposed to 10 ppm EtO was 3.3 pmol/μmol G, and the mean level of 7-HEG in the liver of mice exposed to 33 ppm EtO was 3.75 pmol/μmol G. A copy of a presentation by Dr. Swenberg that includes this data is provided as Appendix A.] Assuming equivalent concentrations of ethylene oxide produce equivalent concentrations of DNA adduct in humans and rodents, the humans were exposed endogenously at the rodent equivalent of 10 to 33 ppm inhaled ethylene oxide. Using a factor of 3 percent ethylene converted to ethylene oxide (human conversion saturation), the human endogenous exposure would be equivalent to an environmental exposure of 333 to 1100 ppm ethylene. Thus, OEHHA's proposed REL of 0.1 ppm ethylene appears to be some 3,300 to 11,000 times lower than what the human body spontaneously produces.

Response. OEHHA acknowledges that the body can produce ethylene. The body also produces the toxic chemical carbon monoxide (CO) from heme and uses nitric oxide (NO) as a hormone. Levels of hydrogen chloride, which can cause inflammation in other tissues, are normally present in the stomach. The relevant information of interest is the adverse effect(s) of exogenous ethylene which is inhaled.

Comment 5. The Panel therefore believes OEHHA is not justified in using ethylene oxide data to establish the REL for ethylene. Because adequate data exist to directly evaluate ethylene, OEHHA should base the REL on the ethylene studies. [Note: If OEHHA nevertheless persists in using ethylene oxide, then its analysis should be revised in accordance with the comments being separately submitted by the Ethylene Oxide Industry Council.]

Response. OEHHA has revised its chronic REL for EtO based in part on the comments from CMA's Ethylene Oxide Industry Council and those from the Chemical Industry Institute of Technology (CIIT). We will be discussing this with the Scientific Review Panel on Toxic Air Contaminants.

Comment 6. OEHHA should derive the REL for ethylene from the chronic study on ethylene. The toxicological database for ethylene includes both a comprehensive lifetime inhalation study in rats (Hamm *et al.*, 1984) and an inhalation reproductive/developmental study in rats (Aveyard and Collins, 1997). These studies provide an adequate and appropriate basis for deriving the REL for ethylene, especially since the pharmacokinetics of ethylene in rats and humans has been shown to be similar (Shen *et al.*, 1989). The existence of the reproductive/developmental study provides confidence that the chronic study did not miss potential sensitivity to reproductive or developmental effects. Because the route of exposure for both studies is inhalation, they are particularly relevant for derivation of the REL, which is an air concentration risk parameter.

Hamm *et al.* (1984) exposed rats to 300, 1000, or 3000 ppm ethylene for 6 hours/day, 5 days/week, for 24 months with no observed toxic effects. Hematology, blood chemistry, and urinalysis tests were performed at six-month intervals throughout the study. Over 24 months, no differences were observed between exposure groups with respect to mortality, clinical blood chemistry, urinalysis, body weights, organ weights or histopathology of a variety of tissues and organs. Inflammatory lesions typical of this strain of rat were distributed equally among all exposure groups. The NOEL in this study was 3000 ppm.

As discussed by OEHHA, a 13-week inhalation study of Sprague-Dawley rats found no treatment related effects at levels up to 10,000 ppm ethylene (Rhudy *et al.*, 1978). Parameters measured included body weight, total weight gains, food consumption, hematology, clinical chemistry, urinalysis, and histopathology.

Aveyard and Collins (1997) evaluated the potential effects of ethylene inhalation on male and female rat reproduction, growth and development using OECD Guideline 421

(Reproduction/ Development Toxicity Screening Test). Administration of ethylene at nominal concentrations of 200, 1000, or 5000 ppm showed no evidence of toxicity. There were no adverse effects on male or female reproductive performance, fertility, pregnancy, maternal and suckling behavior, or growth and development of the offspring from conception to Day 4 post-partum. The general toxicity NOEL was 5000 ppm and the reproductive/developmental toxicity NOEL was 5000 ppm.

The Panel believes that OEHHA should derive the ethylene REL from the chronic rat study, as follows:

Study	Hamm et al. (1984)
Study population	Fischer 344 Rats (120/sex/group)
Exposure Method	Inhalation exposure at 300, 1000 or 3000 ppm
Critical effects	None
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	24 months
NOEL	3000 ppm
Average experimental exposure	535 ppm
Human equivalent conc.	535 ppm (gas with no extrathoracic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	1
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level (REL) for ethylene	5.4 ppm (6.2 mg/m ^{3})

Response. OEHHA staff agree that this is an acceptable approach to a REL and is considering basing the chronic REL for ethylene on the Hamm et al. report. However, since an HEC calculation has been made, an interspecies uncertainty factor of 3 can be used instead of 10. Unfortunately, no critical effect can be assigned from the study by Hamm et al. In the workplace ethylene is considered to be a “simple” asphyxiant. Thus its target organ could be considered to be the respiratory system and/or the blood since asphyxiants prevent oxygen from getting to hemoglobin. However ethylene has been used as an anesthetic in people (for example: Brumbaugh JD. 1928. Effects of ethylene-oxygen anesthesia on the normal human being. JAMA 91:462-465). Such use indicates effects other than asphyxiation. In addition ethylene can be metabolized to ethylene oxide which is a neurotoxicant. Thus, in humans there is evidence to consider ethylene as a gas with systemic effects.

Comment 7. The Panel notes that, given the fact that no effects have been detected in any studies of ethylene, even at very high air concentrations (1% ethylene), this REL is very conservative. The Occupational Safety and Health Administration (OSHA) does not regulate inhalation exposure to ethylene. The American Conference of Governmental and Industrial

Hygienists (ACGIH) has determined ethylene is essentially toxicologically inert. It has not set a threshold limit value (TLV) for ethylene, but has classified it as a "simple asphyxiant," defined as follows:

> Simple Asphyxiants -- "Inert" Gases or Vapors. A number of gases and vapors, when present in high concentrations in air, act primarily as simple asphyxiants without other significant physiologic effects. A TLV may not be recommended for each simple asphyxiant because the limiting factor is the available oxygen.

Response: Ethylene is included because it is listed as a Hot Spots chemical. OEHHA admits that it is difficult to develop a reference exposure level for a simple asphyxiant. However several reports, which are cited in the revised chronic toxicity summary for ethylene, have indicated that ethylene has been used as an anesthetic. This implies that ethylene has neurotoxic effects and is not just a simple asphyxiant.

Comment 8: OEHHA's REL discussion should emphasize the lack of effects observed for ethylene, even at concentrations as high as 10,000 ppm in a subchronic study.

Response: The chronic REL summary states that "The available data indicate that ethylene has a low potential for non-cancer chronic toxicity in experimental animals." Also it states that no effects were seen in the 13 week study where 10,000 ppm were studied.

II. Comments regarding the 1,3-butadiene REL. OEHHA developed a chronic inhalation REL of 8 $\mu g/m^3$ for 1,3-butadiene based on ovarian atrophy in mice exposed by inhalation.

Comment 9. OEHHA should base the butadiene REL on rat data, because human metabolism of butadiene is more similar to the rat than the mouse. Ovarian atrophy in the mouse is not an appropriate endpoint for derivation of the REL. OEHHA notes in the draft Technical Support Document that "the animal species most sensitive to a substance is not necessarily the most similar to humans in developing adverse effects from a particular exposure." In the case of butadiene, use of the most sensitive species - the mouse - is not appropriate, because compelling evidence indicates that the rat is a more appropriate model for estimating risks to humans. The ovarian atrophy observed in the mouse has not been observed in the rat, even when exposed to butadiene at concentrations as high as 8000 ppm. This is due to differences in the metabolism of butadiene by the mouse and the rat. Studies show that human metabolism of butadiene is similar to that of the rat, and not of the mouse. Therefore, direct extrapolation from the mouse ovarian effects is inappropriate to derive a health effect level for human protection.

The Panel previously has submitted comments to OEHHA concerning the potential reproductive toxicity of 1,3-butadiene. For example, in December 1996 the Panel submitted comments on OEHHA's "Draft Prioritized Candidate Chemicals Under Consideration for

Developmental/Reproductive Toxicity Evaluation," dated October 4, 1996. [Note: Letter from Langley A. Spurlock, Vice President, CHEMSTAR, to Cynthia Oshita, Senior Hazardous Materials Specialist, OEHHA, re: Draft Prioritized Candidate Chemicals Under Consideration for Developmental/Reproductive Toxicity Evaluation, October 4, 1996 (Dec. 2, 1996)] In October 1997, the Panel submitted comments in response to OEHHA's request for relevant information on chemicals under consideration for Proposition 65 listing via administrative mechanisms. [Note: *Comments of the Chemical Manufacturers Association Olefins Panel on the Possible Listing of 1,3-Butadiene as a Reproductive Toxicant Via Administrative Mechanisms,* submitted to Cynthia Oshita, OEHHA (Oct. 21, 1997)] Attachments to these comments include relevant excerpts from Panel comments to OSHA and testimony to OSHA by Dr. Mildred Christian, a leading authority on developmental and reproductive toxicity. The Panel urges OEHHA to review these comments and their attachments with respect to developing an REL for butadiene. Upon request, we will submit additional copies of the comments and attachments.

As explained in the previous comments to OEHHA, the mouse is unique in its sensitivity to butadiene. Ovarian atrophy or other reproductive effects have not been observed in the rat at butadiene exposure levels up to 8000 ppm administered by inhalation for two years (Owen *et* al., 1987). In addition, no histopathologic changes were detected in the ovaries of rats, guinea pigs, rabbits, or dogs exposed to butadiene at concentrations up to 6700 ppm for eight months (Carpenter *et al.*, 1944, as discussed in Christian, 1996).

Dr. Glenn Sipes and his colleagues, of the University of Arizona, have developed data that explain the mechanism by which butadiene causes ovarian atrophy in the mouse (Doerr *et al.*, 1996). Their work shows that the monoepoxide metabolite of butadiene causes some ovarian effects in the mouse, but not in the rat. The diepoxide metabolite causes ovarian effects in both the mouse and rat, but is more potent in the mouse and is far more potent in the mouse than is the monoepoxide. In other words, the primary cause of the ovarian atrophy observed in mouse (and not observed in the rat) appears to be the diepoxide metabolite of butadiene.

Rats are much less efficient at metabolizing butadiene to monoepoxide than are mice, and primates - including humans - convert even less butadiene to the monoepoxide than do rats (Csanady, *et* al., 1992; Schmidt and Loeser, 1986; Himmelstein, *et al., 1994;* Himmelstein, *et al.*, 1995; Dahl, *et al*., 1991). Workers exposed to butadiene showed at least 25-fold lower levels of the monoepoxide hemoglobin adduct per ppm-hour than rats, and more than 100-fold lower adduct levels than mice (Osterman-Golkar, *et al*., 1993). Furthermore, the metabolism of the monoepoxide in the mouse proceeds largely by further epoxidation to the diepoxide (Himmelstein, *et al.*, 1997). In contrast, rats form very little diepoxide (Csanady, *et al.*, 1992; Thorton-Manning, *et al.*, 1995), and primates hydrolyze most of the monoepoxide, rather than convert it to diepoxide (Csanady, *et al.*, 1992; Dahl, *et al.*, 1991). Thus, diepoxide levels are much higher in mice than in rats or primates (Thornton-Manning, *et al.*, 1995; Sweeney, *et al.*, 1997; Seaton, *et* al., 1995).

In summary, the diepoxide metabolite of butadiene appears to be responsible for the ovarian atrophy observed in the mouse. Very little diepoxide, if any, is produced through

metabolism in rats, and no atrophy is observed in rats exposed to butadiene. Even less diepoxide is produced in human tissues. Therefore, the data in mice are not relevant to assessment reproductive effects in humans, and the mouse ovarian atrophy is an inappropriate basis for the establishment of an REL.

Response. OEHHA staff agree that the mouse ovary may be more (or much more) sensitive to butadiene due to butadiene's metabolism to the diepoxide and that people are more like the rat in their formation of epoxides from butadiene. The diepoxide could be much more rapidly destroyed in rats than in mice. (In a somewhat analogous situation both mice and rats form a reactive carcinogenic epoxide from aflatoxin. Mice metabolize the aflatoxin epoxide via glutathione much more rapidly than rats, so that the rat is about 1000x as sensitive as the mouse to aflatoxin-induced carcinogenesis.)

Unique may not be an appropriate term in the case of butadiene if mice are really at one end of the spectrum in sensitivity to butadiene. Unique is probably better applied to situations such as male rat kidney tumors due to accumulation of alpha2u globulin which only accumulates in the kidneys of male rats. OEHHA staff still propose using an interspecies uncertainty factor of 3 for this endpoint with butadiene because we believe that pharmacodynamic differences between mice and men are still not adequately counted for.

Comment 10. OEHHA should develop an REL based on rat data. Apart from reproductive toxicity, the mouse NTP study relied upon by OEHHA gave a NOAEL of 200 ppm, based on nonneoplastic hematotoxic effects (NTP, 1993). As for ovarian atrophy, however, these effects in the mouse do not appear applicable to other species. In the chronic study of Sprague-Dawley rats, blood was evaluated from 20 animals of each sex per group after 3, 6, 12, and 18 months of exposure to 0, 1000, or 8000 ppm of butadiene (IISRP, 1981; Owen *et al.*, 1987). Any changes of hematological parameters that occurred were within normal values for the strain and laboratory, and the study authors did not consider them to be toxicologically significant.

Cowles *et al.* (1994) conducted retrospective mortality, prospective morbidity, and hematological analyses of male workers employed in butadiene monomer production from 1948 to 1989. Hematology data was available for 429 of these workers. No hematological differences were seen for any butadiene-exposed employees, including a group exposed to an estimated time-weighted average of 10 ppm, as compared to employees not exposed to butadiene. This is consistent with Checkoway and Williams (1982), who reported minimal changes in the hematology of a subgroup of 8 workers in a styrene-butadiene rubber manufacturing plant, exposed to 20 ppm butadiene, versus 145 workers exposed to less than 2 ppm butadiene. The statistical significance of the changes is questionable due to the very small population and the failure to account for confounding factors such as race, smoking, body size, exercise, and ethanol intake. Checkoway, *et al.* (1984) concluded that the hematologic parameter values for the subgroup of 8 were within the normal range. Both Checkoway, *et al.*, (1984) and IARC (1992) concluded that the changes could not be interpreted as an effect on the bone marrow.

This difference in the hematological effects seen in the mouse study versus rat and human studies is in keeping with the metabolic differences discussed above. *In vitro* and *in vivo* evidence indicates that hematopoietic effects such as macrocytic megaloblastic anemia induced in mice by butadiene exposure are due to the epoxide metabolites, especially the monoepoxide (Colagiovanni, et al., 1993; Irons, et al., 1995). Mice, but not rats or humans, have a subpopulation of primitive hematopoietic progenitor cells which are very sensitive to the monoepoxide metabolite. Species differences in the metabolism of butadiene to the epoxides, as well as the different susceptibility of the hematopoietic system, indicate that the mouse is not the most appropriate species for deriving a chronic REL.

Because human metabolism of butadiene is more similar to that of the rat than that of the mouse, the Panel believes that the REL is more appropriately based on rat data than on mouse data. A suitable study is the two-year chronic inhalation study (IISRP, 1981; Owen, *et al*., 1987). That study provided a NOEL of 1000 ppm, which can be converted to an REL as follows:

Study	IISRP, 1981; Owen, *et al.*, 1987
Study population	Sprague-Dawley rats (100/sex/group)
Exposure method	Discontinuous whole body inhalation exposure (0, 1000, or 8000 ppm)
Critical effects	Minor clinical effects (eye and nose excretions, slight ataxia); increased liver and kidney weights; nephrosis.
LOAEL	8,000 ppm
NOEL	1,000 ppm
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	2 years
Average experimental exposure	178.6 ppm
Human equivalent concentration	178.6 ppm (gas with no extrathoracic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	1.8 ppm (4 mg/m^3)

Response. The commentator has provided a plausible alternative to the chronic REL calculated by OEHHA. However, since there is a 200 ppm NOAEL in mice for a hematological toxicity, the use of the rat 1000 ppm NOAEL may not be appropriate. Yet since no hematologic effects were seen in 2 epidemiologic studies at 10 and 20 ppm butadiene, the use of the hematologic endpoint may also not be appropriate. As stated below, OEHHA prefer to use the mouse data because of the sensitivity of the endpoint.

Comment 11. If OEHHA uses mouse data, it should apply a pharmacokinetic adjustment. For the reasons discussed above, the Panel believes the rat provides a better model for conducting a human health risk assessment of butadiene than does the mouse. If OEHHA nevertheless chooses to base the REL on mouse data, it should use a physiologically-based pharmacokinetic (PBPK) model to adjust that data, due to the great differences in mouse metabolism of butadiene from that of rats and humans. Use of the 200 ppm NOAEL for hematological effects and applying OEHHA's standard adjustments would result in an REL of 0.36 ppm. Without adjustment for the metabolic differences between mice and humans, however, that REL would be extremely conservative.

Extensive work has been done and is continuing to develop and refine PBPK models for butadiene (Himmelstein, *et al.*, 1997; ECETOC, 1997). Upon request, the Panel would be pleased to provide technical support to OEHHA to apply appropriate PBPK adjustments to mouse data for the development of a REL, if OEHHA declines to use rat data for the REL.

Response. OEHHA appreciates the offer of technical support by the commentator. OEHHA staff have some experience in pharmacokinetic modeling of butadiene (Brown, J.P., and Collins, J.F.: Use of microcomputers to apply butadiene metabolic data to public health risk assessment. FASEB J. 7:A1130, 1993). A credible approach might be to use an interspecies uncertainty factor less than the default of 10 (or 3 after an HEC adjustment) for mouse to man since in the case of butadiene humans are not up to (3 to) 10 times more sensitive than mice. Pharmacokinetic information indicates that mice are not less sensitive than people to 1,3-butadiene. However we still need to account for pharmacodynamic differences. Thus we use an interspecies UF of 3 after the HEC adjustment.

OEHHA staff note that USEPA has used a benchmark dose approach to develop a (proposed) reproductive/developmental RfC for butadiene of 0.15 ppb (0.3 $\mu g/m^3$) based on the dominant lethal effect of decreased litter size in mice at birth.

Chemical Manufacturers Association – Phthalate Ester Panel

Comments on the chronic RELs for **phthalic anhydride** were made by the Phthalate Ester Panel of the Chemical Manufacturers Association in a letter dated January 29, 1998. OEHHA proposed a chronic REL for phthalic anhydride of 10 $\mu g/m^3$ based on eye and respiratory irritation, asthma, and bronchitis in 23 workers occupationally exposed for a mean of 13.3 years (Neilsen *et al.* (1988; 1991)). (Comments of the Panel on DEHP were dealt with previously.)

Comment 1: *Phthalic anhydride*. OEHHA should base an interim REL for phthalic anhydride on the ACGIH TLV, and should emphasize in its discussion phthalic anhydride's solid nature and its low oral toxicity.

Response: OEHHA has not based chronic RELs on ACGIH TLVs. USEPA, OEHHA, and even ACGIH have all determined ACGIH TLVs should not be used in developing health-based exposure guidance for general populations including the elderly and children. TLVs lack a consistent basis and are intended to protect only healthy workers from discontinuous exposures, rather than the public from continuous exposures. Many TLVs are not health-based and/or are intended to reduce rather than eliminate the occurrence of adverse health effects.

Comment 2: OEHHA should emphasize in the REL discussion the fact that phthalic anydride is a solid at ambient temperatures, and that it has very low systemic toxicity when ingested.

Response: OEHHA noted the crystalline form of phthalic anhydride at ambient temperatures and its low vapor pressure. Mass concentration units ($\mu g/m^3$) were not converted to volume concentration units (ppb) in the Chronic Toxicity Summary. However as noted above for DEHP, particulate air contaminants may exist at levels hazardous to human health. The particulate nature of phthalic anhydride in inhalation exposure studies in animals administered by Sarlo and Clark (1992) and Sarlo and associates (1994) was clearly presented. Text is being added at several locations in the document to emphasize the particulate nature of DEHP in human and animal exposure studies.

Comment 3: OEHHA based the proposed REL for phthalic anhydride on a pair of studies by Nielsen et al. (1988; 1991). Those studies do not support a correlation between phthalic anhydride exposure and the purported critical effects. The reported effects were minimally adverse and reversible, are commonly reported by workers, and could have been due to colds, allergies, or exposure to other chemicals.

Response: Several categories of response were significantly increased in heavily exposed workers compared with those with limited exposures. The effects noted (asthma, chronic bronchitis, conjunctivitis, and rhinitis) were consistent with a hypersensitization response among repeatedly exposed workers. A similar hypersensitization response was noted in animals exposed to phthalic anhydride dust (Sarlo *et al.*, 1994). The induction of asthma and

bronchitis would not be categorized as a "minimally adverse" response. Reversibility of adverse effects is not a sufficient reason to ignore the finding; among other reasons, the RELs are intended to protect the public from continuous lifetime exposure. That effects noted in occupationally exposed workers may be due, in least in part, to exposure to other substances is a reasonable concern. However, as noted above, the immunologically-based effects noted are consistent with those noted among rats exposed only to phthalic anhydride. As for the contention that effects noted among the heavily exposed workers might be due to colds or allergies, there is no reason to anticipate the heavily exposed workers should be more affected than lightly exposed workers.

Comment 4: No existing chronic or subchronic inhalation studies of phthalic anhydride are appropriate for the derivation of an REL, so OEHHA should not establish a final REL for phthalic anhydride.

Response: As described in the response to comment 8, OEHHA still concludes that the data of Nielsen et al. (1988; 1991) are adequate for the purposes of deriving a chronic REL. As is the case for all chemicals reviewed, additional data would be desirable and will be considered if such data should become available in the future.

Comment 5: As an interim measure, OEHHA should base an interim REL on the ACGIH TLV, adjusted for continuous exposure and variation in sensitivity.

Response: OEHHA has not based chronic RELs on ACGIH TLVs. USEPA, OEHHA, and even ACGIH have all determined ACGIH TLVs should not be used in developing health-based exposure guidance for general populations including the elderly and children. TLVs lack a consistent basis and are intended to protect only healthy workers from discontinuous exposures rather than the public from continuous exposures. Many TLVs are based on feasible control technology, not health, and are intended to reduce rather than eliminate the occurrence of adverse health effects.

Chloropicrin Manufacturers' Task Force (CMTF)

The Chloropicrin Manufacturers' Task Force (CMTF) submitted comments on January 29, 1998 regarding the draft chronic reference exposure level for **chloropicrin** presented in the OEHHA *Air Toxics "Hot Spots" Risk Assessment Guidelines Part II. Technical Support Document for Determining Chronic Reference Exposure Levels*. The members are Ashta Chemicals, Holtrachem Manufacturing, Niklor Chemical, Trinity Manufacturing, Agrevo Canada, Angus Chemical, Dow AgroSciences, Great Lakes Chemical Corp. and Trical Products. OEHHA developed a chronic REL of 4 $\mu g/m^3$ based on respiratory system effects (nasal rhinitis) in rats.

Comment 1. OEHHA's proposed REL for chloropicrin is based on a chronic inhalation oncogenicity study performed by whole-body exposure to rats (Burleigh-Flayer and Benson, 1995). OEHHA identified increased mortality, increased lung and liver weights and rhinitis as effects of chloropicrin inhalation exposure in their summary of the Burleigh-Flayer and Benson study. CMTF disagrees that liver weights were affected by chloropicrin treatment in the chronic rat study. Tables 17-22 of the study final report (Burleigh-Flayer and Benson, 1995) present organ weight data that show male rat liver weights, both absolute and relative to body and brain weight, were unaffected by exposure to chloropicrin. The absolute liver weight of female rats was statistically-significantly depressed in the mid-dose group (as was this group's body weight) but not in the low or high-dose groups. The liver weight of the female animals as compared to their body or their brain weight, i.e., relative liver weight, was not affected by chloropicrin treatment in any dose level in the study. The decrement in absolute liver weight but not relative liver weight observed in the mid-dose female rats is a reflection of the body weight diminution experienced by these animals and is not indicative of a toxic effect in the liver. The study director concluded this, and on page 19 of the study report writes: "Some statistically-significant changes in absolute kidney and liver weight for female animals from the low and/or mid groups were believed to be the result of their lower final body weight and were not believed to be exposure related."

Response. OEHHA reexamined this issue and accepts the commentator's correction that the liver findings involve decreased liver and body weights in the mid-dose female rats, lack a monotonic dose-response relationship, and are not evidence of a direct toxic effect to this organ. Therefore the identification of liver effects as an endpoint is being removed.

Comment 2. OEHHA adjusted the No Observed Adverse Effect Level (NOAEL) from the Burleigh-Flayer and Benson study for continuous exposure (to 0.018ppm) and applied an uncertainty factor of 3 for interspecies uncertainty and an additional factor of 10 for intraspecies uncertainty. The CMTF believes that, because the critical effects that support the derivation of the OEHHA REL are limited to respiratory system irritation and are not progressive, there is no need for an interspecies uncertainty factor. The nonspecific irritation effects seen at the portal of entry and target organ following overexposure to chloropicrin are equivalent across all species tested (Chun and Kintigh, 1993; Yoshida, 1987; Schardein, 1994; Schardein, 1993a and 1993b; Burleigh-Flayer, 1994; NCI, 1978; Wisler, 1995; Ulrich, 1995). Nonspecific irritation at the site of contact was seen in all species evaluated, including dogs,

rabbits, rats and two strains of mice. There is no basis to conclude that humans will respond differently from these mammalian species.

Response. The available data do indicate that chloropicrin is highly reactive and causes effects at the immediate sites of contact. But the effects noted can be more severe than irritation. Kane and associates (1979) noted exfoliation, erosion, ulceration, and necrosis of respiratory and olfactory epithelium of mice exposed to 7.9 ppm chloropicrin for 6 hours per day for 5 days. Fibrosing peribronchitis and peribronchiolitis were noted in the lower respiratory tract. Furthermore there is no evidence comparing the relative toxicity of chloropicrin between rodents and humans. Most notably, increased mortality was observed in the Burleigh-Flayer and Benson study. Secondly, similar effects are commonly noted among different species exposed to the same chemical but the magnitude of exposures causing equivalent response may differ substantially.

Comment 3. Likewise, there is no basis to presume that human respiratory tissue will be differentially susceptible to chloropicrin irritation. Therefore, a 10-fold factor for intraspecies uncertainty is not justified for chloropicrin.

Response. The intraspecies factor is intended to protect sensitive subgroups, such as the elderly and children, and those with preexisting medical conditions that may increase the susceptibility to adverse effects following exposure to chloropicrin. Variability in response among individuals to the same toxic stimuli has been noted in virtually all toxicity studies, although the degree of variability may differ for different chemicals and different endpoints. On the basis of currently available data, OEHHA believes a 10-fold intraspecies uncertainty factor is warranted.

Comment 4. Because the respiratory effects of chloropicrin are concentration and not dose-dependent, duration of exposure is not a factor in producing effects, nor in preventing effects. Accordingly, the OEHHA adjustment of the Burleigh-Flayer exposure to a continuous exposure is unnecessary. According to the American Conference of Governmental Industrial Hygienist (ACGIH), exposure to chloropicrin at a concentration of 0.1 ppm will not result in eye or respiratory irritation, but irritation does occur at concentrations of 0.3 to 0.37 ppm (ACGIH, 1991). Concentration-dependent chemicals are defined as fast-acting chemicals whose toxic effects are immediate, and correlate more closely to concentration than dose. Included in this category are sensory irritants, and chemicals that are corrosive or vesicant in their action. In contrast, the effects of dose-dependent chemicals are a function of both concentration and duration of exposure" (Craig, 1995). Chloropicrin at low levels (0.15-0.3 ppm) produces a clear warning of exposure. At higher exposure levels (1 ppm or more), chloropicrin produces a consistent pattern of pulmonary injury in humans and test animals. The protective warning properties of chloropicrin occur at airborne concentrations of 0.15 ppm. Exposure to chloropicrin below this concentration has no effect and an application of safety, or uncertainty, factors is without rationale. Because the short-term effects, i.e. sensory irritation, are the overriding effects from chloropicrin exposure, chronic toxicity data from animal studies should not be used to establish chloropicrin exposure criteria.

Response. The commentator did not provide any direct evidence to support the contention that effects following chloropicrin exposure are completely independent of exposure duration. Were a large subchronic uncertainty factor applied, the commentator's point might have greater relevance. But in this case no subchronic uncertainty factor was used. Thus the degree to which exposure duration may have lesser importance for this chemical is already reflected in the data collected in the chronic exposure study. The commentator's main point may be thus directed at the approximately 5.6-fold adjustment used to account for the discontinuous (6 hr/day, 5/day per week) exposures. There are no data demonstrating that there would be no difference between continuous and discontinuous exposures in this case, so some adjustment is warranted. In the Kane study, recovery was observed three days after the completion of a 5 day exposure period, indicating that continuous exposure may result in more severe effects than discontinuous exposure (where some recovery will be taking place).

Comment 5. In response to the statement in the draft REL indicating that adequate reproductive toxicity data is a major area of uncertainty in the chloropicrin data base, the CMTF would like to point out the existence of a chloropicrin multi-generation reproductive toxicity study (Schardein, 1994).

Response. OEHHA thanks the commentator for providing information about this unpublished study. As of June 1999 it has not appeared in the peer-reviewed literature. However, OEHHA would like to obtain a copy for review.

Elementis Chromium

Comments on the chronic REL for **chromium VI** were made by R.J. Barnhart, Ph.D., Vice President-Technical, of Elementis Chromium, Corpus Christi, Texas in a letter dated January 27,1998. OEHHA proposed a chronic REL of 0.0008 $\mu g/m^3$ for respiratory effects based on a study by Lindberg and Hedenstierna (1983) of workers exposed to chromic acid.

Comment 1. Page A-161. The table listing specific compounds. The chemical formulas for potassium chromate, sodium chromate, potassium dichromate and sodium dichromate are wrong. Hydrogen atoms should not be included in these formulas.

Response. Comment noted. The hydrogen atoms will be removed. OEHHA regrets the error.

Comment 2. Page A-162. Physical and Chemical Properties. The properties listed are not valid for all the compounds identified on page A-161. These properties are reasonably accurate for chromic acid but not for the other compounds.

Response. The title will be changed to reflect this comment.

Comment 3. Page A-162. Section Ill. Second paragraph. Chromates are no longer used in cooling towers or automobiles to inhibit corrosion in recirculating water.

Response. Chromates have been phased out over the last several years. The reference cited was published in 1988. The California Air Resources Board banned this use in 1989. We will revise the text accordingly.

Comment 4. Page A-162. Section IV. First two paragraphs. In both of these studies the effects of poor personal hygiene practices are probably significant. This is noted in Lucas and Kramkowski (1975). Although personal hygiene practices were not specifically discussed in the Lindberg and Hedenstierna (1983) publication, another study done on chrome plating workers by the same group (Lindberg and Vesterberg, 1983) noted that more than a third of the workers studied (33/91) had "yellow hands" or chrome sores. These are obvious signs of very poor personal hygiene practices that can easily result in the direct transfer of chromic acid to the outer nasal passages and septum. Also, in electroplating the normal operations involve putting objects to be plated in the baths, removing these objects from the baths and adjusting the operating conditions of the bath. These procedures usually require short periods where the operator is directly above the bath subjected to high exposures and long periods away from the bath at much lower exposure. This would produce high peak exposures even though average exposures would be much lower. In fact in Lindberg and Hedenstierna (1983) the following statement is made:

> *The observation that damage to the nasal septum correlated better with short-term peak exposure than with 8-hr mean concentrations of chromic acid clearly underscores the detrimental effects of high peak concentrations of chromic acid.*

Consequently, many of the effects reported are very likely the result of poor personal hygiene or high peak exposures rather than the reported average exposures. When studies of electroplating workers are used for regulatory purposes, these limitations should be recognized.

Response. The poor hygiene practices of the workers in the Lindberg and Hedenstierna (1983) study is unfortunate, both for the workers and for the use of the study as the basis of the chronic REL. Epidemiological studies usually have many complicating factors. However, epidemiological studies of chromium VI workers in other industries exposed to species other than chromic acid have also reported toxicity of the upper respiratory system. Other lung symptoms reported in the key study, such as a diminished forced expiratory flow between Monday morning and Thursday afternoon, are not likely to have resulted from poor personal hygiene.

OEHHA staff attempt to use the best study of a chemical that it can find in the peer-reviewed literature to develop a chronic REL. When a Hazard Index exceeds 1, air district staff consult with OEHHA staff on a case-by-case, chemical-by-chemical basis about the likelihood of adverse health effects. Risk management is an important part of the Air Toxics Hot Spots program.

Comment 5. Page A-163. Section VI. The use of Lindberg and Hedenstierna (1983) for the derivation of a Chronic Reference Exposure Level (REL) for all hexavalent chromium compounds is not appropriate. This study involves workplace exposure to chromic acid. Although chromic acid is a hexavalent chromium compound, it is very unlikely to be a significant component of the hexavalent chromium content of ambient air. Chromic acid is very acidic and highly oxidizing and therefore has very low stability in the environment (Barnhart, 1997). When exposed to the environment it will either react and be chemically reduced to the trivalent chromium state or be neutralized to a dichromate or chromate salt. Under certain conditions these chromate salts can be stable in the environment and therefore regulatory levels for ambient air should be based on these compounds (Finley *et al.*, 1993).

Response. Neither OEHHA nor US EPA agrees that the study of Lindberg and Hedenstierna (1983) is not appropriate. Hexavalent chromium is toxic. It is preferable from the point-of-view of protecting public health to use the data available on the most toxic species present. It would be helpful to know the half-life of the chromium VI ion in the air if that is what the comment about the very low stability of chromic acid in the environment implies. OEHHA's REL is for all chromium VI ions, not just those from chromic acid. In the Air Toxics Hot Spots Program, facilities do not speciate their chromium VI emissions. A 1988 report by the Research Triangle Institute (The fate of hexavalent chromium in the atmosphere. ARB Contract A6-096-32) indicated an average experimental half-life of 13 hours. Since emissions are continuous, there is the potential for continuous exposure. Reports of high percentages of

chromium VI above abandoned hazardous waste sites, as well as notable measurements of CrVI in ambient air and soil near chrome plating facilities, also seem inconsistent with a short half-life for chromium VI.

Comment 6. Page A-164. First paragraph. Both the principal author of the cited study (Lindberg, 1986) and the USEPA (USEPA, 1990) concluded that at average exposures to chromic acid of < 1 $\mu g/m^3$ no effect in the respiratory tract was seen. Therefore, even if this study is considered, the use of an average exposure level of 0.24 $\mu g/m^3$ Cr (VI) and a LOAEL uncertainty factor of 10 is not justified.

Response. Lindberg's conclusion might be applicable for healthy workers, not for sensitive individuals. Workers that were exceptionally sensitive to respiratory irritation might choose to work in a different setting. Despite its 1990 conclusion, US EPA developed a RfC for chromic acid mists and Cr VI aerosols based on the Lindberg and Hedenstierna (1983) report. A LOAEL factor of 10 (or possibly greater) is certainly justified by the nasal ulceration and/or perforation seen in 11 of 24 workers exposed to levels above 2 $\mu g/m^3$ (Table 3 below). The subjective irritation (reported by 4 of 19 workers exposed to levels below 2 $\mu g/m^3$) could justify a UF of 3. However, the atrophy of the nasal mucosa seen below 2 $\mu g/m^3$ in 4 in of 19 workers is considered by OEHHA staff to be a serious adverse effect.

Table 3 (from Lindberg and Hedenstierna, 1983). – Conditions of the Nose and Subjective Symptoms in Groups with Different Mean Values of Exposure and with Different Highest Exposure Values Measured Near the Baths where the Exposed Worker had worked During Some Part of the Day

	8-hr Mean Value of Exposure		Highest Exposure Value		
CR(VI) $\mu g/m^3$	≤1.9	2-20	0.2-1.2	2.5-11	20-46
N	19	24	10	12	14
Subjective irritation	4	11	0	8	4
Atrophy	4	8	1	8	0
Ulceration	0	8*	0	0	7#
Perforation only	0	3	0	0	3

* Two of 8 also had a perforation.
\# Two of 7 also had a perforation.

Comment 8. Based on these comments I recommend that the REL of 0.0008 $\mu g/m^3$ proposed for hexavalent chromium in this draft not be accepted and that all relevant information including animal studies be considered in developing an appropriate REL. Additionally the use of the benchmark dose method (Malsch, *et al.*, 1994) should be considered since it allows the use of a larger database in deriving this value.

Response: OEHHA thanks the commentator for his comments. We have considered relevant information, including animal studies. In the Hot Spots program facilities do not speciate their emissions of chromium VI into aerosols, mists, and particulates. Thus to protect public health OEHHA concentrates on the most toxic species.

US EPA developed 2 RfCs for chromium VI. Neither RfC was based on a benchmark dose approach. The first RfC was 0.008 $\mu g/m^3$ for chromic acid mists and chromium VI aerosols based on the study by Lindberg and Hedenstierna (1983). OEHHA has reviewed the documentation on IRIS for that RfC and disagrees with some of the interpretations made by USEPA, including whether or not nasal atrophy is a severe effect (OEHHA believes that it is) and the exposure concentration selected as the basis of the REL. In addition, for this RfC USEPA decided that the multiplication of 2 intermediate UFs of 3 (which is actually the square root of 10) resulted in 9, not 10.

The second RfC, with the higher value of 0.1 $\mu g/m^3$ for chromium VI particulates, was based on the same studies in rats (Glaser et al., 1985; 1990), which were used by Malsch et al. to develop their value of 0.34 $\mu g/m^3$ by the benchmark approach, a value close to the value USEPA derived using the NOAEL/UF approach. The BC derived by Malsch et al. used the 95% lower confidence limit of the EC_{10} (designated a Maximum Likelihood Estimate) rather than of the EC_{05} preferred by OEHHA. Use of the LCL on an EC_{05} would result in a value even closer to the US EPA value of 0.1.

References cited by commentator**:**

Barnhart, J. (1997). Occurrences, Uses, and Properties of Chromium. *Regulatory Toxicology and Pharmacology* 26(l): 3-7.

Finley, B. L., D. M. Proctor, and D. J. Paustenbach (1992). An Alternative to the USEPA's Proposed Inhalation Reference Concentrations for Hexavalent and Trivalent Chromium. *Regulatory Toxicology and Pharmacology* 16:161-176.

Lindberg, E. (1986). *Health Hazards in Chrome Plating.* Department of Environmental Hygiene, Karolinska Institute, Stockholm.

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Lucas, J. B. and R. S. Kramkowski (1975). Health Hazard Evaluation Determination Report Number 74-87-221. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health.

Malsch, P. A., D. M. Proctor, and B. L. Finley (1994). Estimation of a Chromium Inhalation Reference Concentration Using the Benchmark Dose Method: A Case Study. *Regulatory Toxicology and Pharmacology* 20: 58-82.

United States Environmental Protection Agency (1990). Noncarcinogenic Effects of Chromium. Update to Health Assessment Document. Publ. No. EPA/600/8-87/048F. Office A Research and Development, U.S. Environmental Protection Agency, Washington, DC.

Union Carbide Corporation - Isophorone

Comments on the **isophorone** chronic REL were made by J. M. Cleverdon, Project Safety Manager for Union Carbide Corporation, in a letter dated December 17, 1997. The proposed chronic REL for isophorone (1,1,3-trimethyl-3-cyclohexene-5-one) was based on a probe and final study of inhalation teratology conducted by Bio/dynamics for Exxon Biomedical Sciences in 1983 and 1984. Mice and rats were exposed for 6 hours per day during gestation. Reduced crown-rump length were noted in female rat fetuses at 115 ppm, but not at 50 ppm. Thus a time-weighted gestational exposure NOAEL of 12.5 ppm, an interspecies uncertainty factor of 3, and an intraspecies uncertainty factor of 10 were used to derive a REL of 0.4 ppm (2,000 $\mu g/m^3$). Exencephaly was noted in 4 fetuses of animals exposed to 150 ppm in the probe study (a finding not reproduced in the final study) and this effect was also cited in the summary of critical endpoints observed.

Comment 1. Union Carbide Corporation would like to thank you and your group for allowing us to comment on the draft document Air Toxics Hot Spots Program Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Toxicity Reference Exposure Levels, and specifically on Appendix A.69, Chronic Toxicity Summary - Isophorone. In general, we feel that the Air Toxicology and Epidemiology Section has done a credible job in developing methodologies for determining RELs and that the application of this methodology has been used appropriately in deriving a value of 2,000 $\mu g/m^3$ for isophorone.

We would, however, take exception with the characterization of isophorone as "teratogenic". In the Chronic Toxicity Summary document, it is correctly pointed out on page A-424 (lst full paragraph, 10th sentence) that in a probe study a malformation, exencephaly, was observed in a late resorption in one rat litter from the high exposure concentration group (150 ppm), and in two litters of mice exposed to the high concentration group (in one late resorption from 1 litter, and in two live fetuses from a second litter). The document goes on to state on page A-425, sentence 10: "However, exencephaly is included as a critical effect in this summary because it is considered a serious teratogenic effect that was present at a dose only slightly higher than the LOAEL of the primary study (115 ppm)." We take exception to that statement because it fails to take into consideration the unconventional design of this teratology probe study and the outcome of the definitive developmental toxicology study.

Response. OEHHA has revisited the data bearing on the teratogenicity of isophorone. In this case, as in many other cases examined for this document, there remains considerable uncertainty, and substantial arguments can be made on both sides of the issue. This debate will only be adequately resolved with the acquisition of better data. The number of animals tested, on which the issue rests, is small but the effect observed, exencephaly, is of great concern. The authors of the original report suggested that the exencephaly was likely unrelated to isophorone exposures, but the data are inadequate to obviate concern.

Comment 2. It is very important to keep in mind that this probe study (copy attached) did not employ the typical design of a Segment II developmental toxicity study. Normally, such

studies involve sacrifice shortly before birth. There is a considerable historical database on developmental effects observed shortly before birth, by which time organogenesis is complete. That procedure was not followed in this case, however. Here, the probe study was conducted by exposing female rats and mice on days 6 through 15 of gestation. The mothers were sacrificed on gestation day 16 and the fetuses weighed, measured and examined for external malformations. This examination took place on approximately 4 days (mice) and 6 days (rats) prior to parturition and a critical time period of organogenesis. There is no historical database on which to evaluate the results observed in this probe study at gestation day 16. Thus, it is very difficult to evaluate the biological significance of the findings on day 16.

Response. While there may be limited comparable historical data, the probe study had a 12 member control group, which in any case are the best data on which to compare the exposed groups. In addition, it is unlikely that the results of the exencephaly would be different if the fetuses had been examined at day 20 or 22 of gestation.

Comment 3. This difficulty is compounded by the fact that the definitive study, conducted using substantially more females than in the probe study (22 per group for versus 12 per group in the probe study), found no exencephaly and no significant differences from controls in internal or external malformations at gestation day 20 (rats) and gestation day 18 (mice). If the effect observed in the probe study had been of biological significance, it would likely have appeared in the definitive study; but it did not.

Response. The definitive study, like the probe study, had relatively few exposed individuals. Assuming for the sake of argument that the exencephaly was actually induced by isophorone, the fact that such an endpoint affecting only a minority of individuals would be observed clustered in only one of a series of two small studies is not particularly surprising. The exencephaly may have been a chance occurrence unrelated to isophorone exposure or it may be an effect that occurs with a low incidence rate. Only additional study can resolve this issue.

Comment 4. In addition, in any developmental toxicity study (and in particular in this probe study) there is uncertainty in the exact timing of conception to within a twelve to twenty-four hour period (based upon vaginal smears and/or discovery of a plug). Hours and even minutes are critical in these early stages of embryo development. Observed landmark events can very well be dependent on the precise time of conception relative to terminal sacrifice. The stage of development in the late resorptions is even more uncertain since the exact time of death in these embryos could not be determined.

Response: The experimental control group was subject to the same uncertainties and yet no exencephaly was noted in those animals. Presumably, the initiating events producing exencephaly occur in the early stages of neural tube development. The comment does not seem to consider the irreversible course of events leading to exencephaly.

Comment 5. Considering the arguments above, it is not unreasonable to anticipate that various malformations, including exencephaly, might be observed in a probe study of this design. However, such findings should not be construed to indicate that the material is a teratogenic substance, particularly given the fact that exencephaly was not seen in the definitive study conducted by a more appropriate design where fetal examinations were conducted at term. Indeed, in the definitive study no significant differences from controls were seen for any malformations. The study authors concluded that the exencephaly found in the probe study was not related to the test material in light of the results of the definitive study.

Response: The studies raise a serious concern that can not be discounted on the basis of the issues raised by the commentator. The commentator does raises the legitimate argument that the effects noted could be unrelated to isophorone exposure. Again, this debate will only be resolved with better data relevant to this issue.

Comment 6. The fact that the malformations observed in the probe study were isolated to the high concentration group may be related to the evidence of delays in development identified in the definitive study.

Response: The clustering of malformations in the high-dose group would also be consistent with a dose-response effect by an agent causing the endpoint.

Comment 7. We do not contest the fact that fetal toxicity and delays in development were noted in that study. This finding in the definitive study is consistent with fetal toxicity and delayed development observed in many Segment II developmental toxicity studies conducted with solvents and other chemicals and seen in association with mild maternal toxicity.

Response: The chronic REL document for isophorone cited these effects as the primary finding used to derive the REL. Since there are uncertainties involved in the interpretation of the exencephaly noted in the probe study, the reference to teratogenicity will be removed from Sections I and VI. However, the discussion of the concern that this effect could be related to isophorone exposure will remain as a point of discussion in the document.

Comment 8. In addition to this specific comment on the isophorone, your letter of October 31, 1997 requested comments on a proposal to limit the degree of accuracy of chronic inhalation reference exposure levels to one significant figure. We feel that when significant figures are used in a real sense, accuracy is probably reasonably good to two significant digits, e.g., 95. mg/m^3, 9.5 mg/m^3, 0.095 mg/m^3, but not, for instance, to four significant digits 95.25 mg/m^3, 9.525 mg/m^3 or 0.09525 mg/m^3. We believe that expressing values to one significant digit would not necessarily reflect the accuracy of some measurements in this discipline.

Response: Uncertainty factors as used by OEHHA and USEPA for the development of chronic reference exposure levels are generally based on estimates of the most appropriate

value to the nearest order-of-magnitude (10-fold difference) or at best a 3-fold difference. While we may have more precise information on some components of the risk assessment, the final REL can be no more certain than the weakest link in the chain of data used to derive it. Thus, for example, we can not place any greater confidence in a REL estimate of 9.5 or 9.9 mg/m^3. OEHHA is still considering whether to use one or two significant figures.

Vinyl Acetate Toxicology Group

Comments on the chronic REL for **vinyl acetate** were made by Robert J. Fensterheim, Executive Director of the Vinyl Acetate Toxicology Group, Inc. ("VATG"). The VATG represents all of the North American manufacturers of vinyl acetate and some of the major users of vinyl acetate which include: AT Plastics, Inc.; Borden, Inc.; Celanese Limited; E. I. Du Pont de Nemours and Company; Exxon Biomedical Sciences, Inc.; Millennium Petrochemicals; Rohm and Haas Company; and Union Carbide Corporation. OEHHA proposed use of the US EPA RfC of 200 $\mu g/m^3$ as the chronic REL for vinyl acetate.

Comment 1: OEHHA has proposed an inhalation reference exposure level of based on a two year bioassay by Owen 1988. That study was sponsored by the vinyl acetate industry. In proposing the REL for vinyl acetate, OEHHA elected to make use of the Reference Concentration (RfC) developed by U.S. EPA which is presented in their Integrated Information Risk System (IRIS) database. The VATG support OEHHA's determination to rely on the EPA Reference Concentrations for purposes of establishing RELs, but the RfC must be based on the latest science and be up-to-date. In order to ensure continued consistency, we believe that OEHHA should adopt a provision for presumptive and automatic updating of the REL whenever the EPA RfC is revised. Vinyl acetate, like several other compounds involved in active research and risk assessment activities, will be reevaluated in the near future. On January 2, 1998 (63 FR 75), EPA announced their decision to update the IRIS databases for several compounds including vinyl acetate. This update, which will include a reevaluation of the RfC, is scheduled to start in FY 1998. That update will be partially based on the considerable mechanistic research that the VATG has sponsored. We suggest that in developing the RELs that OEHHA make reference to the IRIS database so that updates to the EPA RfCs can be readily incorporated into the OEHHA RELs program.

Response: The USEPA RfC for vinyl acetate has been in place since 1990. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on Chronic Reference Exposure Levels was drafted in October 1997, are being used as chronic RELs. Use of RfCs as chronic RELs was one action that OEHHA took to implement Governor's Executive Order W-137-96, which concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is appropriate. Appropriate RfCs will be submitted yearly to the SRP for review and possible endorsement. OEHHA intends to harmonize with USEPA as much as possible, but not uncritically and not automatically.