PRELIMINARY DRAFT

TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF PERCHLOROETHYLENE AS A TOXIC AIR CONTAMINANT

PART A REPORT

STATE OF CALIFORNIA
AIR RESOURCES BOARD
STATIONARY SOURCE DIVISION

DECEMBER 1989

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PROPOSED IDENTIFICATION OF PERCHLOROETHYLENE
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REPORT TO THE AIR RESOURCES BOARD ON PERCHLOROETHYLENE

PART A

PUBLIC EXPOSURE TO, SOURCES, AND EMISSIONS OF
PERCHLOROETHYLENE IN CALIFORNIA

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REPORT TO THE AIR RESOURCES BOARD ON PERCHLOROETHYLENE

Part A - Public Exposure To, Sources and Emissions of Atmospheric Perchloroethylene in California

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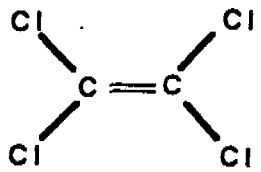
I.

INTRODUCTION

Perchloroethylene is one of the family of chemicals known as chlorinated alkenes; chlorinated aliphatic hydrocarbon compounds containing a double bond. It is known by a variety of synonyms which include perchloroethene, tetrachloroethene, 1,1,2,2-tetrachloroethene, tetrachloroethylene, PERC, PCE, ethylene tetrachloride and Perclene (CAS No. 127-18-4). Perchloroethylene has the chemical formula C_2Cl_4 and the chemical structure is shown in Figure I-1.

Figure I-1

Structure of Perchloroethylene



Perchloroethylene has a wide number of uses in the industrial, governmental, and consumer sectors of the economy. It is used in California in a variety of products and processes, including dry cleaning operations, degreasing operations, adhesives, paints and coatings, aerosols, and specialty chemical production. Perchloroethylene is also used in California in printing inks, silicones, rug shampoos, and as a general solvent in laboratories. Approximately 19,000 tons of perchloroethylene were used in California in 1987. This resulted in approximately 18,000 tons being emitted into the atmosphere.

This report is an evaluation of perchloroethylene uses, emissions, ambient and indoor concentrations, statewide population exposure, and atmospheric persistence and fate. The Air Resources Board (ARB) will consider the findings of this report together with the health effects findings of the Department of Health Services (DHS) to determine if perchloroethylene should be identified as a toxic air contaminant.

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II.

PHYSICAL PROPERTIES OF PERCHLOROETHYLENE

Perchloroethylene is a non-flammable, colorless, dense liquid at room temperature with an ethereal odor similar to chloroform. It is relatively insoluble in water (150 mg/L) but is miscible in alcohol, ether, chloroform, and benzene. Perchloroethylene is not known to contribute to either global warming or to the depletion of the stratospheric ozone layer. Some of the other physical properties of perchloroethylene are shown in Table II-1 below.

Table II-1

Physical Properties of Perchloroethylene

Property	Value	Reference
Boiling Point (760 mm Hg)	121°C	Merck Index, 1983
Conversion (ppb to ug/m^3)	1 ppb = 6.78 ug/m^3	
(ug/m^3 to ppb)	1 ug/ m^3 = 0.15 ppb	
Density, liquid (specific gravity)		
at 15°C	1.6311 gm/cm^3	Merck Index, 1983
at 20°C	1.6230 gm/cm^3	Merck Index, 1983
Molecular weight	165.83	Merck Index, 1983
Partition coefficient		
1-octanol:water (25°C)	339-871:1, (409:1)	U.S. EPA, 1985; Barbari and King, 1982
undecane:water (25°C)	2700:1	Barbari and King, 1982
blood:water (99°F)	~ 31:1	U.S. EPA, 1985
Solubility, water (20°C)	150 mg/L	U.S. EPA, 1985
Vapor pressure (20°C)	14 torr	U.S. EPA, 1985
(25°C)	19 torr	U.S. EPA, 1985

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References for Chapter II

Barbari, T. A.; C. J. King, 1982. "Equilibrium Distribution Coefficients for Extraction of Chlorinated Hydrocarbons and Aromatics from Water into Undecane." Environmental Science & Technology, 16(9):624.

Merck Index, 1983, 10th Edition, Merck and Co., Inc., Rahway, New Jersey.

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III.

PRODUCTION, USES, AND EMISSIONS OF PERCHLOROETHYLENE

Perchloroethylene is one of the most widely used chlorinated hydrocarbon solvents. It is used in a large variety of industrial, governmental and consumer activities. As a result of the extensive use of perchloroethylene as well as the manner in which it is used, substantial amounts of perchloroethylene are released to the atmosphere in California each year.

A. PRODUCTION OF PERCHLOROETHYLENE

Perchloroethylene is produced in the U.S. by five companies at eight facilities (U.S. EPA, 1985b). In 1985 U.S. production of perchloroethylene was 339,000 tons (C&E News, 1987). National production of perchloroethylene in 1985 increased 18 percent from 1984 production and is at approximately the 1975 production level (C&E News, 1987). The U.S. demand for perchloroethylene is forecasted to remain nearly the same through 1990 (CMR, 1986). However, since U.S. production of perchloroethylene depends on imports and exports as well as domestic demand, future production trends are not known. Figure III-1 indicates both production and use of perchloroethylene rose sharply from 1983 through 1985. In addition, Figure III-1 indicates that imports of perchloroethylene rose slightly, while exports dropped slightly during the same time period (C&E News, 1987; U.S. Department of Commerce, Bureau of the Census, FT 246, 1985; U.S. Department of Commerce, Bureau of the Census, FT 446, 1985).

There is one producer of perchloroethylene in California (U.S. EPA, 1985b). The production capacity for this facility is estimated to be 25,000 tons per year (TPY). The facility reported stack emissions of 16 TPY and fugitive emissions of 0.45 TPY. The fugitive emissions were based on screening conducted by a private contractor, however, the EPA calculated the fugitive emissions to be 50 TPY based on a count of various equipment components and typical emission factors for the synthetic organic chemical manufacturing industry. Based on these two fugitive emission rates, the annual emissions from this facility range from 16.45 to 66 TPY (CMR, 1986; U.S. EPA, 1985b).

B. USES AND EMISSIONS OF PERCHLOROETHYLENE

Perchloroethylene has a wide number of uses in the United States in the industrial, governmental, and consumer sectors of the economy. These uses include dry cleaning operations, degreasing operations, production of chlorofluorocarbons, adhesives, aerosols, paints and

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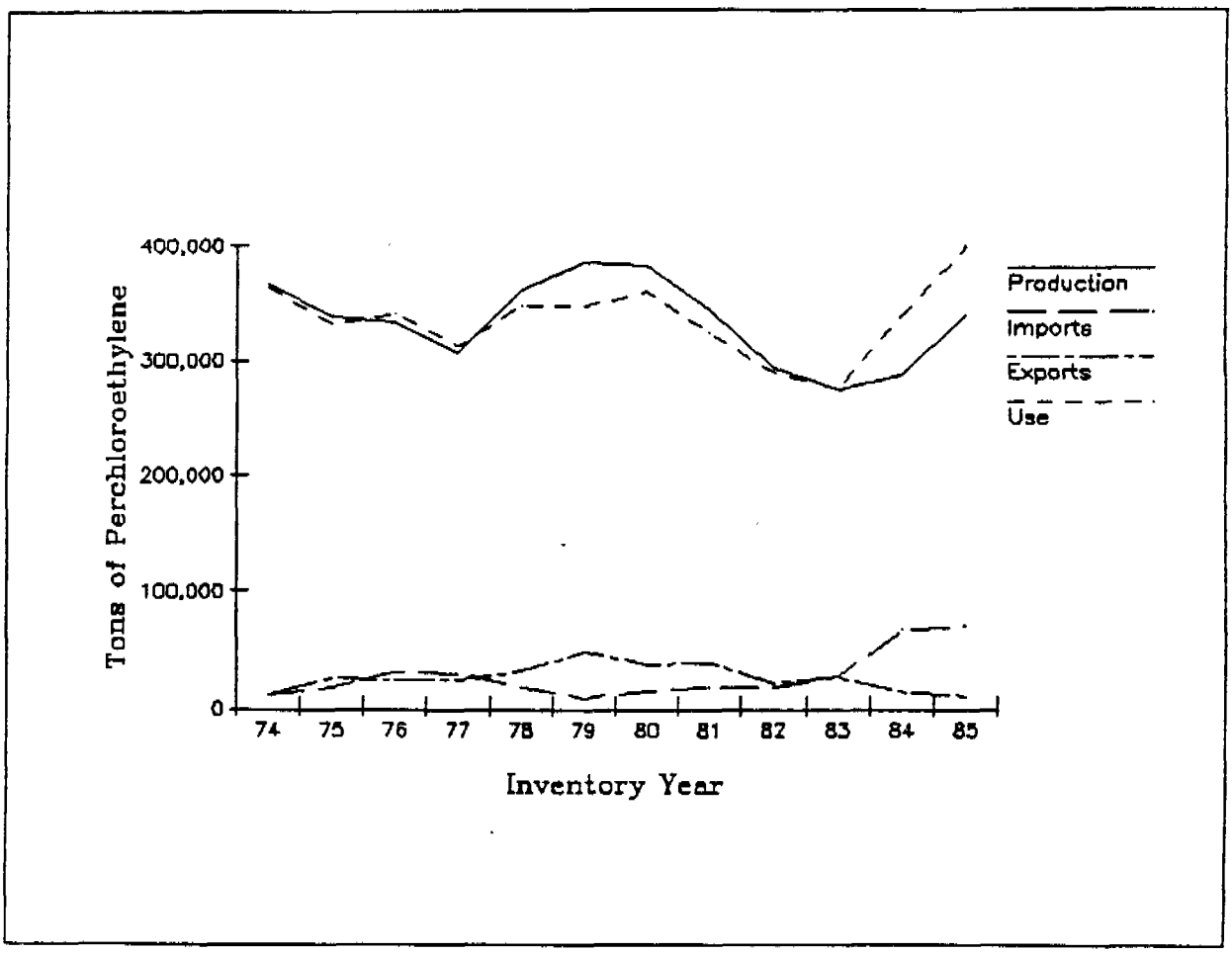
Figure III-1

U.S. Production, Imports, Exports, and Use of Perchloroethylene



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coatings, and specialty chemical production. Included in Figure III-1 is annual perchloroethylene use for 1975-1985 (U.S. EPA, 1985b). Discussions of the methodologies used to estimate these usage and emissions data are included in Appendix A.

Perchloroethylene is widely used in California, with approximately 19,400 tons consumed in the state in 1987 (ARB, 1989). This usage resulted in an estimated 17,600 tons per year of perchloroethylene emissions in the state. Table III-1 presents the 1987 California usage and emissions of perchloroethylene by source type in tons per year. Additional emissions may result from source types that have not yet been identified or for which data is not available.

Perchloroethylene is used in California in the following products and processes: dry cleaning operations, degreasing operations, adhesives, aerosols, paints and coatings, specialty chemical production, printing inks, silicones, rug shampoos, and as a general solvent in laboratories. While a major use of perchloroethylene nationwide is as a chemical intermediate in the production of chlorofluorocarbons (CFCs), there is no chlorofluorocarbon production in California that relies on perchloroethylene as a substrate. Perchloroethylene is also handled during recycling, distribution for use, and disposal as a waste product. These operations may also result in emissions of perchloroethylene to the atmosphere.

Emissions of perchloroethylene in California result primarily from stationary sources. Types of sources that have facilities in California with perchloroethylene emissions greater than 100 TPY include degreasing operations and possibly landfills. Five vapor degreasing facilities in California have been identified as having annual emissions of perchloroethylene that exceed 100 tons. Other source types that have individual facilities with emissions greater than 10 TPY include dry cleaning operations, perchloroethylene production, and possibly publicly owned treatment works (POTWs) and solvent reclamation. POTWs are municipal wastewater treatment facilities.

Some of the uses in the miscellaneous category in Table III-1 may also result in significant emissions. Other source types that emit perchloroethylene include sanitary sewers, groundwater aeration, and surface impoundments. Perchloroethylene is also present in trace concentrations in emissions from waste oil combustion (U.S. EPA, 1986b). The ARB staff suspects that perchloroethylene may be emitted by motor vehicles, based on reports of chlorine emissions from diesel vehicles and the use of chlorinated hydrocarbons as diesel fuel additives (Pacyna, 1986; Tupa & Dover, 1984). Potential emissions sources not evaluated include on-site solvent recovery and industrial wastewater treatment. The major source categories are discussed below.

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Table III-1

Sources, Usage and Emissions of Perchloroethylene in California: 1987

Source Type	Tons Usage	Emissions (Tons/Year)
Direct Uses		
Dry Cleaning	12,857	11,314[a]
Degreasing	3,318	3,053[b]
Adhesives Formulation	335	335[c]
Paints and Coatings	1,317	1,317[c]
Miscellaneous	1,603	1,603[d]
Total	19,430	17,622
Waste Management and Disposal Activities		
POTWs[e]	-	51
Ground Water Aeration and Air Strippers	-	Not Available
Landfills	-	Not Available

a. Assume 0.88 pounds of perchloroethylene is emitted for every pound used (Wolf and Myers, 1987).
b. Assume 0.92 pounds of perchloroethylene is emitted for every pound used (U.S. EPA, 1985a).
c. Assume 100 percent of the perchloroethylene used is emitted.
d. Assume 100 percent of the perchloroethylene used is emitted. This estimate represents emissions from both the identified (961 tons per year) and unidentified miscellaneous sources. Some amounts of perchloroethylene in the miscellaneous category may actually be used in dry cleaning, degreasing, adhesive formulation, and paints and coatings.
e. POTW data is from 1986 inventory.

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1. Dry Cleaning

About two-thirds (12,857 tons) of the perchloroethylene used in California in 1987 was used in the dry cleaning industry. For a dry cleaning plant to be efficient, it needs to recycle its used solvent. Most dry cleaning plants have several pieces of auxiliary equipment (e.g., filters, stills) used in the recovery and purification of perchloroethylene. Carbon adsorbers reduce process vent emissions by about 95 percent and refrigerated condensers reduce emissions by about 70 percent (U.S. EPA, 1989). For control of fugitive emissions, procedures for detecting, repairing, and preventing process leaks, and for minimizing the exposure of perchloroethylene-laden clothes to the atmosphere are used.

The major use of perchloroethylene in California and nationwide is for dry cleaning. Dry cleaning occurs at coin operated facilities, commercial facilities, and industrial cleaners. Coin operated cleaners are usually part of coin operated laundry facilities offering "self-service" dry cleaning to consumers in addition to ordinary washing machines and dryers. Commercial facilities are small neighborhood or franchise dry cleaning shops that clean soiled clothing for the consumer. Industrial dry cleaners are large cleaning plants which supply rental services of uniforms, mats, mops, and similar articles to business or industries (U.S. EPA, 1985b).

Dry cleaning involves the cleaning of fabrics with nonaqueous organic solvents. The dry cleaning process involves three steps: 1) one or more solvent wash cycles; 2) a spin cycle to extract excess solvent; and 3) tumble drying (Morgan, 1985). Dry cleaning operations are typically either transfer operations in which clothes are manually transferred from the washer to the dryer, or dry-to-dry operations in which washing and drying occur in the same unit. Dry-to-dry operations tend to be used in newer installations and these units generally use less perchloroethylene per quantity of clothes cleaned than transfer units (Lauman, 1986).

Steps can be taken to reuse some of the solvent through recycling operations. Due to the high cost of perchloroethylene, on-site solvent recovery is practiced at most large dry cleaning plants. Some of the waste not recovered on-site is sent for solvent recovery off-site (U.S. EPA, 1985b; DeVries, 1986). However, significant quantities of perchloroethylene wastes may be improperly disposed of as municipal waste and not sent for recycling, especially by some commercial dry cleaners (Lucks, 1987).

The ARB staff estimates that the dry cleaning industry in California used an estimated 12,857 tons of perchloroethylene and emitted an estimated 11,314 tons of perchloroethylene to the atmosphere in 1987 (ARB, 1989). This emission estimate assumes that 0.88 pounds of perchloroethylene is emitted for every pound used for dry cleaning (Wolf and Myers, 1987). Based on a conversation with a solvent reclaimer for the dry cleaning industry, the staff estimates that there are approximately 4,200 dry cleaning facilities in the state (Lucks, 1987).

The major sources of emissions from dry cleaning operations are the dryer and the filter residues that result from solvent recovery, followed by the disposal of waste materials and leaks of vapor or liquid from the system (U.S. EPA, 1985b).

2. Degreasing

The second most common use of perchloroethylene in California and nationwide is in degreasing operations. Degreasing is an integral part of many industrial categories such as automobile manufacturing, electronics, furniture manufacturing, appliance manufacturing, and textile, paper, plastic, and glass manufacturing. PEI Associates estimates that there are several thousand cold cleaning, vapor, and conveyor type degreasing units in operation in California (PEI, 1986). There are more than 350 vapor degreasers using perchloroethylene in California (ARB, 1987). A significant portion of the perchloroethylene used for degreasing is sent to solvent reclaimers (U.S. EPA, 1985b).

Approximately 17 percent of the perchloroethylene used in California in 1987 was used in organic solvent cleaning (degreasing) operations. There are three basic types of degreasing equipment: cold cleaners, open top vapor degreasers, and conveyorized cleaners. In California, most of the perchloroethylene emissions from degreasing result from open top vapor degreasers. A large portion of emissions results from loss of solvent vapor from tanks due to diffusion and convection, and carry-out of solvent on cleaned parts. Other emissions result from equipment leaks and from solvent storage and handling. Control techniques include adding equipment covers, increasing freeboard area, adding freeboard chillers, and providing drainage racks. Carbon adsorption may be used to recover solvent vapors. Operating practices that reduce solvent exposure to the atmosphere include keeping covers closed, fully draining cleaned parts, and maintaining moderate conveyor speeds and ventilation rates.

Solvent degreasers function by immersing the part to be cleaned in the liquid or vaporized solvent contained in the degreasing tank. In a typical cold cleaning operation, dirty parts are cleaned manually by spraying and then by soaking in the tank. Open top vapor degreasers clean with the condensation of hot solvent vapor on colder metal parts. Conveyorized degreasers may operate with either cold or vaporized solvent. They are continuously loaded and are usually hooded or enclosed. After cleaning, the parts are either suspended over the tank to drain or placed on an external rack that directs solvents back into the tank (U.S. EPA, 1985b; U.S. EPA, 1977).

It is assumed that approximately 0.92 pounds of perchloroethylene is emitted for every pound of fresh perchloroethylene used in degreasing (U.S. EPA, 1985a). Thus perchloroethylene emissions from degreasing operations in California during 1987 are estimated to be approximately 3,053 tons (ARB, 1989).

Solvent evaporation occurs with all types of degreasing equipment. The major sources of evaporation are the degreasing tank, the carry-out of solvent on cleaned parts, and the disposal of waste solvent. The amount of these emissions varies with the type of equipment used and the operating parameters.

3. Adhesive Formulation

Less than two percent of the perchloroethylene used in California in 1987 was used in adhesive formulation. One hundred percent of the perchloroethylene used in adhesive formulation is assumed to be emitted into the atmosphere upon application of the adhesive. Perchloroethylene emissions from adhesive application in California during 1987 are estimated to be approximately 335 tons (ARB, 1989).

4. Paints and Coatings

Less than seven percent of the perchloroethylene used in California in 1987 was used in paints and coatings formulation. One hundred percent of perchloroethylene used in paints and coatings formulation is assumed to be emitted to the atmosphere upon application of the paint or coating. Perchloroethylene emissions from paints and coatings in California during 1987 are estimated to be approximately 1,317 tons (ARB, 1989).

5. Miscellaneous

About eight percent of the perchloroethylene used in California in 1987 was used in miscellaneous applications. There are not enough data to accurately identify the emissions from each source of perchloroethylene in the miscellaneous category. However, in addition to the source types described above, perchloroethylene is also used as a solvent and carrier in aerosol products, such as spray paints and cleaners; as a solvent in pharmaceutical and textile processing industries; as an ingredient in blended solvents; as a carrier solvent in printing inks, cleaners, polishes, and lubricants; as a recyclable dielectric fluid for power transformers; as a heat transfer medium; and as a pesticide intermediate.

One hundred percent of the perchloroethylene used in the miscellaneous category is assumed to be emitted in the atmosphere. Thus, perchloroethylene emissions from the miscellaneous category in California during 1987 are estimated to be approximately 1,603 tons (ARB, 1989). About 961 tons were actually identified as miscellaneous in the survey; the remaining 642 tons which were not identified are assumed to be miscellaneous. This estimate may be lower if perchloroethylene usage in the miscellaneous category is identified for dry cleaning, degreasing, or other purposes. Also, industry has begun to use perchloroethylene as a dielectric fluid in transformers to replace polychlorinated biphenols (PCBs) (HSIA, 1987).

6. Distribution, Recycling, and Disposal

In addition to the uses discussed above, perchloroethylene is handled by distribution facilities, solvent reclaimers, POTWs, municipal landfills, ground water aeration treatment facilities, surface impoundments, and hazardous waste landfills. Emissions of perchloroethylene result from all of these handling operations. The perchloroethylene handled during distribution, recycling, and disposal operations has already been included in Figure 1 and on Table III-1.

Almost all of the perchloroethylene shipped directly for use in the U.S., other than for use in chlorofluorocarbon (CFC) production, reaches the consumer through chemical distribution. Generally, sales of perchloroethylene to CFC producers are made directly and not through the chemical distribution system. Because there is no CFC production in California where perchloroethylene is used as a substrate, the ARB staff assumed that 100 percent of the perchloroethylene shipped directly into California is sold by chemical distributors. Distribution operations involve transport, storage, and repackaging of perchloroethylene. There are an estimated 500 regional distribution facilities in the U.S. (U.S. EPA, 1985b).

An estimated 24,100 tons of perchloroethylene were sold through distribution facilities in California in 1985. These facilities emitted an estimated 7 tons of perchloroethylene in 1985. Emissions resulting from storage tanks were calculated using equations and assumptions about the throughput of perchloroethylene and the number and size of storage tanks (U.S. EPA, 1985b; U.S. EPA, 1985c).

There are approximately 20 commercial solvent reclaimers in California (CDHS, 1984). The three largest reclaimers process most of the solvents sent for solvent reclamation in California (DeVries, 1986). An estimated 1,940 tons of perchloroethylene were sent for recycling in California in 1985. An estimated 5 to 20 tons of perchloroethylene emissions resulted from solvent reclamation facilities in California during 1985. Emissions primarily result from the storage and handling of waste and reclaimed solvents, although some emissions come from distillation condensers at reclamation facilities.

7. Publicly Owned Treatment Works

Publicly owned treatment works (POTWs) are municipal wastewater treatment facilities. POTWs are potential sources of perchloroethylene emissions because they may receive and treat commercial or industrial discharge containing perchloroethylene. Undetermined quantities of perchloroethylene are discharged to POTWs throughout California. Discharges of perchloroethylene to POTWs are assumed to result primarily from commercial and industrial sources. Perchloroethylene emissions from POTWs in California are estimated to be 51 TPY (Chang et al., 1987). Approximately 20 TPY of these emissions result from POTWs in Los Angeles County and 15 TPY from POTWs in Alameda County (Chang et al., 1987). While there is considerable uncertainty associated with these

estimates, the data are the most complete data available. In addition to the emissions from treatment plants, perchloroethylene is emitted in route to POTWs at pump stations and at certain high points in sewer lines. We do not have data on total emissions from sources such as pump stations or sewer lines.

Major emitters of perchloroethylene were the East Bay Municipal Utility District Wastewater Treatment Facility (13 tons per year), San Jose-Santa Clara Water Pollution Control Plant (7.3 tons per year), and the Joint Water Pollution Control Plant (in L.A. County) (5.9 tons per year).

8. Landfills

Landfills are potential sources of perchloroethylene emissions in California. However, there are presently not enough data available to estimate statewide perchloroethylene emissions from landfills. The quantity of perchloroethylene disposed of at municipal landfills is also undetermined. Perchloroethylene might be disposed of at municipal landfills as residues in discarded aerosol and paint cans, as well as by other means. Estimating landfill emissions is complicated by the variation in landfill contents, surface area, cover depth, and emissions may be large. Furthermore, emissions for some of the state's landfills are reduced by the use of gas recovery well systems. There are about 1,000 active landfills and 1,200 closed landfills in California (Barnickol, 1986).

9. Groundwater Aeration and Air Stripping Towers

In 1987, an EPA contractor identified 21 facilities with air strippers in California (U.S. EPA, 1987a). It is not known how many of these facilities actually treat contaminated groundwater containing perchloroethylene. Perchloroethylene emission estimates were available for only one facility in California. This facility had annual emissions of perchloroethylene of approximately 0.7 tons. There are presently no statewide perchloroethylene emissions data from air stripping towers.

Perchloroethylene is also emitted from ground water aeration treatment facilities throughout the state. Total emissions from such facilities in California have not been determined. The ARB staff estimated that from 1 to 14 TPY of perchloroethylene emissions may result from groundwater aeration facilities in the South Coast Air Basin and the San Francisco Bay Area Air Basin. The upper estimate includes unknown quantities of other contaminants as well as perchloroethylene. This estimate is based on permit information on file at the South Coast Air Quality Management District and the Bay Area Air Quality Management District (SCAQMD, 1987; Lopez, 1987). The quantity of perchloroethylene emissions from different facilities varies widely, depending on the concentration of the contaminant in the groundwater, the flow rate of the water through the treatment process, and the hours of operation.

C. EMISSION TRENDS

In early 1986, the staff of the Chemical Marketing Reporter expected no growth in U.S. consumption of perchloroethylene through the year 1990. This zero growth in usage is accounted for by a projected decrease in the use of perchloroethylene for dry cleaning and degreasing, balanced by an increase in the use of perchloroethylene as a chemical intermediate (CMR, 1986). Two reasons for a near term decline of perchloroethylene usage in dry cleaning are 1) new commercial dry cleaners tend to use more efficient dry-to-dry equipment instead of transfer equipment and 2) industrial dry cleaners are increasingly using water and detergent solutions in place of perchloroethylene (Wolf, 1986; Lauman, 1986; DeVries, 1986). This loss is expected to be offset by growth in demand for trichlorotrifluoroethane (CFC-113) as a solvent in the electronics industry (CMR, 1986). Perchloroethylene is a chemical intermediate in CFC-113 production.

While the net U.S. usage of perchloroethylene will remain fairly constant, ARB staff expects a decline in nationwide emissions of perchloroethylene through 1990. This is because a much larger percentage of the perchloroethylene used in dry cleaning and degreasing operations is emitted than from the use of perchloroethylene as a chemical intermediate. Emissions of perchloroethylene in California are expected to decline at a rate similar to the decline in U.S. emissions.

Through the 1990's, however, perchloroethylene emissions in California may well increase due to projected population increases. The majority of perchloroethylene emissions result from dry cleaning operations and the use of dry cleaning services is related to the population. The population in California is projected to increase approximately 20 percent from 1984 to 2000 (U.S. Department of Commerce, Bureau of Census, 1985). Such an increase in population will probably result in a significant increase in perchloroethylene emissions, provided other factors such as level of control remain equal.

Perchloroethylene may be increasingly used in the future as a dielectric fluid in transformers to replace environmentally persistent materials (HSIA, 1987). Although no data on projected usage are available, the staff expects the emissions from this use to be minimal.

In addition to increases from CFC production, governmental regulation could result in small increases in perchloroethylene emissions from some source types. Efforts to control perchloroethylene residuals from sources such as dry cleaners might result in increased emissions from POTWs and solvent reclamation. In fact, the quantities of perchloroethylene received by solvent reclaimers have increased significantly over the past few years and the trend may continue. Concerns and restrictions on land disposal of halogenated solvents have prompted much of this trend.

D. POTENTIAL SOURCES OF INDOOR PERCHLOROETHYLENE

1. Building Materials and Consumer Products

The National Aeronautics and Space Administration (NASA), has been compiling emission data for volatile organic compounds since 1975. The database covers more than 5,000 materials used in the space program. Some of these materials are commercially available and are used in homes and offices. Based on their analysis of this data base, Ozkaynak, et al. (1987) reported that perchloroethylene would be emitted from a number of common household products such as adhesives, foam, cosmetics and ink.

Recent emission tests conducted in chambers by different investigators found no perchloroethylene emissions from a variety of building materials such as caulks, adhesives, stains, paints, waxes and furniture polishes (Berglund et al., 1987; Knoppel & Schauenburg, 1987; Tichenor, 1987; Wallace et al., 1987b, Girman et al., 1986 and Molhave, 1982).

In a national survey, U.S. EPA (1987c) selected consumer products containing chlorinated solvents for chemical composition analysis. The samples were brand-name products selected randomly from six U.S. cities and represented 67 categories of household solvent products. The survey found perchloroethylene in products from 18 of the 67 categories. The three categories with the highest percentage of brand-name products containing some amount of perchloroethylene were: brake quieters/cleaners (58 percent), water repellents (25 percent) and fabric finishes (20 percent). Other categories with more than ten percent (11 percent - 17 percent) of perchloroethylene-containing products include: specialized aerosol cleaners, ignition wire driers, suede protectors, spot removers and spray cleaners. The concentration of perchloroethylene in individual products varies greatly. Some of the products contain as much as 90 percent perchloroethylene by weight.

2. Dry-Cleaned Materials and Dry Cleaning-Related Activities

Perchloroethylene is the primary solvent for dry cleaning clothing and fabrics. Freshly dry-cleaned garments probably serve as an emission source of indoor perchloroethylene, when brought home. According to a U.S. EPA (1987b) national survey of household solvent usage, the average frequency of household use of dry cleaning services is 0.96 times per month.

In reviewing all of the TEAM study results, Wallace and Clayton (1987) concluded that perchloroethylene levels in air samples and breath samples were elevated for persons who were employed in or who had recently visited a dry cleaning shop. They also concluded that the main source of exposure appears to be wearing and storing dry-cleaned clothes. In following the personal activities of seven individuals, increased exposure of perchloroethylene was associated with visiting dry cleaning shops and laboratories using chemicals, and with using cleaning solvents (Wallace et al., 1987c).

3. Vaporization from Water Sources

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

In California, surface water is generally free of perchloroethylene. In assessing ground water quality, the California Department of Health Services (CDHS, 1986) reported that about 7 percent of the wells for large public water systems were contaminated with perchloroethylene. About half of these wells contained water concentrations of perchloroethylene below 2 ug/l (2 ppb). Water from wells with exceptionally high perchloroethylene concentrations are usually blended with water from wells with lower perchloroethylene concentrations to meet the water quality guideline of 4 ug/l (4 ppb). Based on the information supplied by Spath (1987), the concentration of perchloroethylene in most California domestic water supplies is essentially below 1 ug/l (1 ppb).

Domestic water supply systems may be a source of indoor air emission of perchloroethylene. In the eastern states, some water distribution systems contained vinyl-toluene-lined asbestos cement pipes. The liner was sprayed on the inside of pipes with perchloroethylene-dissolved resin. High levels of perchloroethylene were found in water distributed by this type of system (Larson et al., 1983). The existence of this same water supply system in California is, however, unknown.

4. Other Factors that May Influence Indoor Concentrations

Homes built on or near landfills containing perchloroethylene or related chlorinated hydrocarbons may accumulate perchloroethylene indoors. The rate of accumulation varies, depending heavily on the soil permeability, source strength, air exchange rate and structure of the house. Kliest et al. (1987) reported that houses built on polluted soil had almost four times higher perchloroethylene levels in the crawl-space than houses on clean soil. The relationship between the concentration of a pollutant in the crawl space and its concentration in the living space is still under investigation.

Perchloroethylene from known emission sources may increase the indoor levels of nearby residential or commercial buildings. Of particular concern are small dry cleaning shops which usually locate in densely populated areas. In an EPA study of self-serve laundries with dry cleaning operations, similar perchloroethylene levels, around 10,000 mg/m^3 (1500 ppb), were found in a laundry and in an occupied apartment directly above the laundry (Howie & Elfers, 1981).

Perchloroethylene is a registered pesticide in California for controlling wasps and hornets. However, the California Department of Food and Agriculture does not have any information on product types to indicate perchloroethylene use indoors (Formoli, 1987). As mentioned earlier, perchloroethylene was detected in the EPA analysis of consumer products used as pesticides (Wallace et al., 1987b).

5. Summary of Perchloroethylene Sources

Elevated air concentrations of perchloroethylene in indoor environments appear to result from both indoor sources of perchloroethylene and mechanisms by which outdoor perchloroethylene is concentrated indoors. Consumer products appear to be a significant emission source of indoor perchloroethylene. In addition, dry-cleaned clothing is a likely additional source of indoor perchloroethylene, although the relative contributions from these two emission source categories cannot be quantified. In general, building materials may be a minor source of perchloroethylene.

The possibility of perchloroethylene from outdoor sources becoming concentrated indoors requires more research. The use of water containing perchloroethylene indoors may increase indoor levels of perchloroethylene. The increased number of local dry cleaning shops in densely populated areas may also strongly influence perchloroethylene levels in nearby indoor environments.

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IV.

EXPOSURE TO PERCHLOROETHYLENE

A. AMBIENT MONITORING FOR PERCHLOROETHYLENE

The current toxics sampling network comprises 20 monitors statewide. Nine of these monitors are located in Southern California (south of Bakersfield), while the other 11 are located in the northern portion of the state. The statewide monitoring sites are indicated on Figure IV-1. Data used in the following exposure analysis were collected during the period of July 1988 through June 1989. The data for this period (hereafter referred to as "the study period") represent the most recent period for which the available data are known to be of consistent and verifiable quality. Individual 24-hour samples were collected in Tedlar bags and subsequently analyzed for perchloroethylene using gas chromatography with an electron capture detector. Standard operating procedures for sampling and analysis are provided in Appendix B.

The monitor located in El Monte at the beginning of the study period was subsequently moved to Azusa where it stayed for approximately one month. It was then moved to Burbank where it stayed for the remainder of the study period. Because there are considerable missing data from El Monte, Azusa, and Burbank, data for these sites were not used in estimating a mean annual statewide exposure. The months during which data are available for other monitoring sites are summarized in Table IV-1.

B. AMBIENT CONCENTRATIONS OF PERCHLOROETHYLENE

1. Study Period Data Collected

The number of samples available per site during the study period range from 16 to 23, averaging 20.6 observations per site for the study period. Observations below the 0.01 parts per billion (ppb) limit of detection (LOD), are referred to as being partially observed data (POD). The only observation below the LOD was reported for the San Jose site on August 13, 1989.

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Figure IV-1

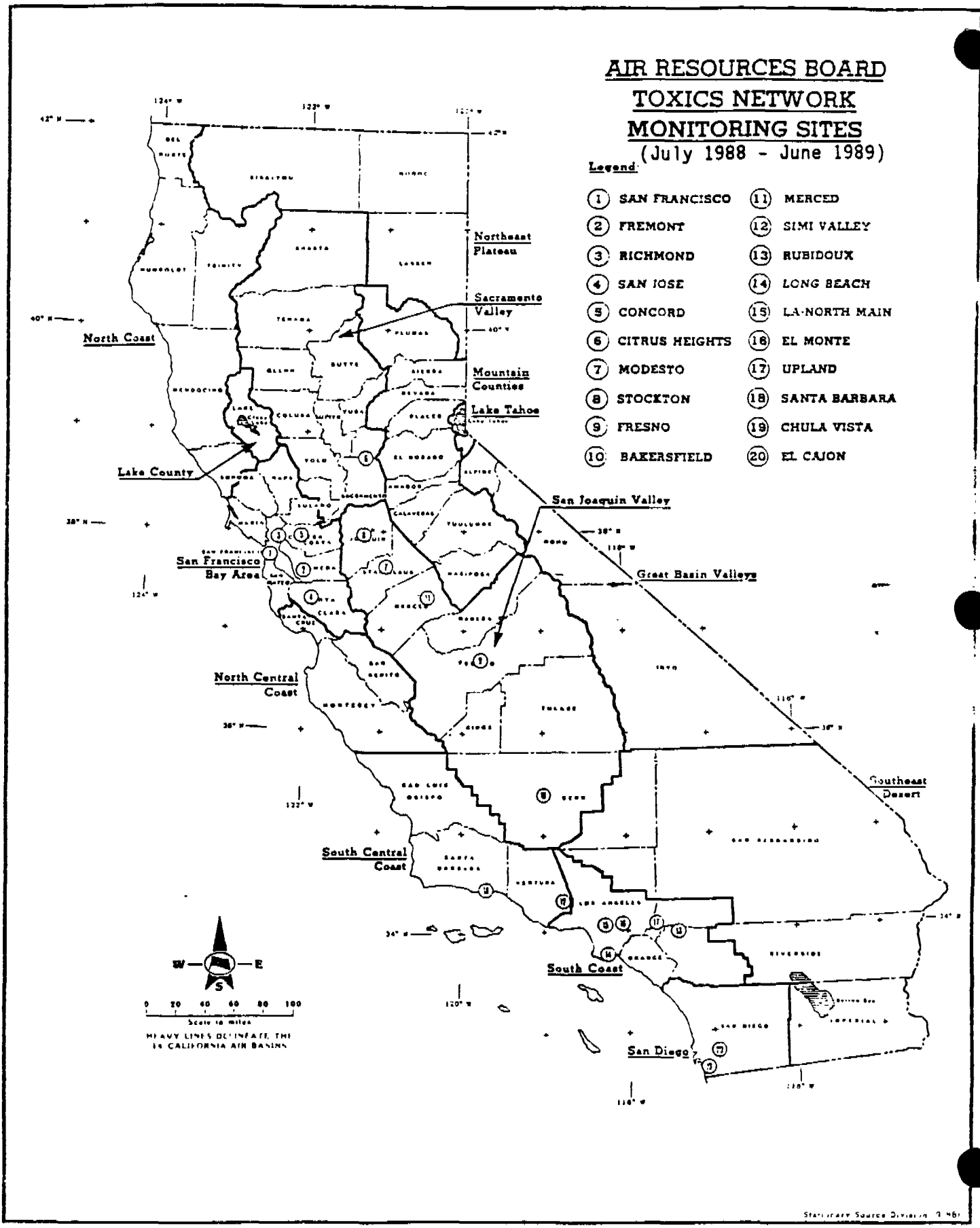

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TABLE IV-1

Months Where At Least One Sample Was
Collected And Analyzed For Perchloroethylene[a]:
July 1988 through June 1989

Site Location	J	A	S	O	N	D	J	F	M	A	M	J	Samples
South Coast Air Basin													
Long Beach	o	o	o	o	o	o	o	o	o		o	o	23
Los Angeles	o	o	o		o	o	o	o	o	o	o	o	18
Rubidoux	o	o	o	o	o	o	o	o	o		o	o	23
Upland	o	o	o	o	o	o	o	o	o	o	o	o	23
South Central Coast Air Basin													
Santa Barbara		o	o	o	o	o	o	o	o	o	o	o	17
Simi Valley	o			o	o	o	o	o	o	o	o	o	23
San Diego Air Basin													
El Cajon	o	o	o	o	o	o	o	o	o	o	o	o	22
Chula Vista	o	o	o	o	o	o	o	o	o		o	o	21
San Francisco Bay Area Air Basin													
Concord	o	o	o	o	o	o	o	o	o	o	o	o	21
Fremont	o	o	o	o	o	o	o	o	o	o	o	o	23
Richmond	o	o	o	o	o	o	o		o	o	o	o	23
San Francisco	o	o			o	o	o	o	o	o	o	o	16
San Jose		o	o	o	o	o	o	o	o	o	o	o	22
San Joaquin Valley Air Basin													
Bakersfield		o	o	o	o	o	o	o	o	o	o	o	18
Fresno	o	o	o	o	o	o	o	o	o	o	o	o	23
Merced	o	o	o	o	o	o		o	o				15
Modesto	o	o	o	o	o	o	o	o	o	o	o	o	23
Stockton		o	o	o	o	o	o	o	o	o	o	o	19
Sacramento Valley Air Basin													
Citrus Heights	o	o	o	o	o		o	o	o	o	o	o	19

a. A "o" indicates at least one sample was collected during the month.

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Even though no value is reported when a concentration is below the LOD, important information is still available from its existence. Obviously, the fewer the data points below the LOD, the less significant their impact on the analysis. Because removing these values from the dataset would bias the sample statistics and exposure estimates, an estimated order statistic approach was used to calculate a replacement value for the POD.[1]

2. Site-Specific Concentrations

The absolute range of concentrations sampled at each site during the study period is summarized in Table IV-2. Minimum, maximum, median and mean concentrations, and standard deviation are reported for each site. Mean perchloroethylene concentrations were calculated as the mean of available monthly means, because this approach provides equal weighting for each month when the number of samples per month varies. Standard deviations were calculated from monthly means so they could be compared with the annual mean concentrations.

The site-specific ranges of the ambient perchloroethylene concentrations listed in Table IV-2 are plotted in Figure IV-2. Minimum concentrations range from POD at San Jose to 0.21 ppb at Los Angeles. Maximum concentrations range from 0.18 ppb at Bakersfield to 4.80 ppb at Simi Valley. Mean annual concentrations range from a minimum of 0.10 ppb at Citrus Heights and Bakersfield to a maximum of 0.70 ppb at Concord.

Two relatively unusual concentrations were reported for Chula Vista; 13.00 ppb on March 6, 1989, and 14.00 ppb on April 4, 1989. Both values are more than 70 standard deviations from the mean of the remaining Chula Vista values. We believe that these values do not represent ambient concentrations and are possibly the result of influences from an unknown nearby source. These values were not included in the calculations of the various exposure estimates (e.g., site, basin and state-wide).

At all 19 monitoring sites, the median of the reported data is less than or equal to the mean of all values. A median concentration that is significantly different from the mean indicates the data has a non-normal distribution. In the past, the distribution of the ambient toxic air contaminant data has generally been assumed to be log-normal. The perchloroethylene data were tested for log-normality using the

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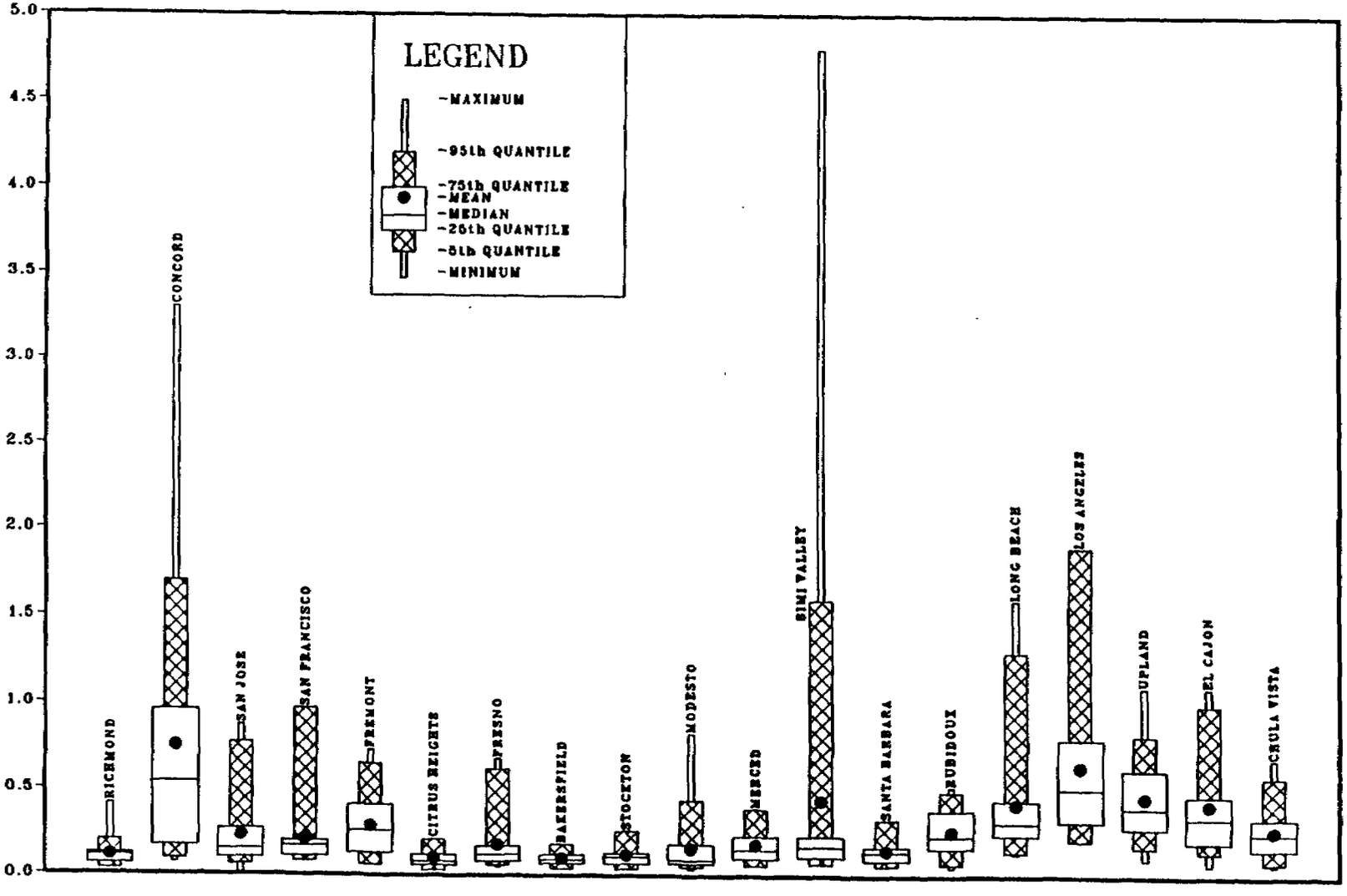
1. Estimating order statistics is our preferred method for estimating values for POD. This method was discussed by Gleit (1985) and uses an iterative algorithm for estimating the order statistics for a finite sample.

Figure IV-2

MEAN ANNUAL PERCHLOROETHYLENE CONCENTRATION

PLOTTED USING EXTENDED BOX PLOTS

BASED ON JULY 1988–JUNE 1989 DATA



Monitoring Sites Throughout California

ARB/TSD:October 89

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TABLE IV-2

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Minimum, Maximum, Median and Means of
Perchloroethylene Samples Collected during
July 1988 through June 1989
(ppb)

Air Basin Site Location	Minimum Conc.	Maximum Conc.	Median Conc.	Mean[a] Conc.	Standard[b] Deviation
South Coast Air Basin					
Long Beach	0.13	1.60	0.31	0.42	0.35
Los Angeles	0.21	1.90	0.51	0.57	0.38
Rubidoux	0.05	0.52	0.23	0.26	0.08
Upland	0.10	1.10	0.40	0.48	0.24
Basin Summary	0.05	1.90	0.35	0.43	0.29
South Central Coast Air Basin					
Santa Barbara	0.06	0.33	0.14	0.16	0.07
Simi Valley	0.07	4.80	0.17	0.39	0.47
Basin Summary	0.06	4.80	0.15	0.28	0.34
San Diego Air Basin					
Chula Vista	0.07	0.69	0.25	0.30	0.17
El Cajon	0.07	1.10	0.34	0.42	0.26
Basin Summary	0.07	1.10	0.27	0.36	0.22
San Francisco Bay Area Air Basin					
Concord	0.07	3.30	0.54	0.70	0.59
Fremont	0.06	0.73	0.26	0.27	0.13
Richmond	0.03	0.41	0.11	0.11	0.06
San Francisco	0.08	0.97	0.17	0.20	0.15
San Jose	POD	0.87	0.15	0.23	0.17
Basin Summary	POD	3.30	0.15	0.30	0.29
San Joaquin Valley Air Basin					
Bakersfield	0.04	0.18	0.09	0.10	0.03
Fresno	0.05	0.68	0.12	0.18	0.14
Merced	0.06	0.39	0.15	0.19	0.06
Modesto	0.04	0.83	0.09	0.16	0.12
Stockton	0.04	0.26	0.11	0.12	0.05
Basin Summary	0.04	0.83	0.12	0.15	0.09
Sacramento Valley Air Basin					
Citrus Heights	0.03	0.21	0.08	0.10	0.05

a. Basin Means are the mean of the site means.

b. Basin Standard Deviations are pooled values of the standard deviations across sites within a basin.

Shapero-Wilk test (Shapero and Wilk, 1965). We found that perchloroethylene data are not distributed log-normally, although they are skewed like a log-normal distribution.

3. Basin-Wide Mean Concentrations

The highest basin-wide mean concentration occurred in the South Coast Air Basin (0.43 ppb), followed by the San Diego Air Basin (0.36 ppb), San Francisco Bay Area Air Basin (0.30 ppb), South Central Coast Air Basin (0.28 ppb), and San Joaquin Valley Air Basin (0.15 ppb). The Sacramento Valley Air Basin was intentionally left out of the basin-wide analysis as there is only one monitoring site in the basin (see Table IV-2).

Air basins are identified to reflect similar geographic and meteorological conditions. Therefore, data are compared as site composites within each basin. Data for all sites within an air basin are ranked within each air basin. For example, the lowest value across all sites within an air basin has rank one. The Kruskal-Wallis test (Conover, 1971) is then used to determine whether within a basin there are data for a site that are significantly different than data for another site.

If the Kruskal-Wallis test statistic is not significant, then the medians are not considered to be different. If the Kruskal-Wallis test statistic is significant, then Fisher's Least Significant Difference test (SAS Institute Inc., 1985) is used to determine the sites considered to be different and those that are similar. The most likely groupings for sites within each basin based on available ranked data are given in Table IV-3. If two sites within a basin have no associated letters in common, then the medians for each of the two sites are considered to be significantly different. It should be noted that test statistics based on rankings of the data rather than the actual reported value will sometimes lead to less than intuitive results.

4. Peak-to-Mean Ratios

Peak-to-mean ratios were calculated to provide possible insights into the nature of perchloroethylene emission release patterns. The technique is based on observations made for criteria pollutants. For example, carbon monoxide is a relatively inert criteria pollutant with generally widespread emissions. Over an annual period, peak-to-mean ratios for carbon monoxide tend to be fairly low, generally less than five. Another criteria pollutant, sulfur dioxide, may be emitted from widespread sources, but is also emitted from localized point sources. Peak-to-mean ratios for sulfur dioxide at sites influenced by localized sources tend to be much greater than five. Ratios between 50 and 90 have been seen at some locations. Based on what we know about the characteristics of the criteria pollutants, we can divide peak-to-mean ratios into low and high ratios. Generally, a low peak-to-mean ratio,

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TABLE IV-3

Summary of Intra-Basin Site Differences
Based on Average Monthly Rankings and Monthly Means

AIR BASIN Site Location	Median[a] Groupings	Monthly Mean Rank	Mean[b] Conc.	Median Conc.
South Coast Air Basin				
Los Angeles	A	5.40	0.64	0.51
Long Beach	A	5.20	0.42	0.31
Upland	A B	4.45	0.46	0.35
Rubidoux	B	2.90	0.26	0.23
South Central Coast Air Basin				
Simi Valley	A	24.18	0.44	0.17
Santa Barbara	A	17.56	0.15	0.14
San Diego Air Basin				
El Cajon	A	25.21	0.42	0.34
Chula Vista	B	18.64	0.27	0.25
San Francisco Bay Area Air Basin				
Concord	A	77.88	0.75	0.54
Fremont	B	61.54	0.29	0.26
San Jose	B	49.46	0.23	0.15
San Francisco	B	48.81	0.21	0.17
Richmond	C	28.04	0.11	0.11
San Joaquin Valley Air Basin				
Merced	A	66.43	0.18	0.15
Fresno	A B	54.02	0.18	0.12
Modesto	B	47.17	0.16	0.09
Stockton	B	46.58	0.12	0.11
Bakersfield	B	39.00	0.10	0.09
Sacramento Valley Air Basin[c]				
Citrus Heights	--	----	0.10	0.08

a. Sites with the same letter are not considered to be significantly different.

b. Means are computed as the mean of all observations.

c. Since there is only one toxic monitoring site in the Sacramento Valley, no results are given for this basin other than the mean.

less than about ten, indicates either relatively constant and/or uniform emission sources or few emission sources but high, fairly constant background concentrations. A high peak-to-mean ratio, generally greater than about ten, usually indicates either intermittent and/or scattered emission sources or scattered emission sources with a highly variable background concentration.

Peak-to-mean ratios for each site during the study period are given in Table IV-4. Ratios for 17 of the 19 sites are less than five. The two sites reporting data having peak-to-mean ratios of five or larger were Simi Valley and Modesto, with peak-to-mean ratios of 10.82 and 5.05, respectively. The high ratio reported for Simi Valley may be due to the influence of a nearby unknown source, however, without further data it is not possible to determine any specific reasons for the relatively high peak-to-mean. The relatively low ratios at all other sites suggest fairly consistent emission patterns across most of the state and throughout the year. Potential isolated large sources do not appear to impact the sampling network significantly.

This is also apparent by comparing the Coefficient of Variation (C.V.) for each site.[2] The C.V. is similar to the peak-to-mean ratio in that it is a unitless number that is used to compare the dispersive tendencies of distributions. Without more refined information regarding the distributional characteristics of perchloroethylene emissions, we cannot determine specifically the factors contributing to the observed distributional patterns.

5. Population Exposure Estimates

Mean population exposure estimates were calculated using the study period perchloroethylene data. Exposures for the South Coast Air Basin and San Francisco Bay Area Air Basin were estimated by interpolating station values to census tract centroids. For the other air basins, a basin-wide mean concentration was estimated from the means for all sites in the basin. It was then assumed that all people in those basins with a sampling site (except Sacramento Valley Air Basin) were exposed to this estimated basin-wide mean concentration. Population data used in the exposure analysis represent 1980 census data updated to 1985 levels. The results of the exposure analysis, which are discussed below, are summarized in Table IV-5. Table IV-6 presents approximate 95 percent Bootstrap Confidence Interval bounds (Efron, 1982) for each mean annual exposure estimate.

The overall statewide perchloroethylene exposure, weighted by population, is estimated to be 0.37 ppb. A total of 20,339,250 people are estimated to reside in the study areas, representing approximately

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2. The Coefficient of Variation is the standard deviation divided by the mean, then multiplied by 100 so as to be expressed as a percentage.

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Table IV-4

Summary of Perchloroethylene Peak-to-Mean Ratios
and Coefficients of Variations (C.V.)
(ppb)

AIR BASIN Site Location	Peak Conc.	Mean[a] Conc.	Peak-to-Mean[b] Ratio	C.V.[c]
South Coast Air Basin				
Long Beach	1.60	0.42	3.85	86.7
Los Angeles	1.90	0.64	2.97	71.4
Rubidoux	0.52	0.26	1.97	52.9
Upland	1.10	0.46	2.39	51.6
South Central Coast Air Basin				
Santa Barbara	0.33	0.15	2.24	52.6
Simi Valley	4.80	0.44	10.82	216.0
San Diego Air Basin				
Chula Vista	0.69	0.27	2.55	60.0
El Cajon	1.10	0.42	2.62	71.0
San Francisco Bay Area Air Basin				
Concord	3.30	0.75	4.42	99.8
Fremont	0.73	0.29	2.54	63.2
Richmond	0.41	0.11	3.73	71.4
San Francisco	0.97	0.21	4.63	101.2
San Jose	0.87	0.23	3.79	94.7
San Joaquin Valley Air Basin				
Bakersfield	0.18	0.10	1.79	41.7
Fresno	0.68	0.18	3.72	95.3
Merced	0.39	0.18	2.14	55.0
Modesto	0.83	0.16	5.05	107.8
Stockton	0.26	0.12	2.25	47.1
Sacramento Valley Air Basin				
Citrus Heights	0.21	0.10	2.20	51.6

a. Means are calculated as the sum of all observations for each site divided by the total number of observations at each site.

b. Peak-to-Mean Ratios are calculated as the largest value reported for each site divided by the average of all observations reported.

c. The Coefficient of Variation is the standard deviation divided by the mean, then multiplied by 100 so as to be expressed as a percentage

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Table IV-5

Mean Perchloroethylene Exposure Estimates
July 1988 through June 1989
(ppb)

Air Basin	Estimated Mean	Population
South Coast	0.44[a]	10,092,133
South Central Coast	0.28[b]	925,822
San Diego	0.36[b]	2,135,872
San Francisco Bay Area	0.25[a]	4,394,374
San Joaquin Valley	0.15[b]	1,901,243
Sacramento Valley[c]	0.10[b]	889,806
Overall Population-Weighted Exposure	0.37	20,339,250

a. Population-weighted exposure estimate

b. Mean for all sites within the basin

c. Exposure estimates are for Sacramento County residents only.

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Table IV-6

Lower Bound, Mean and Upper Bound
Perchloroethylene Concentrations for
July 1988 through June 1989[a]
(ppb)

Air Basin Site Location	Lower Bound	Site Mean	Upper Bound
South Coast Air Basin			
Long Beach	0.29	0.42	0.64
Los Angeles	0.40	0.60	0.84
Rubidoux	0.22	0.26	0.31
Upland	0.37	0.48	0.62
South Central Coast Air Basin			
Santa Barbara	0.12	0.16	0.19
Simi Valley	0.20	0.39	0.62
San Diego Air Basin			
Chula Vista	0.22	0.30	0.40
El Cajon	0.30	0.42	0.57
San Francisco Bay Area Air Basin			
Concord	0.45	0.70	1.04
Fremont	0.21	0.27	0.34
Richmond	0.08	0.11	0.14
San Francisco	0.13	0.20	0.30
San Jose[b]	0.15	0.23	0.34
San Joaquin Valley Air Basin			
Bakersfield	0.08	0.10	0.12
Fresno	0.12	0.18	0.27
Merced	0.16	0.19	0.23
Modesto	0.10	0.16	0.22
Stockton	0.09	0.12	0.15
Sacramento Valley Air Basin			
Citrus Heights	0.07	0.10	0.13

a. Upper and lower bounds represent 95 percent Bootstrap Confidence Interval bounds (Efron, 1982) for each mean annual exposure estimate.

b. One value below the LOD was reported for the San Jose site. The single observation was estimated to be .006 ppb. Using zero or the LOD as a replacement value, after rounding to two decimal places, gave the same annual mean exposure estimate for San Jose.

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80 percent of the state's population. Basin-specific, population-weighted mean concentrations vary from a minimum of 0.15 ppb in the San Joaquin Valley Air Basin (excluding Sacramento County's 0.10 ppb) to a maximum of 0.44 ppb in the South Coast Air Basin.

Figure IV-3 shows the total number of people exposed to various mean annual perchloroethylene concentrations (rounded off to the nearest 0.05 ppb). Figure IV-4 represents the same data as in Figure IV-3, but plotted as the cumulative population exposed to an estimated mean perchloroethylene concentration.

The overall geographic mean perchloroethylene concentration was 0.29 ppb. This value is approximately 22 percent lower than the population-weighted exposure estimate of 0.37 ppb and indicates that the highest concentrations of perchloroethylene tend to be in the areas of higher population density.

C. EXPOSURE TO PERCHLOROETHYLENE NEAR EMISSION SOURCES

To assess the impact of perchloroethylene emission sources on nearby population, the ARB used emissions information in conjunction with meteorological data to estimate population exposure in census tracts surrounding eight facilities that emit perchloroethylene. The following text is a discussion of the data and modeling methodology used to estimate population along with the exposure results.

The concentrations presented in this section do not represent the total ambient air exposure of the people living in the vicinity of the modeled sources. The concentrations reported are those which would exist if the modeled facility was the only perchloroethylene emission source affecting the nearby population. In reality, there are other emission sources, large and small, located in the basin which contribute to the total perchloroethylene concentration that the modeled population is exposed to.

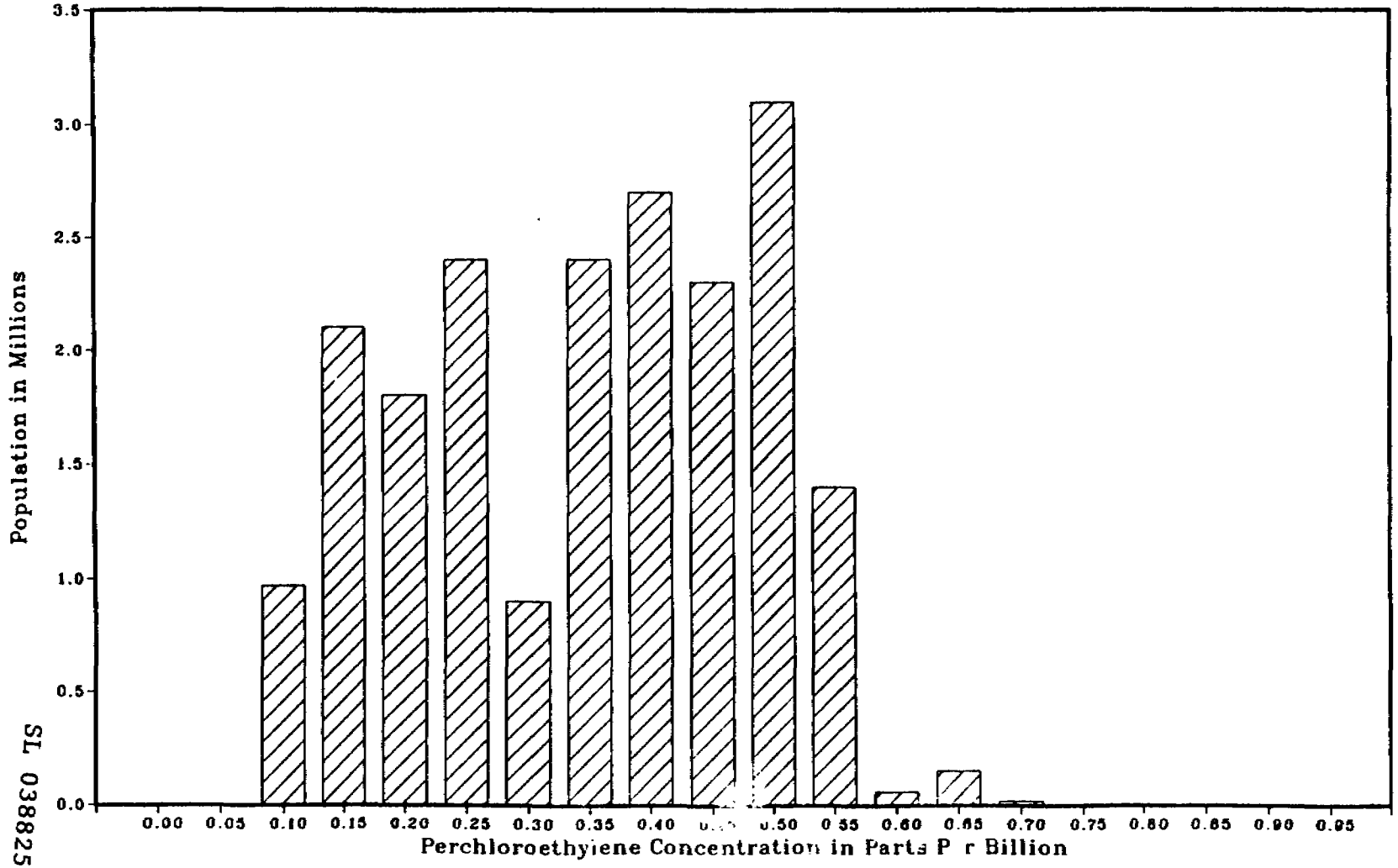
Two 41 kilometer grids with 1 kilometer receptor spacing were utilized to model emissions from eight facilities in the South Coast Air Basin. One grid contains only those facilities near City of Industry and the other grid contains only those facilities near Burbank. The emission sources were approximately centered on each grid and the two grids only slightly overlap.

For each grid, the ISCST air quality model was used to predict above ambient annual average perchloroethylene concentrations. Meteorological data input into the model were obtained from the nearest available meteorological station to each facility. Meteorological data for the City of Industry case were obtained from Los Angeles International Airport records for 1978. Meteorological data for the Burbank case were obtained from Burbank Airport records for 1964. These years of meteorological data were selected because they were the most recent years available and they represent poor years in terms of pollutant dispersion in the South Coast Air Basin.

Figure IV-3

ESTIMATED MEAN ANNUAL PERCHLOROETHYLENE EXPOSURE

BASED ON JULY 1988–JUNE 1989 DATA



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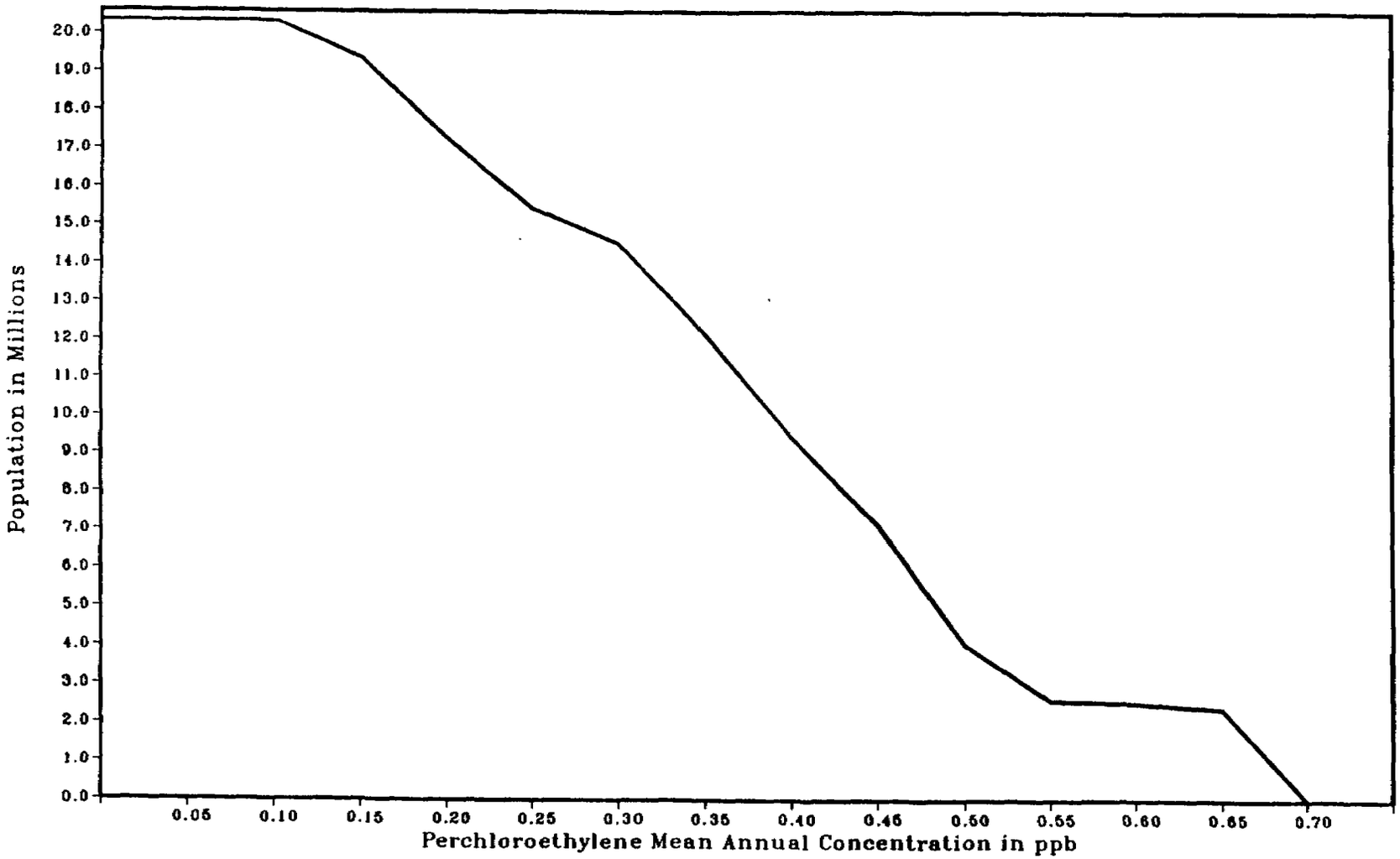
ARB/TSD:September 8

Figure IV-4

ESTIMATED CUMULATIVE PERCHLOROETHYLENE EXPOSURE

BASED ON JULY 1986-JUNE 1989 DATA



ARB/TSD:October 89

Estimates of cumulative impacts from the Burbank and the City of Industry grids are not provided in this analysis. Results indicate that perchloroethylene impacts from the modeled facilities are minimal on the edges of both grids. Thus, the cumulative impacts are not different from these results.

The modeling results were used to calculate the maximum annual average exposure. For City of Industry, over 2,000 people are estimated to be exposed to an annual average concentration of 6 ppb perchloroethylene. This exposure occurred at a receptor approximately two kilometers northeast of one of the modeled facilities. For Burbank, over 600 people are estimated to be exposed to an annual average concentration of 3 ppb perchloroethylene.

The estimated annual average exposure (weighted by population) to perchloroethylene for people living near City of Industry is 0.07 ppb for a population of approximately 2,691,000 people. For Burbank, the estimated annual average exposure (weighted by population) to perchloroethylene is approximately 0.03 ppb for a population of approximately 3,228,000 people.

D. INDOOR AIR EXPOSURE TO PERCHLOROETHYLENE

The best data for estimating indoor air exposure for perchloroethylene come from the Total Exposure Assessment Methodology (TEAM) studies conducted by the Environmental Protection Agency (EPA) during 1980-85 (referred to as TEAM 80/84 in this report; Wallace, 1987; U.S. EPA 1987a,b) and by the EPA and ARB during 1987 (referred to as TEAM 87 in this report; Pellizzari et al., 1989). The TEAM 80/84 studies provided personal sampling data whereas TEAM 87 provided indoor fixed-site sampling data as well. Limited indoor concentration data are also available from a few commercial building studies and from a few European studies.

1. Personal Air Sampling Data

The TEAM 80/84 studies monitored a total of 240 participants in the Los Angeles and Contra Costa areas. Each participant carried a personal air sampler and was monitored for two consecutive 12-hour sampling periods. In the Los Angeles area, field studies were conducted in February 1984 and May 1984. In the February study, the average (arithmetic mean) 24-hour personal air concentration of perchloroethylene was 16 ug/m^3 (2.40 ppb). In the May study, the average 24-hour personal air concentration of perchloroethylene was 15 ug/m^3 (2.25 ppb). The study in the Contra Costa area was conducted in June, 1984, and the average 24-hour personal air concentration was 5.6 ug/m^3 (0.84 ppb). In Table IV-7, the median and maximum concentrations of the overnight (12-hour) personal air samples are presented along with the median and maximum concentrations of concurrent and colocated outdoor ambient air samples (Pellizzari, et al., 1986). The overnight

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Table IV-7

Overnight Indoor and Outdoor Air Levels of
Perchloroethylene in California (6:00 pm to 6:00 am)
(ppb)[a]

	Number of Matched Samples	Indoor[b]		Outdoor	
		Median	Maximum	Median	Maximum
Los Angeles (Feb./84)	25	1.34	14.1	1.1	5.1
Los Angeles (May/84)	23	0.26	8.4	0.2	0.72
Contra Costa (June/84)	10	0.32	1.32	0.04	0.84

a. Original data reported in ug/m^3; conversion factor:
$1\ ug/m^3 = 0.15$ ppb

b. Overnight personal sampler data

Source: Pellizzari et al., 1986

personal sampler data provide a good estimate of indoor air exposure at home since, during this sampling period (6:00 pm - 6:00 am), most participants remained in their homes. The data indicate that median indoor air levels are generally higher than median outdoor air levels. In addition, the data indicate that extremely high levels of perchloroethylene could be found in some homes.

The TEAM 80/84 studies also included other geographical areas besides California. For example, studies were conducted during three seasons in New Jersey. The weighted average overnight air exposure for the three seasons were 11, 9.0 and 13 ug/m^3 (1.65, 1.35 and 1.95 ppb), respectively. The corresponding average outdoor air concentrations were 3.7, 4.0, and 1.9 ug/m^3 (0.56, 0.60, and 0.29 ppb), respectively (Wallace, 1987).

The TEAM 87 study (Pellizzari et al., 1989) was designed as a follow up study of the TEAM 84 study for California. The same Los Angeles areas studied in 1984 were revisited and some of the original participants were included in the TEAM 87 study. A total of 51 and 43 persons participated in the January, 1987 and June, 1987 field studies, respectively. In the January study, the average (arithmetic mean) 24-hour personal air concentration of perchloroethylene was approximately 12 ug/m^3 (1.80 ppb). In the June study, the average 24-hour personal air concentration of perchloroethylene was about 13 ug/m^3 (1.95 ppb). These two-season concentrations are very similar to those obtained in the TEAM 84 study for the Los Angeles areas.

2. Fixed-Site Air Sampling Data

The TEAM 87 study also provides fixed-site monitoring of indoor air concentrations of perchloroethylene (Pellizzari et al., 1989). Air sampling devices were placed in two indoor locations (kitchen and living room) of the homes belonging to people who participated in the personal sampling program. Air samples were collected during the same two seasons. The 24-hour average concentrations of perchloroethylene in the kitchen area were 6.72 ug/m^3 (1.01 ppb) in winter and 2.27 ug/m^3 (0.34 ppb) in summer. The 12-hour average concentrations of perchloroethylene in the living area were 5.27 ug/m^3 (0.79 ppb) in winter and 2.75 ug/m^3 (0.41 ppb) in summer. The 24-hour outdoor average concentrations were 4.41 ug/m^3 (0.66 ppb) in winter and 1.74 ug/m^3 (0.26 ppb) in summer.

Table IV-8 supports the conclusion that indoor air concentrations of perchloroethylene were generally higher than outdoor concentrations during the two sampling seasons. It also indicates that indoor and outdoor air concentrations of perchloroethylene were generally higher during winter than summer months. The average indoor concentrations of the kitchens and the living areas were very similar.

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Table IV-8

24-Hour Average Concentrations of Perchloroethylene
in Indoor and Outdoor Microenvironments
(ppb)[a]

	INDOORS		OUTDOORS
	Kitchen	Living Area[b]	
Winter			
Mean	1.01	0.79	0.66
Median	0.66	0.66	0.53
Summer			
Mean	0.34	0.41	0.26
Median	0.32	0.38	0.21

a. Original data reported in ug/m^3; conversion factor:
1 ug/m^3 = 0.15 ppb

b. 12-hour daytime value only.

Source: Pellizzari et al., 1989

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In studies of indoor air quality in 10 public-access buildings, Wallace et al. (1987a) reported that perchloroethylene was one of the 24 compounds most frequently found out of a total of over 200 identified organic compounds. The 3-day concentration means of perchloroethylene in three newly completed buildings ranged from undetectable to 7 ug/m^3 (1.05 ppb) while the 3-day concentration means for seven old buildings ranged from 1 to 6 ug/m^3 (0.15 to 0.90 ppb) (Sheldon et al., 1988).

Data are also available from several European studies. Although such data may not be representative of California indoor concentrations due to differences in consumer products and life styles, the European data nonetheless confirm the general presence of measurable levels of perchloroethylene in indoor environments. In a study of 14 homes and one office building in Italy, De Bortoli, et al. (1986) detected indoor perchloroethylene concentrations ranging from 3 to 47 ug/m^3 (0.45-7.05 ppb). Lebret, et al. (1986) reported that 30 percent of 300 Dutch homes sampled had indoor air levels of perchloroethylene greater than the detectable limit of 2 ug/m^3 (0.30 ppb). However, the median levels of perchloroethylene sampled in different age-group homes were generally below 2 ug/m^3 (0.30 ppb). Krause, et al. (1987) have also reported preliminary results from a 500-home study in Germany. The observed indoor levels of perchloroethylene ranged from less than 1.0 ug/m^3 and up to 617 ug/m^3 (0.15 to 92.55 ppb) with an average (geometric mean) concentration of 12 ug/m^3 (1.8 ppb).

3. Summary of Indoor and Personal Air Exposure

Perchloroethylene is an ubiquitous indoor air pollutant. The indoor air concentrations of perchloroethylene are generally higher than outdoor air concentrations. TEAM studies conducted in California provide the most representative sampling data for assessing Californians' indoor air exposures. Based on the TEAM 87 data, average residential indoor air concentrations range from 2.75 to 6.72 ug/m^3 (0.41 to 1.01 ppb). Based on personal air sampling data from the TEAM 87 and TEAM 80/84 data, Californians' average personal air exposure to perchloroethylene ranges from 5.6 to 16 ug/m^3 (0.84 to 2.40 ppb).

4. Contribution to Total Exposure

Section 39660.5(d) of the Health and Safety Code states "the state board shall identify the relative contribution to total exposure to the contaminant from indoor concentrations, taking into account both ambient and indoor air environments." Based upon available data and assuming Californians spend 80 to 90 percent of their time indoors (Robinson, 1977), indoor inhalation may be the major route of exposure to perchloroethylene. A comparison of simultaneous indoor and outdoor perchloroethylene concentrations was conducted as part of the TEAM 80/84

study. The results of this comparison (Table IV-7) indicate that indoor perchloroethylene concentrations can be more than 11 times greater than outdoor concentrations. However, this may not always be the case since indoor concentrations of perchloroethylene are dependent upon the use of dry cleaners and consumer products containing perchloroethylene (see Chapter III., Section D. Potential Sources of Indoor Perchloroethylene).

E. OTHER ROUTES OF PERCHLOROETHYLENE EXPOSURE

1. Water Ingestion

The major source of drinking water for California is surface water which does not have detectable perchloroethylene concentrations. The detectable limit of perchloroethylene in water is 0.5 ug/l (0.5 ppb). Although perchloroethylene is the most frequently found contaminant in ground water, only six percent of the wells for large public water systems contain perchloroethylene levels above 0.5 ug/l. This yields a potential exposed population of about 461,000 persons (CDHS, 1986). For small public water systems, less than 0.6 percent of the supplying wells have detectable perchloroethylene levels (Spath, 1987).

Information on private well contamination is very limited. In a limited testing of suspected private wells in Santa Clara County, about eight percent were contaminated with organic chemicals (Hinman et al., 1986). This percentage represents a high estimate since suspected rather than random wells were chosen for testing. In addition, the number of persons supplied by private wells is much less than those supplied by public water systems. Based on this information, perchloroethylene exposure through drinking water is judged to be minimal ordinarily.

2. Food Ingestion

Perchloroethylene is not one of the compounds that have been measured routinely in U.S. food and food products. Using a new technique for VOC analysis in food, Entz and Hollifield (1982) detected low levels of perchloroethylene in different fish from various U.S. waterways and in a variety of jellies and sauces from a food processor in Pennsylvania. However, these data do not provide quantitative estimates of perchloroethylene in food.

A more comprehensive analysis of different food groups was conducted in 1975 by British researchers. They reported that perchloroethylene levels were generally low, with highest levels in margarine and olive oil at 7 ug/kg (McConnell et al., 1975). Based on these British data, Gilbert et al. (1982) estimated that perchloroethylene exposure in the United States via food ingestion was 1.2 ug/day.

The range of total daily intake of perchloroethylene via food consumption in Europe was estimated at 87.4 to 160 ug. These estimates were the results from market basket surveys in European countries as summarized in a Dutch criteria document (Ministerie van Volkshuisvesting, 1984). These high estimates of perchloroethylene in food may not be applicable to California since food sources and food consumption patterns are different between Europeans and Californians.

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

Estimates of the presented daily dose of perchloroethylene from different environmental media are provided in Table IV-9. The presented dose represents an amount of a chemical presented to an individual (host) without consideration of any subsequent biological interactions between the host and the chemical. From the Table, indoor air exposure appears to be the most significant medium of exposure to perchloroethylene.

1. Indoor Air

Data from the 24-hour air monitoring in the kitchen area were used to calculate the presented daily dose from residential indoor air exposure. In addition, 24-hour personal air monitoring data were used to estimate the total air exposures. Total air exposures include exposures through residential and non-residential indoor air, plus outdoor air.

2. Food

The estimated daily dose of perchloroethylene through food ingestion is highly uncertain since no California or U.S. data are available. In addition, European data are themselves not consistent and are not considered likely to represent Californians' food consumption habits. Therefore, the exposure estimate through food ingestion may be high; the relevance of the European food market survey data is unknown.

3. Drinking Water

The relative contribution of drinking water to daily exposures of perchloroethylene appears to be minimal. The quality of data used for making the estimates is relatively good.

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Table IV-9

Estimated Doses of Perchloroethylene
from Exposure through Different Media

Media	Average Presented Daily Dose (inhaled or ingested)	References
AIR		
Residential Indoor Air	90 ug[a]	Pellizzari et al., 1989
Personal air data	246 ug[b]	Pellizzari et al., 1989; U.S. EPA, 1987b
FOOD		
British data	1.2 ug	Gilbert et al., 1982; McConnell et al., 1975
European food market survey	(87-160 ug)	Ministerie van Volkhuisvesting, 1984
WATER-FOR DRINKING PURPOSES		
Surface Water	1 ug	CDHS, 1986; Spath, 1987
Ground Water Supply		
Large public water system	0.6 ug	CDHS, 1986; Spath, 1987
Small public water system	1 ug	CDHS, 1986; Spath, 1987

Calculations:

(Assume the average person inhales 20 m^3 of air daily)

a. Let C1= the average (arithmetic mean) of 6.72 and 2.27 ug/m^3, the means of 24-hour kitchen air concentrations from the TEAM 87 winter and summer studies. When C1 = 4.5 ug/m^3, presented daily dose = C1 x 20 m^3 = 90 ug

b. Let C2= the average (arithmetic mean) of 16, 15, 13, 12 and 5.6 ug/m^3, the means of 24-hour personal air concentrations from the TEAM 87 and TEAM 80/84 summer and winter studies. Personal air exposures include exposures through residential and non-residential indoor air, plus outdoor air. When C2 = 12.32 ug/m^3, presented daily dose = C2 x 20 m^3 = 246 ug

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V.

ATMOSPHERIC PERSISTENCE AND FATE OF PERCHLOROETHYLENE

The atmospheric persistence of a pollutant is its tendency to remain in the atmosphere in its original form. In analyzing human exposure to perchloroethylene, its persistence is important for two reasons: 1) if the removal time is long compared to the time needed to advect (disperse by wind) the pollutant across an air basin, the concentration throughout the basin can be inferred from measurements at specific locations; and 2) if attenuation of concentration in the plume from a source occurs mostly by dispersion of the plume rather than by chemical or physical removal (i.e. if the pollutant is persistent), routine modeling procedures like Gaussian modeling can be used to estimate the local effect of the source. If removal is fast (i.e. if the pollutant is not persistent), much more complicated modeling may be needed to estimate local effects.

A. ATMOSPHERIC PERSISTENCE OF PERCHLOROETHYLENE

There are chemical and physical mechanisms that operate to remove pollutants from the troposphere (the lower part of our atmosphere). These mechanisms include: photolysis (degradation by solar radiation), photo-oxidation (reactions with reactive species found in polluted atmospheres), adsorption on particles that fall out of the air (dry deposition), and wet deposition from interaction with fog or rain (wash-out). Chemical mechanisms appear to be the dominant force responsible for removing perchloroethylene from the atmosphere.

Two commonly used measures of persistence are half-life ($t_{1/2}$) and lifetime (τ). Half-life is defined as the time required for the concentration of a reactant to fall to one-half of its initial value, whereas lifetime is defined as the time it takes for the reactant concentration to fall to $1/e$ of its initial value (where $e = 2.718$), or approximately 37 percent of its original value (Finlayson-Pitts and Pitts, 1986). For the rest of this discussion we will describe the persistence of perchloroethylene in terms of lifetime.

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1. Chemical Removal Mechanisms

The atmospheric lifetime of perchloroethylene is related to the rate constant for the photo-chemical reactions that occur and the concentration of the reactants involved in the atmospheric reactions. For a second order reaction of perchloroethylene with atmospheric oxidants (e.g. hydroxyl radical, ozone, or NO_3 radical), the following relationship holds:

perchloroethylene + B $\xrightarrow{k_2}$ products, then $\tau = 1/ (k_2 [B])$

(where k_2 is the 2nd order reaction rate constant, and [B] is the concentration of the atmospheric oxidant).

Of the chlorinated ethenes, perchloroethylene is the least reactive to electrophilic attack. This reduced reactivity is believed to be a consequence of the electron-inductive effect of the four chlorine atoms, which reduce the electron density about the double bond and, by doing so, reduce the reactivity of the double bond (U.S. EPA, 1985). The four chlorine atoms also provide steric protection to the double bond which would also decrease the reactivity of the double bond.

However, Howard (1976) reports that the effect of the four chlorine atoms may not completely account for the unusually low reactivity of perchloroethylene to electrophilic attack. Halogenated ethenes such as C_2F_3Cl, C_2FCl_3, and sterically hindered ethenes such as tetramethylethene do not demonstrate the dramatic decrease in reactivity relative to other ethene derivatives as does perchloroethylene. Howard speculates that the bonding in C_2Cl_4 may differ from other ethenes. The electrons from the chlorine atoms in this planar symmetrical molecule could be involved in the pi electron system of the double bond, which could have a major effect on the nature of the bonding and the reactivity of the molecule.

There are three principal photo-chemical reactions that can affect the atmospheric persistence of perchloroethylene. These are: 1) attack during daylight hours by hydroxyl radicals (OH radicals); 2) attack at night by NO_3 radicals; and 3) attack by ozone (O_3) (Finlayson-Pitts and Pitts, 1986).

a. Reaction with OH Radicals

The principal mechanism for perchloroethylene removal from the atmosphere appears to involve reaction with OH radicals. The lifetime of perchloroethylene as a consequence of this reaction (τ_{OH}) is inversely proportional to the atmospheric concentration of OH radicals and the reaction rate constant, k^{OH}. The reaction can be expressed as follows:

$$\tau_{OH} = 1/\ k^{OH}\ [OH] \quad \text{or} \quad (k^{OH}\ [OH])^{-1}$$

Atkinson (1986) reviewed the work of several investigators studying the kinetics and mechanics of OH radical reactions. Based on this work Atkinson produced a formula for calculating the k^{OH} for perchloroethylene:

$$k^{OH} = 9.64 \times 10^{-12}\ e^{-(1209)/T}$$

(where T is the absolute temperature in ^{o}K).

Using this formula, Atkinson estimated the rate constant for the reaction of perchloroethylene with OH radicals to be 1.67×10^{-13} cm^3 $molecule^{-1}$ $second^{-1}$ at $298^{o}K$. Using a comparable rate constant of 1.7×10^{-13} cm^3 $molecule^{-1}$ $second^{-1}$ at $300^{o}K$, Singh et al. (1981) calculated a lifetime for perchloroethylene in the troposphere of 68 days. This calculation was based on 12 hours per day of sunlight and a 24-hour hydroxyl radical concentration of 1×10^{6} molecules per cubic centimeter, which has been reported as a reasonable estimate (Cupitt, 1983). The OH radical concentration may be somewhat lower during winter months. By using a seasonally averaged OH radical concentration of 4×10^{5} molecules per cubic centimeter one can calculate a lifetime of 292 days. Conversely, OH radical concentrations can be somewhat higher in heavily polluted atmospheres (i.e. higher criteria pollutant concentrations that are involved in OH radical formation). These results indicate that, depending on atmospheric conditions, the lifetime of perchloroethylene, as a result of its reaction with OH radicals, may range from slightly greater than two months to almost one year.

b. Reactions with Nitrate Radicals and Ozone

The lifetime of perchloroethylene as a result of its reaction with nitrate radicals and ozone can be determined in the same manner as was done above with OH radicals, $\tau = 1/\ (k_2\ [B])$. Based on a nitrate

reaction rate with perchloroethylene of <6 x 10^{-17} cm^3 $molecule^{-1}$ sec^{-1} and a 12 hour nighttime nitrate radical concentration of 10 ppt (2.4 x 10^8 $molecule/cm^3$), the calculated lifetime of perchloroethylene with respect to reaction with nitrate radicals is >4.4 years (Atkinson, 1989).

Based on an ozone reaction rate with perchloroethylene of <2 x 10^{-23} cm^3 $molecule^{-1}$ sec^{-1} (Mathias et al., 1974) and a tropospheric ozone concentration of 1 x 10^{12} $molecule/cm^3$ (Cupitt, 1980), the lifetime of perchloroethylene as a consequence of its reaction with ozone is >1000 years (Atkinson, 1989). Both nitrate radicals and ozone chemical reaction removal processes are too long to compete with the OH radical reaction.

c. Other Reactions

Several chamber studies indicate perchloroethylene is more reactive than expected from calculations of its reactions with OH radicals (Dimitriades, et al., 1983). This has been studied by researchers interested in perchloroethylene's contribution to ozone/oxidant problems in the urban atmosphere. Dimitriades argues that the smog chamber reactions of perchloroethylene are dominated by chlorine atom substitution rather than OH radical attachment and that the chlorine atom reactions are the reason for the increased reactivity of perchloroethylene in the smog chambers. Although this reaction occurs under laboratory conditions, Dimitriades contends that this reaction does not occur at a high enough rate in the atmosphere to affect the reactivity of perchloroethylene. Other hydrocarbons present in the atmosphere will react much more rapidly with available chlorine atoms, effectively scavenging the atoms and preventing chlorine atom-initiated photooxidation from being a major degradation process. In addition, in real urban atmospheres, other organic gases are present at concentrations several hundred times as high as perchloroethylene. The source of the chlorine atoms in the chamber studies was not elucidated by Dimitriades.

2. Physical Removal Mechanisms

We have not found estimates of the rates for the physical removal of perchloroethylene from the atmosphere. However, Cupitt (1980), has estimated the lifetime of ethylene dichloride under conditions of removal by rain washout, dry deposition, and adsorption on aerosols (that fall out) as 390 years, 13 years, and 25 years, respectively. Physical removal is dependent on several physical properties of a substance, including the polarity (dipole moment), solubility in water, adsorptivity on particles (e.g., on carbon), and its vapor pressure. Since perchloroethylene is comparable to ethylene dichloride in all of these properties, we have assumed that perchloroethylene has similarly

long removal times for these removal processes. Therefore, chemical removal mechanisms will be the predominant factors influencing the persistence and fate of perchloroethylene.

B. FATE OF PERCHLOROETHYLENE IN THE ATMOSPHERE

The reaction of perchloroethylene with OH radicals is predicted to occur as shown below and illustrated in Figure V-1 (Graedel, 1978).

$$Cl_2C{:}CCl_2 + OH \text{ ------> } HOCCl_2CCl_2$$

$$HOCCl_2CCl_2 + O_2 \text{------> } HOCCl_2CCl_2O_2$$

$$HOCCl_2CCl_2O_2 + NO \text{ ------> } HOCCl_2CCl_2O + NO_2$$

$$HOCCl_2CCl_2O \text{ -------> } HOCCl_2 + COCl_2$$

$$HOCCl_2 + O_2 \text{ ------> } COCl_2 + HO_2$$

Lillian (1975) predicted that perchloroethylene should lead to the formation of large quantities of phosgene in the atmosphere. Singh (1976) investigated the environmental significance of the production of phosgene from perchloroethylene in the atmosphere. Singh estimated that the photooxidation of perchloroethylene could result in phosgene levels in the low ppb range in urban areas under adverse meteorological conditions. The low reactivity of perchloroethylene determined in the more recent smog chamber studies by Dimitriades (1983) suggest that only trace levels of phosgene would be expected to be formed (U.S. EPA, 1985).

In addition, the photooxidation of perchloroethylene is believed to lead to the production of other potentially toxic compounds in the atmosphere. Singh (1977) predicted that the major environmental impact of chloroethenes in general, and perchloroethylene in particular, is likely to be the decomposition of these compounds into highly toxic species. Chamber studies conducted by Gay (1976) found that the chlorinated photooxidation products of perchloroethylene are hydrogen chloride, phosgene, trichloroacetyl chloride. On the other hand, no phosgene was detected from perchloroethylene degradation during smog chamber studies conducted by Dimitriades in 1983. Trichloroacetyl chloride can further decompose to form carbon tetrachloride (Singh, 1977). Singh estimated that as much as eight percent by weight of the atmospheric perchloroethylene could eventually be converted into carbon tetrachloride. However, this reaction is believed to occur through a chlorine atom substitution process that is not likely to occur at a substantial rate in the atmosphere as opposed to a smog chamber. This chlorine substitution reaction is illustrated in Figure V-1.

Finally, a possible reaction pathway for the atmospheric oxidation of perchloroethylene to oxalyl chloride has been suggested and is presented below (Howard, 1976):

$$OH + Cl_2C{:}CCl_2 \text{------} > CCl_2CCl_2OH$$

$$CCl_2CCl_2OH + O_2 \text{------} > O_2CCl_2CCl_2OH$$

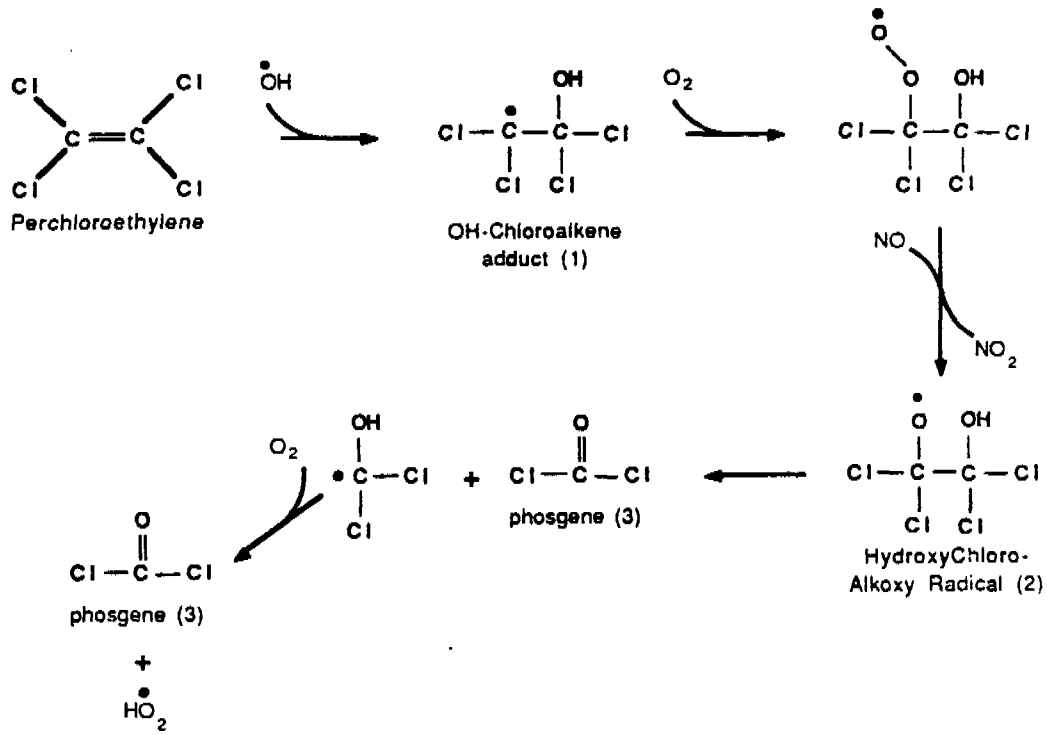
$$O_2CCl_2CCl_2OH + NO \text{------} > COClCCl_2OH + NO_2 + Cl$$

$$OH + COClCCl_2OH \text{-------} > COClCOCl + H_2O + Cl$$

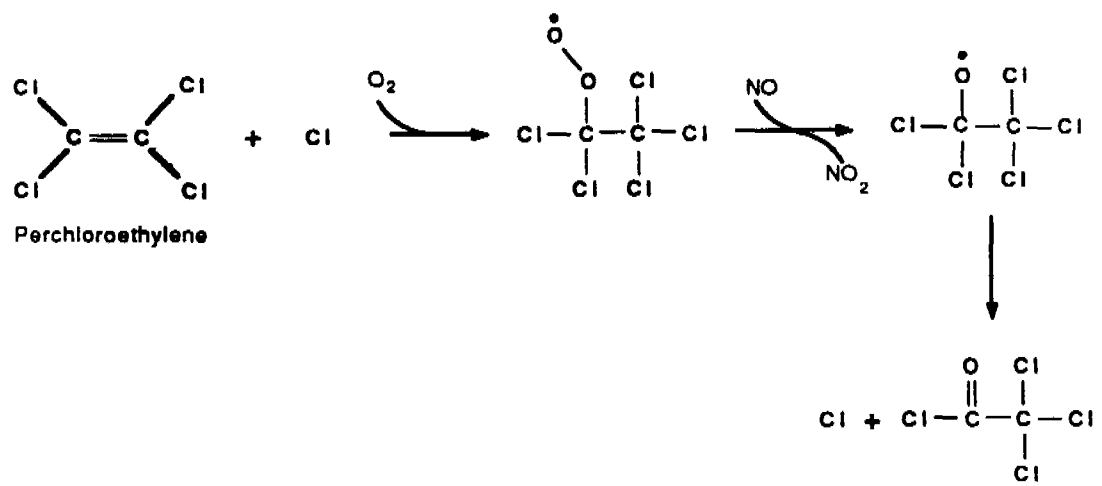
FIGURE V-1

FATE OF PERCHLOROETHYLENE

Reactions with OH Radicals



Reaction Products via Chlorine Substitution



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APPENDICES

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Appendix A

Methods for Estimating Usage and Emissions
of Perchloroethylene in California

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APPENDIX A

METHODS FOR ESTIMATING USAGE AND EMISSIONS OF PERCHLOROETHYLENE IN CALIFORNIA

The usage and emission estimates for a couple of source categories are based on the estimated shipments of perchloroethylene into California. The ARB staff estimated total shipments as a combination of two types of shipments: 1) direct shipments for use in degreasing and dry cleaning operations, and 2) shipments of perchloroethylene incorporated into products for other uses. Domestic manufacturers estimate that they shipped 19,850 tons of perchloroethylene into California in 1985 for use in degreasing and dry cleaning (Morgan, 1986). In addition, an undetermined quantity of perchloroethylene imported from foreign countries was used in California in degreasing and dry cleaning. This quantity was assumed to be proportional to the ratio of the quantity used in California for degreasing and dry cleaning to the quantity produced and used in the U.S. This quantity is estimated as follows:

- o 70,000 tons imported into the U.S. in 1985; (U.S. Department of Commerce, Bureau of Census, FT 246, 1985).
- o 328,000 tons produced and used in the U.S. in 1985 (i.e., U.S. production minus exports); (C&E News, 1987), (U.S. Department of Commerce, Bureau of Census, FT 446, 1985).
- o 19,850 tons shipped from the U.S. producers in 1985 for degreasing and dry cleaning use in California; so

$$(70{,}000 \text{ tons}) \left\{ \frac{19{,}850 \text{ tons}}{328{,}000 \text{ tons}} \right\} = 4{,}240 \text{ tons.}$$

Thus, the total quantity of perchloroethylene shipped directly into California in 1985 is estimated to the nearest hundred tons to be:

19,850 tons + 4,240 tons = 24,100 tons.

Additional perchloroethylene that was incorporated into products was also shipped into California. The ARB staff assumes that the perchloroethylene in adhesives, aerosols, paints and coatings, and miscellaneous uses was incorporated into products. Usage in these categories is estimated below in the section on "Other Uses" to total 2,500 tons. This estimate is for 1983 and the ARB staff assumes the same quantity for 1985. This estimate accounts for imported as well as domestically produced perchloroethylene.

Thus, the total quantity of perchloroethylene used in California in 1985 is estimated to the nearest hundred tons to be:

Total Usage: 24,100 tons + 2,500 tons = 26,600 tons.

DRY CLEANING:

The quantity of perchloroethylene used in dry cleaning in California in 1985 is estimated by summing 1) the quantity shipped into California by domestic producers for use in dry cleaning and 2) an estimate of the

quantity of imported perchloroethylene used in California for dry cleaning. Domestic manufacturers estimate that they shipped 14,930 tons of perchloroethylene into California in 1985 for use in dry cleaning (Morgan, 1986). The quantity of perchloroethylene imported into California from foreign markets for use in dry cleaning operations is estimated as:

- o 70,000 tons imported into the U.S. in 1985; (U.S. Department of Commerce, Bureau of Census, FT 246, 1985).
- o 328,000 tons produced and used in the U.S. in 1985 (i.e., U.S. production minus exports); (C&E News, 1987), (U.S. Department of Commerce, Bureau of Census, FT 446, 1985).
- o 14,930 tons shipped in 1985 from U.S. producers to California for dry cleaning; so

$$(70{,}000 \text{ tons}) \left\{ \frac{14{,}930 \text{ tons}}{328{,}000 \text{ tons}} \right\} = 3{,}190 \text{ tons.}$$

Thus, the total quantity of perchloroethylene shipped into California in 1985 for dry cleaning is estimated to the nearest hundred tons to be:

Dry Cleaning Usage: 14,930 tons + 3,190 tons = 18,100 tons.

To estimate emissions, the ARB staff used information that 0.88 pound of perchloroethylene is emitted for every pound of fresh perchloroethylene used in dry cleaning in the U.S. (Wolf & Meyers, 1987). Thus, an estimate of perchloroethylene emissions from dry cleaning rounded to the nearest hundred tons is:

Dry Cleaning Emissions: (18,100 tons) (0.88 lb./lb.) = 15,900 tons.

A quick check of this emission estimate was made by using a more general approach. One of the studies cited above includes an emission estimate for dry cleaning in the U.S. of 126,500 tons in 1985 (Wolf & Meyers, 1987). The ARB staff adjusted this estimate by the proportion of the U.S. population in California, i.e. 11 percent (U.S. Department of Commerce, Bureau of Census, 106th Ed., 1985). Estimated emissions using this approach are 13,900 tons. Given the uncertainty that is introduced by using a ratio of populations, this estimate compares well with the original estimate of 15,850 tons of perchloroethylene emissions.

The ARB staff allocated perchloroethylene emissions to different sectors of the dry cleaning industry by using EPA estimates of U.S. usage in 1983. The EPA estimates are: (Bath/EPA, 1986).

Coin-Operated Usage: 23,060 tons per year;
Commercial Usage: 91,100 tons per year;
Industrial Usage: 14,360 tons per year.

For example, the estimate rounded to the nearest hundred tons for commercial dry cleaning is:

$$\text{Calif. Commercial Emis.} = (\text{Total Calif. Emis.}) \frac{(\text{U.S. Commercial Usage})}{(\text{Total U.S. Usage})}$$

$$= (15{,}900 \text{ tons}) \left\{ \frac{91{,}100 \text{ tons}}{128{,}520 \text{ tons}} \right\}$$

$$= 11{,}300 \text{ tons.}$$

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DEGREASING:

The quantity of perchloroethylene used in degreasing in California in 1985 is estimated with the same type of approach used above to estimate the use of perchloroethylene in dry cleaning. Usage is estimated as the sum of 1) the quantity shipped into California by domestic producers and 2) an estimate of the quantity of imported perchloroethylene used in California for degreasing. Domestic manufacturers estimate that they shipped 4,925 tons of perchloroethylene into California in 1985 for use in degreasing (Shimp, 1986). The quantity of perchloroethylene imported to the U.S. for use in degreasing operations in California is estimated as:

- o 70,000 tons imported into the U.S. in 1985; (U.S. Department of Commerce, Bureau of Census FT 246, 1985).
- o 328,000 tons produced and used in the U.S. in 1985 (i.e., U.S. production minus exports); (C&E News, 1987), (U.S. Department of Commerce, Bureau of Census FT 446, 1985).
- o 4,925 tons shipped in 1985 from U.S. producers to California for degreasing; so

$$(70{,}000 \text{ tons}) \left\{ \frac{4{,}925 \text{ tons}}{328{,}000 \text{ tons}} \right\} = 1{,}050 \text{ tons.}$$

Thus, the total quantity of perchloroethylene shipped into California in 1985 for degreasing is estimated to the nearest hundred tons to be:

Degreasing Usage: 4,925 tons + 1,050 tons = 6,000 tons.

The ARB staff estimated emissions by using a typical factor for the proportion of perchloroethylene usage that is emitted. An EPA report estimated that 0.92 pound of perchloroethylene is emitted for every pound of fresh perchloroethylene used in degreasing in the U.S. (EPA, 1985). Thus, degreaser emissions rounded to the nearest hundred tons are estimated as:

Degreasing Emissions: (5,940 tons) (0.92 lb./lb.) = 5,500 tons.

OTHER USES:

The EPA reported U.S. usage of perchloroethylene for adhesives, aerosols, paints and coatings, and miscellaneous in 1983 (EPA, 1985). Population fractions were used to estimate California usage from U.S. usage for these categories. California's population was estimated to be 11 percent of the U.S. population in 1985 (U.S. Department of Commerce, Bureau of Census, 106th Ed., 1985). Thus, California usage was estimated as 11 percent of U.S. usage for these categories, or 2,500 tons. Emissions were estimated as less than or equal to usage.

The emissions estimate for the use of perchloroethylene in specialty chemical production is based on information supplied by Dow Chemical in Pittsburg, California, to an EPA contractor (Radian Corp., 1986). The Dow Chemical facility is the only known facility using perchloroethylene in chemical production in California. No usage information was available for the facility.

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DISTRIBUTION:

An estimated 24,100 TPY of perchloroethylene were sold through distribution facilities in California. This quantity includes the above estimates of the perchloroethylene used in California for dry cleaning and degreasing. Emissions from perchloroethylene distribution primarily result from storage in large tanks during distribution. Additional perchloroethylene usage in California was assumed to be incorporated in products and therefore not stored in large tanks. EPA data on the estimated emissions from national distribution were used in estimating the California emissions (EPA, 1985). Emissions were calculated as:

$$(24{,}100 \text{ TPY distributed in CA}) \frac{(55 \text{ TPY emitted in U.S.})}{(178{,}000 \text{ TPY distributed in U.S.})} = 7 \text{ TPY.}$$

SOLVENT RECLAMATION:

An estimated 1,940 TPY of perchloroethylene were sent for recycling in California in 1985. The quantity of perchloroethylene sent for recycling in California was estimated by using: 1) the quantity of halogenated solvent reported on hazardous waste manifests as sent to recyclers, and 2) the estimated percent of perchloroethylene contained in the halogenated solvents.

The California Department of Health Services reported that 9,685 tons of halogenated solvents were sent for solvent reclamation in California in 1985 (Radian Corp., 1986). A representative of one of the largest solvent reclaimers in the State estimated that 20 percent of the halogenated solvent sent for solvent reclamation is perchloroethylene (DHS, 1986). Thus, the quantity of perchloroethylene sent for solvent reclamation was estimated as:

(9,685 TPY) (.20) = 1,940 TPY.

Industry representatives estimated emission losses for a solvent as volatile as perchloroethylene to be one quarter to one percent of the perchloroethylene received (DHS, 1986), (Schneider, 1986a), (Schneider, 1986b), (O'Morrow, 1986). Thus, perchloroethylene emissions are estimated as:

(1,940 TPY) (.0025 to .01) = 5 to 20 TPY.

POTWs:

See the discussion on POTWs in the body of the report.

MUNICIPAL LANDFILLS:

The estimate of perchloroethylene emissions from a typical municipal landfill is based on 1) a mean surface gas concentration of perchloroethylene of 0.3 parts per million, 2) a typical volume of landfill gas emitted per square foot of landfill surface per day of 0.8 SCFT/ft^2/day (SCFT stands for standard cubic foot), and 3) an estimated surface area of a landfill of 40 acres. The Gas Research Institute reported a mean

concentration of 0.3 parts per million (volume) of perchloroethylene for 83 surface gas samples from nine landfills in the U.S. (Roehl Disposal Corp., 1986). This same reference estimates that a typical volume of methane emitted from a landfill surface is 0.4 SCFT/ft^2/day. ARB staff assumed that landfill gas is approximately 50 percent methane. ARB staff also assumed a typical size of a municipal landfill to be 40 acres.

HAZARDOUS WASTE LANDFILLS:

Emission estimates for individual hazardous waste landfills are presented based on three methods of estimation, including: EPA estimates based on source monitoring at three hazardous waste landfills; ARB staff estimates of emissions from a hazardous waste landfill of median size; and EPA estimates of modeled emissions. The EPA reported mass emission rates for three California landfills, including two active and one inactive landfill. The perchloroethylene emission rates were as follows: 3.64 TPY for a 215,000 ft^2 active landfill; 0.03 TPY for a 16,000 ft^2 area of another active landfill and 0.30 TPY for a 7,200 ft^2 section of the same landfill; and 0.003 TPY for a 32,400 ft^2 inactive landfill (G.R.I., 1982), (EPA, 1984). ARB staff developed emission estimates for a typical landfill based on the above EPA source monitoring data and data on the median size of a landfill. Data on the median size (971,450 ft^2) of a hazardous waste landfill in the U.S. were taken from a article published in the Journal of the Air Pollution Control Association (EPA, 1985). The range of perchloroethylene emissions from an active landfill of median size is estimated from the above data as:

Low estimate: $\frac{(0.03\ TPY)}{(16{,}000\ ft^2)}$ (971,450 ft^2) = 1.8 TPY.

High estimate: $\frac{(3.64\ TPY)}{(215{,}000\ ft^2)}$ (971,450 ft^2) = 16.4 TPY.

The emission estimate for an inactive landfill of median size was calculated in a similar manner.

SURFACE IMPOUNDMENTS:

See the discussion on surface impoundments in the body of the report.

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APPENDIX B

Standard Methods of Analysis for Tetrachloroethylene

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METHOD NO. ADDL002

STANDARD OPERATING PROCEDURE FOR THE DETERMINATION OF VOLATILE ORGANICS IN AMBIENT AIR USING TENAX TRAP PRECONCENTRATION GAS CHROMATOGRAPHY AND TANDEM PHOTOIONIZATION/ELECTRON CAPTURE DETECTORS

1.0 SCOPE

This document describes a procedure for the determination of volatile halogenated hydrocarbons and aromatics having a boiling point of less than 120°C. This procedure is based on documents received from the ARB Haagen-Smit Laboratory, El Monte, as well as EPA Method TO1.

2.0 SUMMARY OF PROCEDURE

Ambient air is continuously sampled and collected in a Tedlar bag over a 24 hour period and immediately sent to the laboratory for analysis. A sample from the bag is drawn through a sampling valve attached to a Tekmar LSC-2 Tenax Sample Concentrator (see Figure I) with a vacuum pump at 50 cc/min for four minutes (total sample volume: 200 cc). The organic constituents are trapped on Tenax and when the collection is complete, the Tenax is purged with 40 cc of helium to remove any trapped moisture. The sample is then thermally desorbed onto the head of the GC column. The GC column is temperature programmed and component peaks

eluting from the column are sequentially detected and quantified, first by a photoionization detector (PID) and then by an electron capture detector (ECD). The components are identified based on retention times. Positive identification or confirmation requires the use of an appropriately configured GC/MS.

3.0 INTERFERENCES/LIMITATIONS

a. Components having similar GC retention times will interfere, causing misidentification and/or faulty quantitation.

b. Because of the very low sample concentrations, extreme care must be taken to insure that the sample is not degraded or contaminated by the Tedlar sampling bag, sampling apparatus, or delayed delivery to the laboratory. Exposure of the Tedlar sampling bag to temperatures greater than 25°C should be minimized.

c. Only components of the sample which can be detected by PID/ECD detectors will be quantified.

4.0 APPARATUS

a. Varian Model 6000 Gas Chromatograph/PID/ECD system equipped with a Varian Vista 402 dual channel data system.

b. Tekmar LSC-2 Sample Concentrator equipped with Tenax trap and sampling valves as shown in Figure 1.

c. Matheson Model 8240 Mass Flow Controller accurately calibrated in the 5-100 cc/min range.

d. Laboratory timer, accurate to within 0.1 minutes.

e. Gas tight microliter syringe, 50 ul.

f. GC column - 10' x 2 mm i.d. glass column packed with 1 percent SP-1000 on Carbopack B, 60/80 mesh.

5.0 REAGENTS

a. Primary Gas Standard (Scott Specialty Gases - Research Triangle Institute Certified Series 1)

Compound	Concentration (ppb)
Chloroform	107
Carbon tetrachloride	105
Perchloroethene	106
Vinyl chloride	104
Benzene	107

b. Primary Gas Standard (Scott Specialty Gases - Research Triangle Institute Certified Series 2)

Compound	Concentration (ppb)
1,2-Dichloroethane	101
1,1,1-Trichloroethane	98
Trichloroethene	100
1,2-Dibromoethane	102

c. Stock Gas Standard - Scott-Marrin Blend (assayed against primary cylinders)

Compound	Concentration (ppb)
Dichloromethane	4272
Chloroform	528
1,2-Dichloroethane	3104
1,1,1-Trichloroethane	424
Carbon tetrachloride	46
Trichloroethene	336
1,2-Dibromoethane	5
Perchloroethene	43
Vinyl chloride	4736
Benzene	1888

d. Control Gas Standard - Scott-Marrin Blend (assayed against primary cylinder)

Compound	Concentration (ppb)
Dichloromethane	6
Chloroform	0.2
1,2-Dichloroethane	0.2
1,1,1-Trichloroethane	3.6
Carbon tetrachloride	0.3
Trichloroethene	1.8
1,2-Dibromoethane	2.5
Perchloroethene	1.2
Vinyl chloride	3.3
Benzene	4.8

e. Surrogate Gas Standard (Scott-Marrin Blend)

Compound	Concentration (ppm)
Bromochloromethane	10
1,3-Bromochloropropane	33

6.0 PROCEDURES

a. Sample Trapping

1. The preconcentration system is shown in Figure 1.

2. The high concentration inlet is used for high concentration calibration standards and for other samples with concentrations higher than ambient levels. The sample is introduced through the high concentration inlet and 6 port valve into an appropriate size loop of known volume. The sample then passes through a 10 port valve, mass flow meter, and vacuum pump. Before an analysis, the system is leak checked by blocking the sample inlet port and observing that the mass flow meter reading drops to zero. The high concentration inlet then is connected to a Tedlar sample bag valve and the gas bag valve opened. The loop is then flushed with sample gas for three minutes. After three minutes of flushing, the 6 port valve is reset so that the sample contained in the loop is carried into the trap by the helium purge gas. This continues for three minutes to ensure that all of the contents of the loop are trapped.

3. Ambient samples are introduced from Tedlar bags as described above, except that the sample loop is bypassed and the sample goes directly to the 10 port valve. After flushing the system with sample for three minutes, the 10 port valve is reset so that 200 cc's of sample is trapped (50 cc/min. for four minutes). After sample trapping is complete, the Tenax trap is flushed with 40 cc of helium to remove water vapor and any nonadsorbed reactive gases.

4. In both ambient and high concentration cases, after the sample has been trapped, the Tekmar LSC-2 heats the Tenax trap to 180°C while the trap is swept with the G.C.'s internal carrier gas for four minutes. The contents of the trap are thus desorbed and collected on the head of the G.C. column. The trap is baked out after the end of the desorption cycle. In the bakeout cycle, the trap is flushed with helium purge gas for eight minutes while being held at 225°C in order to prepare the trap for the next cycle. After bakeout the trap is isolated from the system and ready for the next sample.

b. Analysis

1. The concentrated sample is separated under the chromatographic condition detailed below. The resulting chromatogram (see Figure II) is then integrated and quantified by reference to calibration standard gases.

2. Instrument Conditions:

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GC: Column: 10' x 2 mm i.d. glass column, packed with 1 percent SP-1000 on Carbopack B 60/80 mesh

Temperatures: Injection: 200°C
Detector: 350°C
Oven: 45°C, hold for four minutes, 5°C/min ramp, to 210°C, hold for eight minutes

Flow Rates: Carrier: He, 20 c.c/min
ECD make up: N_2, 40 c.c/min

Detectors: ECD: Range X 10, Attenuation X 32
PID: Range X 1, Attenuation X 32, 10.2 ev lamp

Conc: Tekmar LSC-2: Purge: 4 minutes
Desorb: 4 minutes at 180°C
Bake: 8 minutes at 225°C

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3. All blanks, standards, control samples, and ambient samples are spiked with surrogate compounds by injecting 50 microliters of the surrogate gas standard (5.e.) during sample trapping. The surrogate compounds, chosen such that they simulate the characteristics of the analytes of interest and are unlikely to occur in the environment, are added to insure that systematic errors or equipment failures will be noted and corrected promptly.

4. The first step in a calibration is to analyze a system blank. This is done by trapping and analyzing a 200 cc sample of auxiliary carrier gas. The system blank must be free of interfering peaks. A system blank must also be run after a high concentration sample is analyzed in order to detect any carry-over within the system.

5. A calibration is performed using a 1.25 cc loop of stock standard gas (5.c.). Two hundred cubic centimeters of helium gas is passed through the loop to carry the standard onto the trap. The calibration analysis is made as a normal analysis. The calculated concentration value for each component should be inspected to insure consistency with previous analyses. The stored chromatographic information may then be used to recalculate the response factors for the subsequent analyses. The G.C. data system will not accept updated response factors which are in excess of plus or minus 15 percent of historic data.

6. Following calibration, 200 cc of the control sample (5.d.) is concentrated on the trap and analyzed. The control sample data are plotted on control charts of the normal Shewhart type. Upper and lower warning limits are plus or minus two times the standard deviation. Any analysis which falls outside the upper and lower warning limits is repeated and the laboratory quality control officer is advised. Upper and lower control limits are plus or minus three times the standard deviation. If any analysis falls outside the upper or lower control limit, the method is discontinued until the out of control situation is remedied. The laboratory quality control officer is advised and provided with written documentation of the out of control condition and how it was remedied. All data generated prior to the out of control situation must be reviewed for possible decertification by laboratory management.

7. Multipoint calibrations are conducted monthly. Each multipoint calibration includes a trap blank and three standard concentration levels to bracket the concentration ranges expected in ambient air. If subsequent data indicate that the resulting least squares analyses are consistently acceptable, less frequent multipoint calibrations may be made.

7.0 PERFORMANCE

a. All ambient field samples are analyzed in duplicate. The relative error between analyses must be less than 20 percent. Duplicate analyses having greater than 20 percent relative error must be decertified.

b. The percent recovery of the surrogate is recorded in the instrument laboratory workbook for each analysis. If this value is outside the 80% to 120% range, the sample analysis must be repeated.

8.0 METHOD SENSITIVITY, PRECISION AND ACCURACY

The method sensitivity, precision and accuracy are outlined in Table I. These data were produced with gaseous calibration standards, and using carrier gas as the sample matrix. The relative accuracy of the method, with the exception of dichloromethane, is based on reference to the Research Triangle Institute Certified Gas Standards (NBS traceable). Authoritative reference calibration standards for dichloromethane ar under development at NBS but are not yet available. The concentration value of the present standard was assigned by the commercial manufacturer and found to be in good agreement with diluted pure dichloromethane prepared in our laboratory. The absolute accuracy of the method has not been determined by interlaboratory testing.

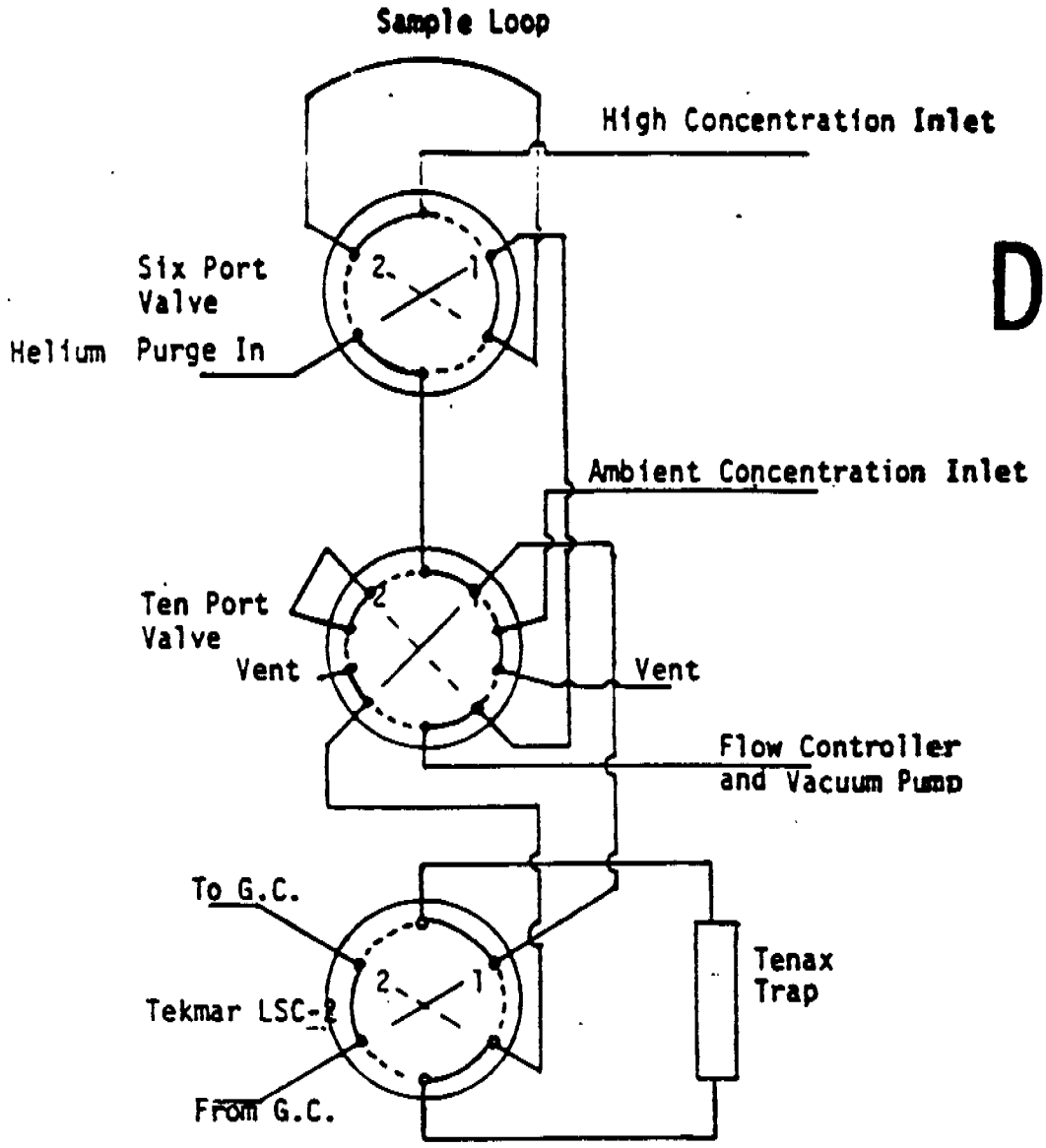

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Figure 1. Schematic of concentrator system. Sampling Conditions are: 200 cc volume, purge at 40cc/min, 1 min., desorb at 180 C for 4 min., bake for 8 min. at 225 C.

SYSTEM GUIDE

Operational Step	Valve Position			
	6-Port	10-Port	LSC-2	Purge Gas
Loop Fill	1	1	1	Off
Loop Trap	2	1	1	On
Ambient Trap	1	2	1	Off
Trap Desorb	1	1	2	Off
Trap Bake Out	1	1	1	On

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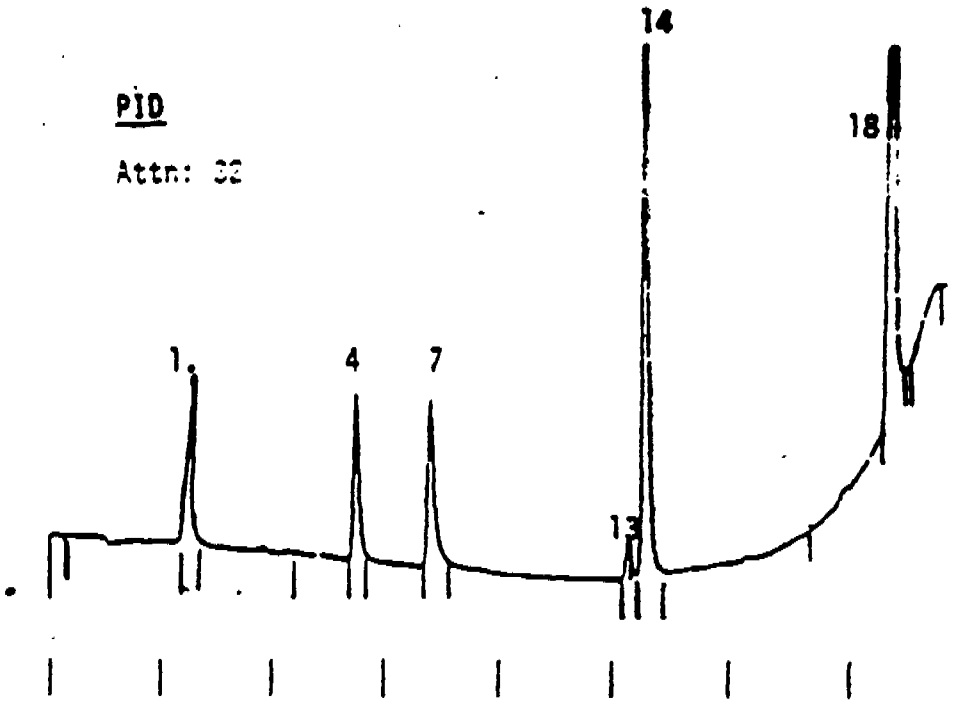

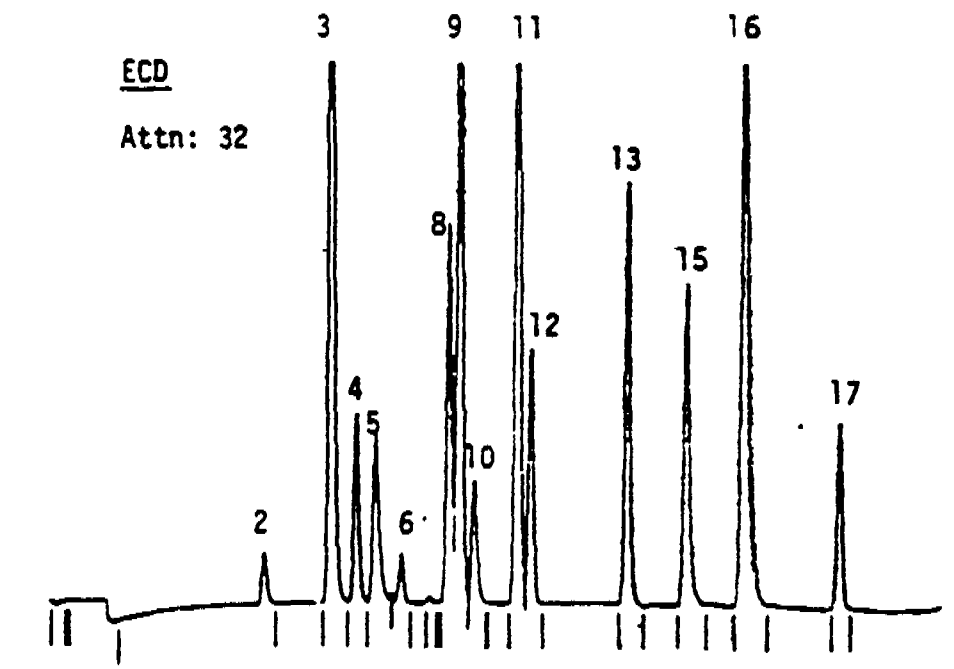

1. Vinyl Chloride
2. Dichloromethane
3. Trichlorofluoromethane
4. 1,1-Dichloroethylene
5. Bromochloromethane
6. 1,1-Dichloroethane
7. t-1,2-Dichloroethylene
8. Chloroform
9. Freon 113
10. 1,2-Dichloroethane
11. 1,1,1-Trichloroethane
12. Carbon Tetrachloride
13. Trichloroethylene
14. Benzene
15. 1,2-Dibromoethane
16. Bromochloropropane
17. Tetrachloroethylene
18. Toluene

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Table I

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Method Sensitivity and Precision

Compound	Correlation Coefficient	Slope	R.S.D* (Percent)	Detector	LOD ppbv
Vinyl Chloride	0.997	0.946	16	PID	0.8
Dichloromethane	0.999	0.975	5	ECD	0.6
1,1-Dichloroethylene	0.991	0.966	6	ECD	0.05
Chloroform	0.999	0.901	3	ECD	0.02
1,2-Dichloroethane	0.999	1.054	7	ECD	0.1
1,1,1-Trichloroethane	0.999	0.989	9	ECD	0.01
Carbon Tetrachloride	0.999	0.980	6	ECD	0.005
Trichloroethylene	0.999	0.992	6	ECD	0.02
Benzene	0.998	0.950	10	PID	0.5
1,2-Dibromoethane	0.974	1.067	9	ECD	0.005
Tetrachloroethylene	0.994	1.080	10	ECD	0.01

* R.S.D. - Relative Standard Deviation at 5 x LOD, n = 5

PRELIMINARY DRAFT

TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF PERCHLOROETHYLENE AS A TOXIC AIR CONTAMINANT

PART B REPORT

STATE OF CALIFORNIA
AIR RESOURCES BOARD
STATIONARY SOURCE DIVISION

DRAFT

HEALTH EFFECTS OF
TETRACHLOROETHYLENE (PCE)

CALIFORNIA DEPARTMENT OF HEALTH SERVICES

JANUARY, 1989

DRAFT

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1. EXECUTIVE SUMMARY

Tetrachloroethylene, commonly referred to as perchloroethylene (PCE), is a volatile organic hydrocarbon with a chloroform-like odor used as a solvent in dry cleaning operations, a metal degreaser, a chemical intermediate in the synthesis of fluorocarbons, and in coffee decaffeination. Perchloroethylene is a lipophilic compound which readily diffuses into the blood and subsequently into adipose tissue where it accumulates due to its relative stability and slow metabolism. The main metabolic pathway for PCE in humans appears to involve its oxidation by cytochrome P-450-dependent mixed-function oxidases (referred to as P-450) to 1,1,2,2-tetrachloroethylene oxide. Following an apparently spontaneous chloride migration, the metabolites trichloroacetyl chloride and trichloroacetic acid are formed. Trichloroacetic acid accounts for about 60% of the trichlorocompounds found in urine after exposure to PCE. The chemical nature of the remaining 40% of trichlorocompounds has not been established, but is assumed to be trichloroethanol. Trichloro compounds account for most of the metabolism of PCE in rodents. However, the human PCE metabolic data are very incomplete and other unidentified products are also produced. Following P-450 metabolism and several dechlorination steps, oxalic acid and carbon dioxide (CO_2) also may be produced in humans since they are common metabolic products in animals.

Perchloroethylene is eliminated from the body by two major processes: At high concentrations (>50 ppm), the majority of absorbed PCE is excreted unchanged in the exhaled air while the remainder may undergo metabolism and

excretion as urinary metabolites. At lower concentrations, relatively less PCE is exhaled.

Perchloroethylene has moderate acute toxicity, with the liver being its principal target organ. Acute inhalation exposure of mice to 200 ppm for four hours produced moderate fatty infiltration in the liver. Chronic exposure of laboratory animals to 100 ppm PCE caused major liver damage. The products of PCE metabolism are thought to promote liver toxicity. The extent of PCE metabolism was directly proportional to observed liver cell damage in animal experiments. The method by which PCE causes liver toxicity is not known, but metabolites of PCE may bind covalently to cell components. These bound metabolites have a slow turnover rate in the liver and accumulate upon chronic exposure. In particular, PCE appears to damage *mitochondria*.

Perchloroethylene causes skin and eye irritation. Prolonged PCE exposure can produce erythema, burns, and blistering. It has been associated with tachycardia and sudden death from cardiac failure, and PCE may sensitize the heart to the effects of endogenous epinephrine. Massive acute exposure to PCE induces central nervous system (CNS) depression that can progress to loss of consciousness, anesthesia, and respiratory failure. Inhalation exposure of pregnant rodents to 300 ppm PCE produced maternal toxicity and fetotoxicity manifested as developmental delays and altered performance in behavioral tests in the offspring of exposed mice and rats.

The No-Observed-Adverse-Effect-Level (NOAEL) for chronic inhalation in rats was reported to be 70 ppm PCE. However, rats are less susceptible than mice

to hepatotoxicity, the most sensitive noncancer endpoint for toxicity. Mice chronically exposed to 100 ppm PCE exhibited liver degeneration and necrosis, whereas 200 ppm PCE given to rats under the same regimen did not result in hepatic lesions. A NOAEL for mice has not been established. Humans have shown signs of liver toxicity after chronic exposure to 232-385 ppm PCE, indicating that humans may be as susceptible as mice to the hepatotoxic effects of PCE. Maximum concentrations of PCE measured in urban areas were approximately 5 ppb, a level well below the NOAEL. Consequently, California Department of Health Services (CDHS) staff do not expect noncarcinogenic adverse health effects to occur from acute or chronic exposure to PCE in ambient air.

The current 8-hour threshold limit value (TLV-TWA) for PCE in the workplace is set at 50 ppm, to provide a margin of safety against eye and respiratory discomfort and subjective complaints experienced at exposure levels of 100-200 ppm (ACGIH, 1986). The National Institute for Occupational Safety and Health (NIOSH) does not suggest a safe exposure level but recommends reducing exposure to the lowest feasible limit to prevent potential carcinogenic effects (NIOSH, 1985).

Perchloroethylene increased the incidence of hepatocellular tumors in laboratory mice after oral and inhalation exposure and mononuclear cell leukemia in rats after inhalation. A lifetime inhalation bioassay was conducted by the National Toxicology Program (NTP) in which mice (of both sexes) were exposed to 100 or 200 ppm of PCE and rats (of both sexes) were exposed to 200 or 400 ppm PCE (NTP, 1986). Both concentrations of PCE resulted in a statistically significant increase in hepatocellular carcinoma

and adenoma in treated mice of both sexes. The incidence of mononuclear cell leukemia was significantly increased in rats of both sexes. The NTP concluded that, under the conditions of their study, there was clear evidence of carcinogenicity of PCE for male F344/N rats, some evidence of carcinogenicity of PCE for female F344/N rats, and clear evidence of carcinogenicity of PCE for both sexes of B6C3F1 mice. In an earlier study by the National Cancer Institute (NCI, 1977) male and female mice developed hepatocellular carcinoma after oral gavage exposure to PCE 5 days/week over 78 weeks. Rats receiving PCE via gavage did not develop significant increases in tumors, but early mortality in treated animals limits the usefulness of this study in characterizing the oral carcinogenicity of PCE in rats.

Epidemiological studies have provided some indication that the use of dry-cleaning solvents, primarily PCE, poses an increased risk of cancer in exposed workers. However, investigators were unable to differentiate among exposures to various solvents, and possible confounding factors like smoking were not evaluated. Therefore, the usefulness of these reports in the assessment of the human cancer risk from PCE exposure is limited.

The International Agency for Research on Cancer (IARC) reviewed the carcinogenicity data on PCE and placed it in category 2B, with sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (IARC, 1987). The CDHS staff agree with IARC's conclusion. Prior to the publication of the results of the NTP (1986) inhalation bioassay the EPA concluded that the evidence for carcinogenicity of PCE in animals was limited and that the available epidemiological data for human

carcinogenicity was inconclusive. Therefore PCE was placed in group C, as a possible human carcinogen (EPA, 1985a). However, in light of the NTP inhalation bioassay the classification is being reconsidered and it is likely that PCE will be placed in group 2B, as a probable human carcinogen.

Perchloroethylene has generally produced negative results in genotoxicity assays using bacterial systems, but reportedly produced a dose-dependent increase in base-pair substitutions and frameshift mutations in Salmonella typhimurium TA 100 with metabolic activation (Cerna and Kypenova, 1977). An increase in mitotic recombinations and gene conversions were also reported in Saccharomyces cerevisiae strain D7 after exposure to PCE without metabolic activation (Callen et al., 1980). Perchloroethylene oxide, the first intermediate formed by microsomal oxidation, exhibited a dose-dependent mutagenic response in Salmonella typhimurium TA 1535. Trichloroethanol, another metabolite of PCE, induced sister chromatid exchange in cultured human lymphocytes. These responses indicate that PCE itself and/or some of its metabolites are potentially genotoxic. The U.S. Environmental Protection Agency (EPA), after reviewing the literature on the mutagenicity of PCE, concluded that inadequate information exists to classify PCE as either a mutagen or a nonmutagen (EPA, 1985). The staff of the CDHS agrees that PCE's mutagenicity has not been clearly established, but the positive results in some of the genotoxicity assays with PCE indicate a possible interaction with DNA and the potential for PCE to be an active genotoxin. CDHS staff have found no evidence of a carcinogenic threshold level. Thus, although the mutagenic activity of PCE is unclear, the staff recommends that PCE be considered as not having a threshold for carcinogenicity.

Results from the 1986 NTP inhalation study were used as the basis for estimating the carcinogenic risk of PCE to humans. In this bioassay, PCE was 99.9% pure, and animals were exposed 6 hours/day, 5 days/week for 103 weeks. The mice in the 100 and 200 ppm dose groups were exposed to a time-weighted average (TWA) of 16 and 32 ppm, respectively (e.g., 100 ppm x 6 hours/24 hours x 5 days/7 days). Similarly, rats in the 200 and 400 ppm dose groups were exposed to a TWA of 33 and 66 ppm, respectively.

The CDHS staff used the applied dose, adjusted to continuous lifetime exposure, to calculate the carcinogenic potency of PCE. A metabolized dose was not included in the suggested range of risks for several reasons. The metabolized dose adjustment did not reduce the uncertainties in the PCE risk assessement, but instead elucidated new areas of uncertainty. Uncertainties of low dose extrapolation were compounded by uncertainties in dose calculations. The current data available on the quantity of PCE metabolized by different pathways in different species is incomplete. This uncertainty is evident in the huge range of the metabolized doses obtained from different pharmacokinetic models. For example, the metabolized dose calculated by several methods, for the production of male mouse liver tumors vary by five-fold (19.5 mg/kg-day to 93.8 mg/kg-day). The metabolized dose approach, as it has been applied to PCE, assumes that oxidative metabolism leads to the production of carcinogenic metabolites; but the ultimate carcinogen(s) has not been well characterized. The extent of oxidative metabolism has generally been inferred from the production of "trichloro" metabolites. Metabolism to nontrichloro metabolites has not been quantified in humans, and a mass balance approach identifying the distribution and excretion of inhaled PCE has not been conducted. In humans, urinary

trichloro compounds account only for 1-2% of the inhaled PCE following exposure to concentrations of approximately 100 ppm, whereas 60-80% of the PCE taken in is exhaled unchanged through the lungs during the exposure. This implies that 20-40% of the absorbed PCE is stored (presumably in adipose tissue) and is slowly released over time. The high storage capacity and the slow release of PCE from adipose tissue prevent verification of the mass balance relationship proposed by pharmacokinetic models between PCE absorbed and PCE metabolized or excreted either as urinary metabolites or unchanged by the lungs. The residual PCE could be metabolized to trichloro compounds over time, or to nonchlorinated metabolites such as CO_2 and oxalic acid that could not be easily associated with PCE metabolism without use of radiolabeled PCE.

Data on the amount of PCE metabolized at ambient concentrations less than 1 ppb) are not available. However, several studies indicate that PCE metabolism increases as the concentration decreases. Extrapolation of metabolism rates to ambient levels indicates that up to 100% of the PCE may be metabolized by mice and rats. Humans may metabolize up to 60% at ambient levels compared to the 4% level estimated from experiments using concentrations 100,000-fold greater than ambient levels. Pharmacokinetic models generally do not account for individual differences in metabolism and storage. A high variability of body burden of PCE was found for different people tested (Guberan and Fernandez, 1974; Hake and Stewart, 1977; Stewart et al., 1970). The body burden depended on such factors as age, sex, exercise or workload, body mass, adipose tissue mass, pulmonary dysfunctional states, and individual differences in the intrinsic capacity to metabolize PCE.

The pathways of PCE metabolism are speculative at this point in time, but it is known that cytochrome P-450 is involved. The presence and basal activity of cytochrome P-450-dependent enzymes are determined genetically, but such systems may be altered by components of the diet. Pretreatment of rats with inducers of P-450 increased PCE metabolism five- to seven-fold. Epidemiologic evidence relating enzyme induction to components of human diet are not available at this time, but appears likely. Human variability in PCE metabolism could be accounted for through the incorporation of generic safety factors, although none of the available pharmacokinetic models has incorporated such a safety factor. Finally, chronic studies in mice and occupational studies in humans indicate that mice and humans appear to have similar sensitivity to PCE's induction of noncarcinogenic liver effects. Since carcinogenic and noncarcinogenic effects are thought to occur via the same metabolic pathway, the fifty-fold species difference suggested by the metabolized dose calculations does not appear justified. Thus, it appears premature to use the metabolized dose in current estimations of human risk to PCE. However, due to the importance of the area of study, calculations using such methods were presented in Section 5.

For the low-dose PCE risk assessment, the Crump multistage polynomial (Crump, 1981) was chosen. This model, rather than a time dependent form of the multistage model, was chosen because most tumors were discovered only at the time of sacrifice, and survival in this study was relatively good. The amount absorbed per unit surface area was taken as the correct measure of dose and the so-called surface area correction factor was used to determine human exposure.

Using the data of both rats and mice from the NTP 1986 study, the number of extra cancer cases expected from a lifetime exposure to 1 ppb (6.89 $\mu g/m^3$) of PCE was estimated to be between 31 to 144 cases per million persons exposed. This corresponds to a range of unit risks of 5 to 21 x 10^{-6} for a lifetime continuous exposure to 1 $\mu g/m^3$ of PCE. This range represents the upper limit of plausible excess cancer cases. The potency for the upperbound risk due to lifetime exposure to 1 $\mu g/m^3$ of PCE in air (2.9 x 10^{-7} to 9.5 x 10^{-7}) calculated using a metabolized dose method suggested by the EPA (EPA Review Draft, 1986), is one order of magnitude lower than that derived by CDHS. However, the EPA reported that the complete range of potencies for all methods and dose-tumor incidence data evaluated for 1 $\mu g/m^3$ of PCE in air (2.9 x 10^{-7} to 1.1 x 10^{-5}) includes the above range of 5 to 21 x 10^{-6} derived by CDHS. Consequently, the range of risks calculated from analysis of animal studies recommended by CDHS for the purpose of estimating cancer risk, lie between 31 x 10^{-6}/ppb (5 x $10^{-6}/\mu g/m^3$) and 144 x 10^{-6}/ppb) (21 x $10^{-6}/\mu g/m^3$).

The mean environmental concentration measured by the Air Resources Board staff is 0.43 ppb in the South Coast Air Basin; that is, more than four orders of magnitude below the time-weighted average values used in the animal bioassay. Based on the CDHS potency evaluation and the annual average of 0.43 ppb PCE in the South Coast Air Basin, an upper limit of 133 to 619 additional lifetime cancer cases are estimated in the 10 million residents of the South Coast Air Basin as a result of PCE exposure. The calculations represent the upper range of plausible excess cancer risk: the actual risk, which cannot be calculated, may be insignificant. Based on the finding of carcinogenicity and the results of the risk assessment, the

risk assessment, the staff of CDHS concludes that, PCE is an air pollutant which may cause or contribute to an increase in mortality or in serious illness, or which may pose a present or potential hazard to human health.

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EVALUATION PERSPECTIVE

I. Exposure Sources

A. Air Levels

1. Mean ambient levels measured outdoors in the South Coast Air basin: 0.43.

2. Ambient levels measured in "hot spots": Information not available.

3. Indoor Air: PCE concentrations measured in indoor air vary depending on the quantity released from water and consumer product sources, the time since release, and the size of the room. The mean indoor air concentration measured in the U.S. ranged from 0.34 to 1.01 ppb. Maximum concentrations in homes reached levels of 14.1 ppb.

B. Reported Levels in Water

1. National Data: Ambient waters: mean concentration was 1 μg/L in 1,102 surface water measurements in 45 states.

2. California drinking water: PCE was present in 199 wells out of 2,947 sampled. The median concentration of the 199 wells was 1.9 μg/L with the highest concentration being 166 μg/L.

C. Reported Levels In Food

1. Highest levels were reported in butter, margarine, and olive oil. Butter contained 13 μg/kg and olive oil and margarine contained 7 μg/kg.

II. Pharmacokinetics

A. Absorption

1. Approximately 50 to 62% of the respired PCE is absorbed by humans.

B. Metabolism

1. The amount of PCE metabolized by P-450 varies depending on the animal species tested and concentration applied. The metabolite most often measured in urine is tricholoracetic acid (TCA). Other metabolites found are trichloroethanol, oxalic acid, carbon dioxide (CO_2), chloride, dichloroacetic acid, ethylene glycol, and, possibly, thioether. Up to 47% of the PCE inspired may be metabolized by P-450. Much of the PCE inspired by humans is unaccounted for in disposition studies.

C. Excretion

1. Much of the PCE inhaled is exhaled unchanged by lungs. Some PCE has been detected in urine as trichloro metabolites. PCE has a considerably longer half-life in humans than in rodents.

D. Bioaccumulation

1. PCE accumulates in tissues following chronic exposure.

E. Conclusions

1. Metabolism of PCE is complex and only partially characterized in humans. Particularly, the products and rates of metabolism are poorly understood.

2. Metabolism and storage are influenced by factors such as age, sex, exercise or workload, body mass and adipose tissue mass, and pulmonary dysfunction.

III. Quantitative Risk Assessment

A. Shape of the Dose-Response Curve

1. Animal: The data for male mice liver tumors (adenomas and carcinomas combined) were consistent with a linear dose-response relationship (applied dose). However, only three data points were available: a control and two exposures.

2. Human: NA.

B. Range of extrapolation

1. Ratio of animal experimental concentration to ambient concentrations: Approximately 10^6.

C. Range of Risks

1. The human risks associated with a continuous, lifetime exposure to perchloroethylene have been estimated using the linearized multistage model from animal carcinogenicity bioassays. Human risks estimated from animal data range from 31 to 144 x 10^{-6}/ppb or 5 to 21 x $10^{-6}/(\mu g/m^3)$.

2. The range of risks, estimated by fitting the multistage polynomial (Crump, 1981) to the 1986 NTP rat and mouse inhalation study ranges from 8.1-to-1.4-fold.

MLE to 95% UCL:
- male mice -- 8.1-fold
- female mice -- 1.4-fold
- male rats -- 1.65-fold
- female rats -- 1.6-fold

IV. National and International Evaluation

A. U.S. Environmental Protection Agency

1. Genotoxicity Tests: Inadequate information to classify PCE as a mutagen or nonmutagen.

2. Animal carcinogenicity tests: Prior to the NTP (1986) inhalation bioassay EPA determined there was limited evidence of animal carcinogenicity (EPA, 1985a). EPA is currently reevaluating that position.

3. Human Evidence: Insufficient data to assess human carcinogenicity.

4. The EPA placed PCE in the fourth quartile of 53 carcinogens for which EPA has calculated potencies.

5. Conclusions: PCE is a possible human carcinogen. However, as a result of the NTP 1986 study, EPA is reviewing the classification of PCE. It is likely that they will conclude there is sufficient animal evidence and classify it as a probable human carcinogen.

B. International Agency for Research on Cancer (IARC)

1. Animal carcinogenicity assays: Sufficient vidence of animal carcinogenicity by inhalation.

2. Human Evidence: Inadequate evidence of human carcinogenicity.

3. Conclusion: PCE is a possible human carcinogen, classified by IARC as a category 2B carcinogen (IARC, 1987).

C. Conclusions

1. Inadequate information exists to clearly classify PCE as genotoxic or nongenotoxic.

2. Data from epidemiological studies are of very limited use for the risk assessment of PCE due to the presence of other causative factors.

3. PCE should be considered a potential human carcinogen.

4. Risk estimates should be based on "applied dose" due to the absence of sufficient information in humans on metabolism of PCE.

5. The upper 95% CI of human risks estimated from animal data range from 31 to 144 x 10^{-6}/ppb (5 to 21 x 10^{-6}/($\mu g/m^3$)).

2. PHARMACOKINETICS AND METABOLISM

Perchloroethylene is readily absorbed through the lungs and gastrointestinal tract and, to a lesser extent, may be absorbed through the skin. Once in the body, PCE disperses into all tissues. Steady-state tissue concentrations are a function of the absorbed dose, partitioning factors, and pharmacokinetic properties, such as rate of metabolic conversion and elimination. The percentage of PCE absorbed by humans via inhalation has been reported at 50% (Ohtsuki et al., 1983) and 62% (Bolanowska and Golacka, 1972).

The primary metabolic pathway of PCE is thought to involve oxidation to an epoxide as the first step, although this epoxide intermediate has never been isolated in vivo. The epoxide undergoes rearrangement to form trichloroacetyl chloride and, ultimately, trichloroacetic acid (TCA), which has been identified in urine (Yllner, 1961; Daniel, 1963; Moslen et al., 1977; Costa and Ivanetich, 1980). Studies in which radiolabeled PCE was administered to animals have occasionally recovered oxalic acid as a significant urinary metabolite (Yllner, 1961; Dimitrieva, 1967; Pegg et al., 1979). Carbon dioxide is also commonly produced (Pegg et al., 1979; Schumann et al., 1980). Other metabolites detected include trichloroethanol, chloride, dichloroacetic acid, and ethylene glycol (Daniel, 1963; Dimitrieva 1967, Ikeda and Ohtsuji, 1972; Ikeda et al., 1972; Koppel et al., 1985; Monster et al., 1983; Yllner, 1961).

This section presents an overview of published studies on the absorption, distribution, metabolism, and elimination of PCE. Studies that have defined

the rate and extent of each of these processes in humans and in rodents are emphasized. Proposed metabolic pathways are discussed in some depth because metabolism is responsible for the transformation of PCE to one or more reactive species.

ABSORPTION

This section reviews the relevant data on PCE uptake through ingestion, dermal absorption, and inhalation.

Ingestion

Absorption of PCE from the gastrointestinal tract has been measured indirectly as percent of dose recovered. The percentage of dose recovered after administration of PCE is similar in mice and rats, varying between 80 to 100%. Peak blood concentrations measured in rats one hour after a 500 mg/kg dose shows PCE is absorbed rapidly (Pegg et al., 1979).

Little information exists regarding amount or rate of oral absorption of PCE in humans. Koppel and associates (1985) reported that the blood concentration of PCE following an oral dose of 400 mg was described by a two-compartment model with half-lives of 160 minutes and 33 hours (unpublished data cited in Koppel et al., 1985). The same authors (Koppel et al., 1985) measured the concentration of PCE in blood at 21.5 μg/mL within one hour of ingestion of 12 to 16 grams. Although far from definitive, these reports suggest fairly rapid and complete oral absorption

Dermal absorption

Jakobsen and co-workers (1982) measured the absorption of PCE through guinea pig skin. Animals were in contact with liquid PCE for 6 hours. During the exposure, blood PCE concentrations rose rapidly, and peaked within 30 minutes Tsuruta (1975) estimated the rate of absorption of PCE through mouse skin to be 24 nmol/min-cm^2 of skin. Percutaneous penetration of PCE vapor in humans exposed to ambient air concentrations of 600 ppm is approximately one percent of pulmonary absorption (Riihimaki and Pfaffli, 1978). Studies in which volunteers immersed their thumbs in liquid PCE measured a peak concentration of 0.3 ppm in expired air within 40 minutes; concentrations decreased thereafter. PCE has a relatively slow rate of elimination in breath. The relatively low concentration of PCE in exhaled air suggests that dermal absorption is limited (Hake and Stewart, 1977; Stewart and Dodd, 1964).

Pulmonary Uptake

PCE is effectively absorbed through the lungs during inhalation. Yllner (1961) reported the average pulmonary absorption of mice exposed to approximately 2000 ppm (reported as 1.3 mg PCE/g of mouse in a 2.7 liter chamber) to be 70%. In these animals, absorption varied from 42 to 87%. In a study by Pegg and co-workers (1979), the peak blood concentration of PCE in rats during a 6-hour exposure to 600 ppm was approximately 10 μg/mL.

During inhalation exposure, PCE diffuses across the lungs and dissolves into the bloodstream. The rate of transfer depends on the blood/gas partition

coefficient for PCE. One estimate placed the human blood/gas coefficient of PCE at 16 (Monster et al., 1979), while Gargas and colleagues (1986) reports this coefficient value at 10.3. Both values reflect the fact that PCE is lipophilic and readily diffuses into the blood. The uptake of PCE by the lungs is also determined by the alveolar ventilation rate, exposure concentration, exposure duration, and metabolism.

Several experimental human studies have quantified PCE absorption in terms of "percent uptake" (one minus the ratio of alveolar to ambient air concentration and multiplied by 100%). However, unless a steady state absorption rate is approximated at very low exposure concentration (near 1 ppb), the net quantities of PCE retained following environmental exposure may not be accurately quantified. The percentage of PCE absorbed in humans through the lungs has been estimated at 62% (Bolanowska and Golacka, 1972). After a 6-hour exposure of five volunteers to 54 ppm PCE (reported as 0.39 mg/L), retention of PCE reportedly stabilized after 1 1/2 hours and ranged from 55 to 70%. The report of a steady state condition by Bolanowska and Golacka (1972) differs from the data of Fernandez and associates (1976) who studied humans exposed to 100 ppm PCE. The latter investigators found that alveolar air concentrations continued to steadily increase after 8 hours although the air level had reached 55 ppm. Ohtsuki and co-workers (1983) estimated that the percentage of PCE absorbed by humans was 50%, although the specific derivation of the value was not described.

Monster and colleagues (1979) observed an inverse relationship between uptake and exposure duration in humans over the course of a 4-hour inhalation exposure to 72 or 144 ppm PCE. Th net uptak at the end of 4

hours was appr ximately 60% of that during the first hour. This observation indicates that net uptake decreases as blood and tissue concentrations of PCE equilibrate with PCE in the air space of the lungs. Net uptake is affected by differences in ventilation rate. When volunteers were exposed to 142 ppm while under a work load (i.e., an increased ventilation rate), the uptake of PCE increased to over two times what it was at rest (Monster et al., 1979).

Fernandez and co-workers (1976) exposed humans to 100 ppm PCE for 8 hours and measured the concentration in alveolar air. Alveolar concentration rose rapidly in the first half hour and then continued to increase throughout the experiment although at a slower rate, reflecting a sustained decline in percent uptake observed.

At steady state, the amount of PCE taken up or retained will be equal to the amount of PCE metabolized. As pointed out by Guberan and Fernandez (1974), the alveolar concentration of PCE rises more rapidly during the first phase of uptake. PCE concentrations in rapidly perfused tissues will reach approximate steady state concentrations long before they are achieved in poorly perfused or highly lipophilic tissues. For example, during an 8-hour exposure to 100 ppm, tissues such as the liver will reach half of their maximum concentration in 34 minutes, while adipose tissue will reach half of its maximum concentration in 3 1/4 hours. Following exposure, PCE may continue to perfuse into adipose tissue and excretion from this tissue will be slow (Guberan and Fernandez, 1974). Since the uptake or retention rate varies as a function of tissue, time and a number of other variables, the results in these studies relating uptake to metabolism may overestimate

metab lism since the quantity of PCE stored in adipose tissue has not been accounted for.

Table 2-1 summarizes the absorption and recovery of experimentally administered PCE in animals. Table 2-2 lists parameters of absorption, metabolism, and disposition of PCE in humans.

DISTRIBUTION AND BIOACCUMULATION

PCE diffuses into the bloodstream and distributes to tissues, primarily to organs and fat. Seventy-two hours after oral or inhalation exposure to tetrachloro[^{14}C]ethylene, measurable radioactivity was found in the liver, kidneys, fat, lungs, heart, and adrenal glands of rats. The major part of the radioactivity was concentrated in the liver, kidneys, and fat (Pegg et al., 1979). A similar distribution was observed by Frantz and Watanabe after PCE was administered to rats in a saturated drinking-water solution (containing approximately 150 ppm PCE) (Frantz and Watanabe, 1983).

The binding of metabolites of PCE to hepatic macromolecules has been measured by Pegg and associates (1979), Schumann and co-workers (1980), and Mitoma and colleagues (1985). Savolainen and associates (1977) gave rats 200 ppm PCE for 6 hour/day for 4 days, and observed substantial levels of PCE in perirenal fat within 17 hours after the end of the exposure (Savolainen et al., 1977).

Information on the distribution of PCE in humans comes largely from reports of accidental exposures (Stewart et al., 1961a; Stewart, 1969; Hake and

TABLE 2-1. ABSORPTION AND RECOVERY OF TETRACHLOROETHYLENE (PCE) IN ANIMALS

Parameter	Value	Species (weight)	Route	Concentration or dose	Exposure duration	Reference
Percent absorbed (average)	70.0 (range 42 to 87)	Mouse	Inhalation	1.3 mg/g	2 h	Yllner, 1961
Percent of dose recovered[a,b] (48 h post exposure)	79.65	Mouse	Oral	900 mg/kg	5 d/wk; 4 wk	Mitoma et al., 1985
Percent of dose recovered (72 h post exposure)	94.6	Mouse (18-31 g)	Oral	500 mg/kg	Single exposure	Schumann et al., 1980
Percent of dose recovered (48 h post exposure)	84.4	Rat	Oral	1000 mg/kg	5 d/wk; 4 wk	Mitoma et al., 1985
Percent of dose recovered (72 h post exposure)	103.0	Rat (250 g)	Oral	1 mg/kg	Single exposure	Pegg et al., 1979
Percent of dose recovered (72 h post exposure)	91.2	Rat (250 g)	Oral	500 mg/kg	Single exposure	Pegg et al., 1979
Percent of dose recovered (72 h post exposure)	100.0	Rat (275 to 285 g)	Oral, in drinking water	8.1 mg/kg (approx.)	12 h	Frantz and Watanabe, 1983

TABLE 2-1. (Continued)

Parameter	Value	Species (weight)	Route	Concentration or dose	Exposure duration	Reference
Percent of dose recovered (72 h post exposure)	99.9	Rat (250 g)	Inhalation	10 ppm	6 h	Pegg et al., 1979
Percent of dose recovered (72 h post exposure)	100.0	Rat (250 g)	Inhalation	600 ppm	6 h	Pegg et al., 1979
Percent of dose recovered (72 h post exposure)	88.0	Mouse	Inhalation	10 ppm	6 h	Schumann et al., 1980
Percutaneous absorption rate	24 n/mol/min/cm^2	Mouse	Dermal			Tsuruta, 1975
Time to peak blood concentration	1 h (approx.)	Rat (250 g)	Oral	500 mg/kg	Single exposure	Pegg et al., 1979
Time to peak blood concentration	0.5 h	Guinea pig	Dermal		6 h	Jakobsen et al., 1982
Total pulmonary uptake	0.40 mg/animal (16.5 mg/kg)	Mouse	Inhalation	10 ppm	6 h	Pegg et al., 1979
Total pulmonary uptake	1.48 mg/animal (5.9 mg/kg)	Rat	Inhalation	10 ppm	6 h	Pegg et al., 1979

TABLE 2-1. (Continued)

Parameter	Value	Species (weight)	Route	Concentration or dose	Exposure duration	Reference
Total pulmonary uptake	77.5 mg/animal (310 mg/kg)	Rat	Inhalation	600 ppm	6 h	Pegg et al., 1979

[a] Percent of dose recovered refers to the portion of administered dose of PCE accounted for by measurements of breath, metabolites, excreta, and tissue.

[b] The percent recovered is considered to be indicative of percent absorption; however, the two parameters are not identical (D'Souza et al., 1985; U.S. EPA, 1985a).

TABLE 2-2. ABSORPTION, METABOLISM, AND DISPOSITION OF PCE IN HUMANS

Parameter	Value	Route	Concentration or dose	Duration	Reference
Percent absorbed through lungs	50	Inhalation			Ohtsuki et al., 1983
Percent absorbed through lungs	62 to 64	Inhalation[a]	72 or 144 ppm	4 h	Monster et al., 1979
Average pulmonary uptake	1350 mg	Inhalation	150 ppm	8 h	Fernandez et al., 1976
Average pulmonary uptake	455 mg	Inhalation	72 ppm	4 h	Monster et al., 1979
Average pulmonary uptake	945 mg	Inhalation	144 ppm	4 h	Monster et al., 1979
Percent retention	55 to 70	Inhalation	54 ppm (390 mg/L)	4-6 h	Bolanowska and Golacka, 1972
Time to peak concentration					
- exhaled air	15 to 40 min	Dermal		10 min	Stewart and Dodd, 1964
- lung tissue	8 h	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
- whole body	8 h	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
- organs	8 h	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
- fat	12 h	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
- blood	0.5 h	Inhalation	72 to 142 ppm	4 h	Monster et al., 1979

TABLE 2-2. (Continued)

Parameter	Value	Route	Concentration or dose	Duration	Reference
Percent metabolized	1 to 3	Inhalation	50 ppm	8 h	Ikeda et al., 1972 Ohtsuki et al., 1983
Percent metabolized	47	Inhalation	57 ppm (390 mg/L)	4-6 h	Bolanowska and Golacka, 1972
Percent eliminated unchanged via lungs	38	Inhalation	50 ppm	8 h	Ikeda et al., 1972 Ohtsuki et al., 1983
Percent eliminated unchanged via lungs	25	Inhalation	57 ppm (390 mg/L)	4 to 6 h	Bolanowska and Golacka, 1972
Body burden	1000 mg	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
Adipose burden	500 mg (approximate)	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
Predicted biological $t_{1/2}$ [b]	71.5 h	Inhalation	100 ppm	8 h	Guberan and Fernandez, 1974
Respiratory $t_{1/2}$	65 h	Inhalation	100 ppm	7 h (single exposure)	Ikeda and Imamura, 1973 (based on Stewart et al., 1970)
Urinary metabolite $t_{1/2}$	144 h	Inhalation	10 to 100 ppm	8 h/d;5 d	Ikeda and Imamura, 1973

TABLE 2-2. (Continued)

Parameter	Value	Route	Concentration or dose	Duration	Reference
Time to steady-state equilibrium, adipose tissue	125 h	Inhalation	100 ppm	8 h/d	Monster et al., 1979
Saturation of metabolism	NA[c]	Inhalation	100 ppm	8 h	Ohtsuki et al., 1983
Elimination $t_{1/2}$	160 min 33 h	Oral	400 mg	Single exposure	Koppel et al., 1985

[a] Values calculated from average estimated uptake/min.
[b] $t_{1/2}$ denotes half-life.
[c] NA: not applicable.

nervous system (CNS) depression, cardiac arrhythmias, alteration of kidney function, and liver injury. These observations provide indirect evidence that PCE distributes to the nervous system, liver, and kidneys. Additionally, tissue concentrations in the liver and brain have been measured at levels ten to 50 times greater than those in blood following fatal intoxication (Lukaszewski, 1979).

Perchloroethylene is a relatively stable molecule and is metabolized slowly. Perchloroethylene is soluble in lipids and this factor, along with its slow rate of metabolism lead to its accumulation in tissue following repeated exposure (Filser and Bolt, 1979; Loew et al., 1983).

On the basis of a model of PCE uptake, distribution, and elimination, Guberan and Fernandez (1974) predicted that the solvent would disperse primarily to three body compartments: adipose tissue, muscle, and tissues rich in blood vessels. It was estimated that the body burden of a 70-kg man exposed to 100 ppm PCE for 8 hours would be 1000 mg. More than one half of the PCE would accumulate in fat; substantial amounts would also be concentrated in muscles.

The rate of uptake and the time required for equilibration of tissue concentrations (for a given concentration of PCE in inspired air) depend on the solubility of the substance, the volume of each tissue, and on the rate of blood flow through the tissue. Because the blood supply to adipose tissue is less than to other tissues and because PCE is more soluble in fat than in blood, it takes a correspondingly greater time for equilibrium concentrations to be reached. Assuming a single 8-hour exposure to PCE, the

time required for fat to reach about 50% of its capacity is 25 hours (Monster et al., 1979; Guberan and Fernandez, 1974).

Once whole-body, steady-state concentrations are reached (compared to concentrations in air), the amount of PCE in each tissue depends on the tissue/blood partition coefficient. Since PCE is lipophilic, the adipose/blood partition coefficient is the highest of any tissue type (at 37°C the adipose/blood partition coefficient is about 107) (Guberan and Fernandez, 1974). Guberan and Fernandez state that daily occupational exposure to PCE at 100 ppm, 8 hours/day, would lead to accumulation of PCE in fat.

Savolainen and co-workers noted accumulation of PCE in the blood, liver, fat, kidneys, and brain of rats following 5 days of inhalation exposure at 200 ppm (Savolainen et al., 1977) . The PCE levels in perirenal fat, brain, and lungs rose continuously during the experiment. Concentrations in blood and liver also increased, but the rate of accumulation slowed by the third day.

Evidence of PCE accumulation is also available from a study that measured the concentration of PCE in exhaled air. When human volunteers were exposed to 100 ppm, 7 hours/day for 5 days, the concentration of PCE in expired air increased with each exposure. This suggests that PCE had accumulated in the tissues on each consecutive day of exposure and had not been eliminated between exposures (Hake and Stewart, 1977).

METABOLISM AND ELIMINATION

Among the most important enzyme systems for metabolism of toxic substances are the mixed-function oxygenases (MFO). These enzymes are concentrated in the liver, kidneys, lungs, and skin, and are present in other tissues as well. Mixed-function oxygenases catalyze the addition of oxygen to compounds, which facilitates their excretion from the body. Oxidation of a compound can function as a mechanism of detoxification or can transform it to a reactive (toxic) substance.

Evidence that MFO's are directly involved in the metabolism of PCE comes from the work of several investigators. Moslen and colleagues (1977) demonstrated that a number of substances, including phenobarbital (PBT) and Aroclor 1254, induced hepatic MFO. Pretreatment of rats with either of these compounds, followed by administration of PCE, increased the metabolism of PCE five to seven times over controls. Costa and Ivanetich (1980) showed that substances that inhibit cytochrome P-450, a component of MFO's, also inhibit metabolism of PCE in rats. Induction of cytochrome P-450 by PBT or pregnenolone-16α-carbonitrile increased the metabolism of PCE. The solvent was also shown to bind to the active site of P-450 in rat hepatic microsomes.

The first step in the general metabolism of PCE is thought to be transformation to an epoxide by the MFO, although this epoxide has never been isolated in vivo (Bonse et al., 1975; Greim et al., 1975). The epoxide of PCE apparently rearranges spontaneously with migration of a chlorine to

form trichloroacetyl chloride and, ultimately, trichloroacetic acid (Moslen et al., 1977; Leibman and Ortiz, 1977; Reichert, 1983). Trichloroethanol has also been reported as a metabolite; however, a pathway has not been proposed that explains its formation (Ikeda and Ohtsuji, 1972; Ikeda et al., 1972; Monster et al., 1983; Koppel et al., 1985).

As yet, it is not clear if conjugation (phase II) reactions are involved in the metabolism of PCE (Pegg et al., 1979; Lafuente and Mallol, 1986). Although not consistently reported, the production of oxalic acid and CO_2 as metabolites of PCE has been documented in rodents (Yllner, 1961; Pegg et al., 1979; Schumann et al., 1980). Their formation argues for a second and possibly minor pathway of oxidative metabolism for rats and mice.

It has been proposed that oxalic acid and CO_2 are formed as end-products of a metabolic pathway that also includes epoxide formation as the first step (Pegg et al., 1979). In this scheme, chloroethylene glycol is formed from the epoxide by the action of epoxide hydrolase. This reaction is followed by hydrolysis to oxalic acid and/or decarboxylation to CO_2 and possibly formic acid.

Chloride, dichloroacetic acid,and ethylene glycol have also been reported as urinary metabolites of PCE in rodents (Daniel, 1963; Yllner, 1961; Dimitrieva, 1967). It appears that these substances are minor metabolites, since each has been reported by only one investigator. Little is known about their formation. Figure 2-1 shows the structure of metabolites as well as the proposed metabolic pathways.

There are some similarities in the urinary metabolites produced by humans and rodents following exposure to PCE. Trichloroacetic acid has been identified in all species. Tables 2-3 and 2-4 list the metabolites identified in humans, mice, and rats, as well as the conditions of exposure.

Yllner was the first to analyze urinary metabolites of PCE in mice. Although 18% of the radiolabeled compound was not accounted for, 52% of the portion metabolized was recovered as trichloroacetic acid (TCA), 11% as oxalic acid, and a trace amount as dichloroacetic acid (Yllner, 1961). Daniel fed labeled PCE to rats and found TCA (0.6%) and inorganic chloride as the only metabolites (Daniel, 1963). Total urinary metabolite production in rats was measured by Moslen and co-workers (1977). They did not identify the actual metabolites, with the exception of TCA (which was the major metabolite produced). Pegg and associates and Dimitrieva identified oxalic acid as the primary product of PCE metabolism in rats (Pegg et al., 1979; Dimitrieva, 1967). Carbon dioxide has been recovered as a metabolite of PCE in mice (Schumann et al., 1980) and in rats (Pegg et al., 1979).

Trichloracetic acid, trichloroethanol, and an unidentified organic chloride have been measured in urine from humans exposed to PCE. Based on the Yllner (1961) study in mice, Ogata and colleagues measured only trichloro compounds in the urine of human volunteers (Ogata et al., 1971). In this study the major metabolite was an unidentified organic chloride. In some instances, identification of trichloroethanol has been by the Fujiwara reaction (Ikeda et al., 1972; Ikeda and Ohtsuji, 1972). The results of this test are qualitative and the accuracy is questionable. However, Monster and co-workers (1983) and Koppel and associates (1985) determined the presence of

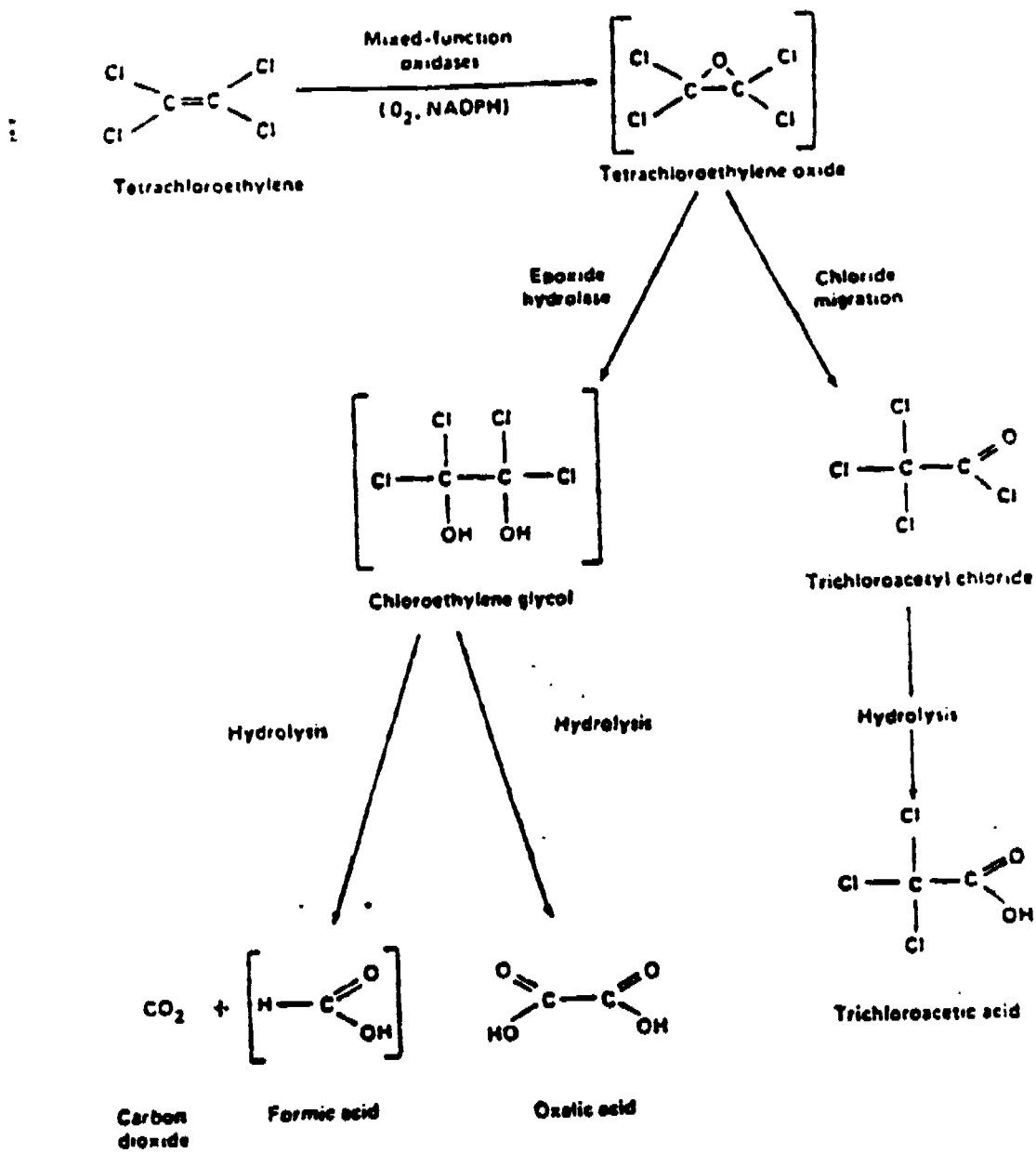

Figure 2-1. Metabolic pathways of PCE (brackets denote compounds that have not been isolated in vivo) (Daniel, 1963; Pegg, 1979; Costa and Ivanetich, 1980). Although trichloroethanol, dichloroacetic acid, ethylene glycol, and a thioether have been identified as urinary metabolites, the route(s) by which each formed has not been characterized.

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TABLE 2-3. PCE METABOLITE PRODUCTION IN RODENTS

Metabolite	Species (no. of animals)	Concentration or dose	Route of exposure	Duration of exposure	Reference
Trichloroacetic acid	Mouse (5)	1.3 mg/g	Inhalation	2 h	Yllner, 1961
	Rat (6)	1000 mg/kg	Oral	Single exposure	Daniel, 1963
	Rat (NA)	5 mg/L	Inhalation	5 h/d for 3 d	Dimitrieva, 1967
	Rat (8)	200 ppm	Inhalation	8 h	Ikeda and Ohtsuji, 1972
	Rat (7)	2.78 mmol/kg	Intraperitoneal	Single exposure	Ikeda and Ohtsuji, 1972
	Mouse (1)	200 ppm	Inhalation	8 h	Ikeda and Ohtsuji, 1972
	Mouse (2)	2.78 mmol/kg	Intraperitoneal	Single exposure	Ikeda and Ohtsuji, 1972
	Rat (4)	0.75 mL/kg	Gavage	Single exposure	Moslen et al., 1977
	Mouse (4 to 24 per dose level)	20 to 2000 mg/kg	Gavage	5 d/wk for 6 wk	Buben and O'Flaherty, 1985
Trichloroethanol	Rat (8)	200 ppm	Inhalation	8 h	Ikeda and Ohtsuji, 1972
	Mouse (1)	200 ppm	Inhalation	8 h	Ikeda and Ohtsuji, 1972
	Rat (7)	2.78 mmol/kg	Intraperitoneal	Single exposure	Ikeda and Ohtsuji, 1972
	Mouse (2)	2.78 mmol/kg	Intraperitoneal	Single exposure	Ikeda and Ohtsuji, 1972

TABLE 2-3. (Continued)

Metabolite	Species (no. of animals)	Concentration or dose	Route of exposure	Duration of exposure	Reference
Oxalic acid	Mouse (5)	1.3 mg/g	Inhalation	2 h	Yllner, 1961
	Rat (NA)	5 mg/L	Inhalation	5 h/d for 3 d	Dimitrieva, 1967
	Rat (3)	10 or 600 ppm	Inhalation	6 h	Pegg et al., 1979
	Rat (3)	1 or 500 mg/kg	Gavage	Single exposure	Pegg et al., 1979
Carbon dioxide	Rat (3)	10 or 600 ppm	Inhalation	6 h	Pegg et al., 1979
	Rat (3)	1 or 500 mg/kg	Gavage	Single exposure	Pegg et al., 1979
	Mouse (3)	10 or 600 ppm	Inhalation	6 h	Schumann et al., 1980
	Mouse (3)	1 or 500 mg/kg	Gavage	Single exposure	Schumann et al., 1980
Dichloroacetic acid	Mouse (5)	1.3 mg/g	Inhalation	2 h	Yllner, 1961
Ethylene glycol	Rat (NA)	5 mg/L	Inhalation	5 h/d for 3 d	Dimitrieva, 1967
Chloride	Rat (6)	1000 mg/kg	Oral	Single exposure	Daniel, 1963

TABLE 2-4. PCE METABOLITE PRODUCTION IN HUMANS

Metabolite	No.of individuals	Concentration or dose	Route of exposure	Duration of exposure	Reference
Trichloroacetic acid	85	10 to 400 ppm	Inhalation	8 h/d, 6 d/wk	Ikeda et al., 1972
	5	390 mg/L	Inhalation	6 h (single exposure)	Bolanowska and Golacka, 1972
	4	20 to 70 ppm	Inhalation	Daily (intermittent)	Ikeda and Ohtsuji, 1972
	66	200 to 400 ppm	Inhalation	Daily (intermittent)	Ikeda and Ohtsuji, 1972
	24	100 to 200 ppm	Inhalation	1 to 8 h	Fernandez et al., 1976
	6	70 or 140 ppm	Inhalation	4 h (single exposure)	Monster and Houtkooper, 1979
	5	7 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
	9	47 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
	9	53 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
	1	8 to 10 mL	Oral	Single exposure	Koppel et al., 1985
Trichloroethanol	85	10 to 400 ppm	Inhalation	8 h/d, 6 d/wk	Ikeda et al., 1972
	4	20 to 70 ppm	Inhalation	Daily (intermittent)	Ikeda and Ohtsuji, 1972
	66	200 to 400 ppm	Inhalation	Daily (intermittent)	Ikeda and Ohtsuji, 1972

TABLE 2-4. (Continued)

Metabolite	No.of individuals	Concentration or dose	Route of exposure	Duration of exposure	Reference
	24	100 to 200 ppm	Inhalation	Daily (intermittent)	Ikeda and Ohtsuji, 1972
	6	70 or 140 ppm	Inhalation	4 h (single exposure)	Monster and Houtkooper, 1979
	5	7 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
	9	47 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
	9	53 ppm[a]	Inhalation	37 to 54 h/wk	Monster et al., 1983
Thioether derivative	6	15 to 50 ppm	Inhalation	8 h/d, 5 d/wk	Lafuente and Mallol, 1986

[a]Values represent the median of the time-weighted-average exposures for individuals.

trichloroethanol by gas chromatography. Still other studies have failed to detect trichloroethanol; therefore, it is far from clear under what circumstances this substance is formed (Monster et al., 1979; Fernandez et al., 1976). Measurements of human metabolite production are confounded by the fact that CO_2, oxalic acid, and chlorine are normal products of metabolism. Their presence as products of PCE metabolism could be quantified only by the administration of radiolabeled PCE--a procedure that has not been undertaken in humans. Furthermore, studies in humans have primarily focused on quantifying the amount of trichloro compounds detectable in urine and not on accounting for all the metabolic products of PCE.

Lafuente and Mallol have reported the presence of a thioether derivative of PCE in the urine of women occupationally exposed to PCE (Lafuente and Mallol, 1986). A gradual increase in thioether production was observed over the course of a week. This increase appears to have been associated with continued exposure to PCE (with concomitant accumulation) over the work week. However, measured amounts of thioether in exposed women were reported not to be statistically different from levels found in nonexposed individuals.

The recent identification of thioether derivatives in humans exposed to PCE, coupled with problems associated with accurate and complete identification of metabolites, and the fact that the bulk of an absorbed human dose has not been accounted for indicates that not all human metabolites of PCE have been identified. Characterization of PCE metabolites in rodents may be incomplete as well, since no complete mass-balance studies have been

conducted. Although the major metabolites recovered in all species are presumably produced by the similar enzymes, many uncertainties remain. Based on present information, humans and rodents appear to metabolize PCE in qualitatively similar ways.

Perchloroethylene is eliminated from the body by two major processes: metabolism followed by excretion of urinary metabolites and pulmonary elimination of unchanged PCE. Although some PCE may be eliminated through the skin, preliminary measurements indicate that this is a minor route in humans (Bolanowska and Golacka, 1972). Except for the Schumann and associates (1980) study, most of the PCE systemically absorbed under experimental conditions (e.g., in mice, rats, and humans) was eliminated unchanged in expired air, so that metabolic degradation and subsequent elimination appear to account for less than 50% of absorbed PCE. Experimental data reviewed below indicate that PCE metabolism is dose-dependent and saturable, and that the amount of PCE metabolized appears to be species-dependent as well.

When the production of urinary metabolites was measured in mice exposed for two hours to approximately 2000 ppm (reported as 1.3 mg/g of PCE in a 2.7 liter chamber), Yllner found that only 2% of an inhaled dose was excreted by this route (Yllner, 1961). Seventy percent of the parent compound was recovered in expired air. Pegg and colleagues (1979) compared the metabolism of PCE in Sprague-Dawley rats at different doses and routes of exposure. The PCE was administered by gavage (1 or 500 mg/kg) or by inhalation (10 or 600 ppm). The primary route of elimination of PCE occurred through the lungs as the unmetabolized parent compound. Urinary

excretion of metabolites accounted for the majority of the remaining PCE. The percentage of PCE metabolized was dose dependent: elimination of unmetabolized PCE in expired air following oral exposure increased from 72% after 1 mg/kg to 90% after a dose of 500 mg/kg. There was a corresponding decrease in metabolites from 28 to 10%. An analogous pattern was seen after inhalation exposure. At 10 ppm, 68% of the dose was eliminated unchanged through the lungs and 32% was recovered as metabolites. Treatment at 600 ppm caused an increase in pulmonary elimination to 88% of the dose with a concomitant decrease in metabolites to 12%. Thus, it is likely that exposure to concentrations below 10 ppm would result in a decrease in the pulmonary elimination of PCE and in an increase in relative metabolism of PCE. Pulmonary elimination of PCE was linear and had a half-life of approximately 7 hours. The half-life was independent of dose or route of administration. The half-life of PCE in blood was 6 and 7 hours, after oral and inhalation exposure, respectively.

The pharmacokinetics of PCE in Sprague-Dawley rats and B6C3F1 mice were studied by Schumann and co-workers (1980). Rats were given a single oral dose of 500 mg/kg PCE or were exposed to 10 ppm ^{14}C-PCE by inhalation. The authors reported that at 10 ppm the major route of elimination was excretion of unmetabolized PCE in expired air, although supporting data were not provided. Some PCE was metabolized, and metabolites were recovered in the urine. After an oral dose of 500 mg/kg of labeled PCE, radioactivity was measured in the expired air, urine, feces, and carcass. The relative importance of each route in the elimination of PCE was not discussed.

The elimination of PCE by B6C3F1 mice differed, depending on the dose and possibly on the route of administration from that found in Sprague-Dawley rats. Metabolism, with urinary excretion of PCE, was the primary route of elimination after inhalation exposure at 10 ppm; 62.5% of the dose was recovered as urinary metabolites and only 12% was excreted through the lungs. Eighty-three percent of a single oral dose (500 mg/kg) was eliminated through the lungs, while 10.3% appeared as urinary metabolites (Schumann et al., 1980).

The fate of PCE in Sprague-Dawley rats fed PCE in their drinking water was reported by Frantz and Watanabe (1983). Animals were given PCE in a saturated solution over a 12-hour period, resulting in an average dose of 8.1 mg/kg. Treatment was followed by a 72-hour observation period prior to sacrifice. Most of the PCE (87.9%) was eliminated unmetabolized via the lungs. Although urinary excretion was the second largest route of elimination, the amount metabolized was relatively small (7.2%). The half-life of pulmonary elimination was 7.1 hours. This is nearly identical to the value determined by Pegg and colleagues (1979) after oral doses of PCE were given to rats.

Mitoma and co-workers studied the metabolic disposition of PCE in Osborne-Mendel rats and B6C3F1 mice (Mitoma et al., 1985). However, the relatively short follow-up period of 48 hours used in this study tends to underestimate the quantity of metabolites excreted. Substantial differences between species in the amount of PCE eliminated unchanged in expired air were noted. There were also differences in the percentage of dose metabolized. Rats eliminated 79% through their lungs and metabolized 5% of a 1000 mg/kg dose.

Pulmonary elimination by mice (of a 900 mg/kg dose) was 57.5%, while 22% was metabolized. The actual amount of PCE metabolized (measured as mmol/kg) also differed by species. Mice metabolized approximately four times as much of the total dose of PCE as rats. However, in both species as the dose was quadrupled, the amount metabolized only increased about 2.5-fold. These data suggest that metabolism approaches saturation at high doses in both species. Conversely, at low concentrations the proportion of PCE metabolized increases.

Buben and O'Flaherty also demonstrated that oxidative metabolism of PCE in Swiss mice decreases with increasing dose and appears to be a saturable process (Buben and O'Flaherty, 1985). Animals received 0, 20, 100, 200, 500, 1000, 1500, or 2000 mg/kg-day of PCE by gavage and were followed for 72 hours post exposure. Trichloroacetic acid was measured as an index of PCE metabolite production; the estimated maximum rate of urinary metabolite excretion was 136 mg/kg-day. As the dose increased, the percentage of the dose metabolized decreased. At the lowest doses, approximately 25% of the PCE was metabolized. This amount decreased to 5% at the highest doses. Tables 2-5 and 2-6 summarize data on the metabolism of PCE in rats and mice, respectively. Table 2-7 lists some pharmacologic constants of PCE in rodents.

The data reviewed above indicate that metabolism of PCE in both rats and mice displays saturable kinetics. The percentage of dose metabolized decreases as the dose is increased until the amount metabolized is no longer a function of the dose (a zero-order reaction). The extent of metabolism of PCE appears species-dependent. Rats consistently metabolize a relatively

smaller amount of PCE regardless of the route of administration. Mice typically metabolize a greater percentage of a dose than rats.

Measurements of PCE metabolism in humans have many uncertainties associated with them. Total trichlorinated metabolites in urine have usually been determined colorimetrically and therefore are difficult to evaluate quantitatively. By this method, production of chlorinated metabolites is equated with the amount metabolized. This approach does not account for the possibility that some metabolites may be produced that are not chlorinated, such as CO_2, the thioether, and oxalic acid.

Studies of PCE metabolism in humans have consistently considered TCA to be a principal metabolite. However, a major purpose of the studies has been to ascertain if PCE exposure in the workplace can be quantified by measurements of trichloro compounds in urine. Thus, the studies do not reflect an attempt to measure all possible metabolites of PCE.

Trichloroacetic acid production has also been measured to estimate the extent of metabolism of PCE and to characterize the kinetics of urinary elimination. Volunteers exposed to 87 ppm of PCE for 3 hours excreted about 0.40 mg/h of TCA (Ogata et al., 1971). Monster and colleagues analyzed the TCA content of blood and urine from volunteers exposed to 72 or 144 ppm of PCE for 4 hours (Monster et al., 1979). The mean production of TCA (over a 70-hour period) was 6.0 and 11.0 mg, respectively. Blood levels of TCA increased over the course of the experiment and continued to rise until about 20 hours after the end of exposure. The TCA was eliminated from blood by first-order processes; the half-life of elimination was 65 to 90 hours.

TABLE 2-5. METABOLISM AND DISPOSITION OF TETRACHLOROETHYLENE IN RATS

Route (n)[b]	Concentration or dose[c]	Exposure duration	Post exposure period	Percent metabolized[a]: Urinary metabolites	Percent metabolized[a]: Total metabolites[d]	Percent eliminated unchanged via lungs	Reference
Oral (3)	1 mg/kg	Single exposure	72 h	16.5	28.5	71.5	Pegg et al., 1979
Inhalation (3)	10 ppm (12.2 mg/kg)	6 h	72 h	18.7	32	68	Pegg et al., 1979
Oral (in drinking water) (4)	8 mg/kg	12 h	72 h	7.2	12	88	Frantz and Watanabe, 1983
Inhalation (3)	600 ppm (732 mg/kg)	6 h	72 h	6	12	88	Pegg et al., 1979
Oral (3)	500 mg/kg	Single exposure	72 h	4.6	10	90	Pegg et al., 1979
Oral (4)	1000 mg/kg	5 d/wk; 4 wk	42 h	2.4	5	79	Mitoma et al., 1985

[a] These values represent the percent of recovered dose that was metabolized.
[b] n = number of treated animals.
[c] For inhalation exposures, the dose in mg/kg was calculated assuming a breathing rate of 0.18 m3/d, and an average weight of 250 g per animal.
[d] These values represent metabolite recovery from all routes of excretion.

TABLE 2-6. METABOLISM AND DISPOSITION OF TETRACHLOROETHYLENE IN MICE

Route (n)[a]	Concentration or dose[b]	Exposure duration	Post exposure period	Percent metabolized: Urinary metabolites[c]	Percent metabolized: Total metabolites[d]	Percent eliminated unchanged via lungs	Reference
Oral (12-15)	20 mg/kg	5 d/wk; 6 wk	0 h	25	NA[e]	NA	Buben and O'Flaherty, 1985
Inhalation (3)	10 ppm (29 mg/kg)	6 hr	72 h	62.5	88.0	12	Schumann et al., 1980
Inhalation (N/A)	1.3 mg/g	2 h	96 h	20	NA	70	Yllner, 1961
Oral (12-15)	200 mg/kg	5 d/wk; 6 wk	0 h	15.5	NA	NA	Buben and O'Flaherty, 1985
Oral (12-15)	500 mg/kg	5 d/wk; 6 wk	0 h	12.6	NA	NA	Buben and O'Flaherty, 1985
Oral (3)	500 mg/kg	Single exposure	72 h	10.3	17.4	82.6	Schumann et al., 1980
Oral (4)	900 mg/kg	5 d/wk; 4 wk	48 h	14.4	22.2	57.5	Mitoma et al., 1985
Oral (12-15)	1000 mg/kg	5 d/wk; 6 wk	0 h	8.1	NA	NA	Buben and O'Flaherty, 1985

TABLE 2-6. (Continued)

Route (n)[a]	Concentration or dose[b]	Exposure duration	Post exposure period	Percent metabolized: Urinary metabolites[c]	Percent metabolized: Total metabolites[d]	Percent eliminated unchanged via lungs	Reference
Oral (4-6)	2000 mg/kg	5 d/wk; 6 wk	0 h	5.1	NA	NA	Buben and O'Flaherty, 1985

[a] n = number of treated animals.
[b] For inhalation exposure(s), the dose in mg/kg was calculated assuming a breathing rate of 0.0345 m^3/d, and an average weight of 20 g per animal.
[c] These values represent recovery of urinary metabolites only.
[d] These values represent recovery from all routes of exposure, with the exception of expired tetrachloroethylene.
[e] NA: not available.

TABLE 2-7. PHARMACOLOGIC CONSTANTS OF TETRACHLOROETHYLENE IN RODENTS

Parameter	Value	Species (weight)	Route	Concentration or dose	Exposure duration	Reference
Blood elimination $t_{1/2}$[a]	6 h	Rat (250 g)	Oral	500 mg/kg	Single exposure	Pegg et al., 1979
Blood elimination $t_{1/2}$[a]	7 h	Rat (250 g)	Inhalation	600 ppm	6 h	Pegg et al., 1979
Pulmonary elimination $t_{1/2}$[a]	7 h (approx.)	Rat (250 g)	Oral and inhalation	1 or 500 mg/kg and 10 or 600 ppm	Single exposure 6 h	Pegg et al., 1979
Blood k_{eq} (elimination constant)	0.12 h-1	Rat (250 g)	Oral	500 mg/kg	Single exposure	Pegg et al., 1979
Blood k_{eq} (elimination constant)	0.10 h-1	Rat (250 g)	Inhalation	600 ppm	6 h	Pegg et al., 1979
Pulmonary k_{eq} (elimination constant)	0.10 h-1	Rat (250 g)	Oral and inhalation	1 or 500 mg/kg and 10 or 600 ppm	Single exposure	Pegg et al., 1979
V_{max} (maximum amount of urinary metabolites formed and excreted in 24 h)	136 mg/kg-d	Mouse	Oral	20 to 2000 mg/kg	5 d/wk; 6 wk	Buben and O'Flaherty, 1985
V_{max} (maximal velocity metabolic elimination)	/7 mmol/h-kg	Rat (200 to 250 g)	Inhalation	1000 ppm (initial concentration)	12 h	Filser and Bolt, 1979
K_{eq} (equilibrium constant between gas phase and animal tissue)	105	Rat 200 to 250 g)	Inhalation	1000 ppm	12 h	Filser and Bolt, 1979

TABLE 2-7. (Continued)

Parameter	Value	Species (weight)	Route	Concentration or dose	Exposure duration	Reference
Body burden	5.9 mg/kg	Rat (250 g)	Inhalation	10 ppm	6 h	Pegg et al., 1979
Body burden	310 mg/kg	Rat (250 g)	Inhalation	600 ppm	6 h	Pegg et al., 1979
Body burden	16.5 mg/kg	Mouse	Inhalation	10 ppm	6 h	Schumann et al., 1980

[a] $t_{1/2}$ is the half-time of elimination.

Urinary eliminati n of TCA followed the disappearance of TCA from blood. Fernandez and associates measured excretion of TCA from individuals exposed to 150 ppm for 8 hours (Fernandez et al., 1976). Over a 72-hour collection period, the average amount of TCA produced was 25 mg. This is equivalent to about 0.34 mg of TCA per hour. Ikeda (1977) and Ikeda and Imamura (1973) qualitatively measured the half-life of urinary trichloro compounds and calculated the mean half-life to be 144 hours (range of 123 to 190 hours). The lengthy half-life may result from the continued formation of metabolites from PCE mobilized from tissues where it has accumulated.

Measurements of TCA production suggest that human metabolism of PCE via this pathway represents only a small portion of the absorbed dose. For example, the values published by Monster and associates (6.0 and 11.0 mg TCA after a 4-hour exposure to 72 or 144 ppm PCE) respectively, represent only about 1 to 2% of the estimated absorbed dose (Monster et al., 1979). Ogata and co-workers reported that TCA excretion was equivalent to 1.8% of the retained PCE with total excretion of organic chloride accounting for only 2.8% of the retained dose (Ogata et al., 1971). These data agree with those of Fernandez and colleagues, who estimated that 1350 mg of PCE would be absorbed after exposure to 150 ppm PCE for 8 hours (Fernandez et al., (1976). Ikeda and co-workers and Ohtsuki and associates have estimated that only about 2% of an 8-hour exposure to 50 ppm PCE would be metabolized and that 38% would be eliminated through the lungs unchanged by the end of the exposure period; the remaining 60% of the inhaled dose was hypothesized to be stored in the body and available for subsequent metabolism and/or pulmonary elimination (Ikeda et al., 1972; Ohtsuki et al., 1983). Ohtsuki and colleagues found that human urinary metabolite production did not appear

to be linearly related to exposure concentration. A graph of total trichloro compounds (from urine) plotted against PCE concentrations in air showed that metabolite production appeared to be dose-dependent, leveling off at approximately 400 ppm PCE (8-hour exposure). This suggested metabolic saturation; however, no statistical test of departure from linearity was performed in this study and a questionable nonlinear model was assumed.

Bolanowska and Golacka proposed that at steady state approximately 62% of respired PCE remains in the body, (based on their measurements of inspired and exhaled PCE) (Bolanowska and Golacka, 1972). Of the retained dose an estimated 25% is later exhaled. Thus, 75% of the retained dose, or 47% of the respired dose, is available for metabolism. At steady state, absorbed dose equals metabolized dose. However, since the steady state probably is not been attained, less than 47% of the respired dose is metabolized, with the balance representing the quantity of PCE accumulating in adipose tissue. These calculations are much higher than those obtained by other studies of PCE uptake and metabolism in humans (Ogata et al., 1971; Ikeda et al., 1972; Fernandez et al., 1976; Ikeda, 1977; Monster et al., 1979; Ohtsuki et al., 1983). However, the difference in large part may be due to Bolanowska and Golacka's consideration of total metabolism and not focusing solely on trichloro compounds as other investigators have done. Ogata and co-workers only analyzed for the excretion of trichloroacetic acid and an unidentified organic chlorine compound (Ogata et al., 1971). Ikeda and associates only measured the production of trichloro compounds and creatinine (Ikeda et al., 1972) . Fernandez and co-workers measured only the excretion of TCA (Fernandez et al., 1976). Monster and fellow researchers analyzed urine for

TCA and trichloroethanol (Monster et al., 1976). Ohtsuki and colleagues measured only total trichloro compounds in the urine (Ohtsuki et al., 1983). In fact, Bolanowska and Golacka reported that trichloro compound excretion in urine accounted for a few percent of the PCE retained, which is similar to results reported in the other investigations. Consequently, it appears that up to approximately 47% of the respired PCE may be metabolized based on the 1972 Bolanowska and Golacka study, which examined inhaled, retained, and exhaled PCE in humans.

A long period of time is necessary for pulmonary elimination of unmetabolized PCE. Stewart and co-workers have analyzed the pulmonary excretion of PCE following experimental human exposures and found that it is biphasic (Stewart et al., 1970; Hake and Stewart, 1977). Initially, elimination is rapid but the second phase is prolonged, with a half-life of approximately 65 hours. Monster and co-workers determined that human pulmonary elimination of PCE has three different phases, with half-lives of 12 to 16 hours, 30 to 40 hours, and 55 to 50 hours, respectively (Monster et al., 1979). Bolanowska and Golacka identified four phases for pulmonary excretion of PCE, with half-lives of 0.025 hours, 0.6 hours, 4.8 hours, and 34 hours, respectively (Bolanowska and Golacka, 1978). Fernandez and associates note that humans exposed to 100 ppm for 8 hours required about 2 weeks to eliminate PCE (Fernandez et al., 1976).

3. TOXIC EFFECTS IN ANIMALS

Estimates of human health risks resulting from exposure to a toxic substance are frequently based on an assessment of animal dose-response data because specific human data are often inadequate for this purpose. In this section, animal PCE toxicity studies are reviewed, including data from bioassays conducted to evaluate the carcinogenicity of PCE. Bioassay results are also used as the basis of the quantitative assessment of carcinogenic potency in Section 5. The toxicity of PCE has also been reviewed by IARC (1979), Reichert (1983), WHO (1984), and the U.S. EPA (1980, 1982, 1984b, 1985a, and 1985b).

The discussion of PCE toxicity begins with analyses of toxic effects to major body organs and systems. For these effects, Appendix A presents a review and summary of dose-response information for different routes and periods of exposure. The information in Appendix A would be relevant to the development of safety limits for PCE exposure in terms of preventing acute, subchronic, and noncarcinogenic chronic toxicological end points in the absence of adequate human-toxicity data. Studies dealing with the teratogenicity of PCE are examined. The section reviews the mutagenic potential of PCE and its metabolites and summarizes the results of animal carcinogenicity bioassays.

TOXIC EFFECTS ON ORGANS AND SYSTEMS

Hepatic Toxicity

Cornish and fellow researchers administered 0.3 to 2.0 mL/kg (0.33 to 4.95 mg/kg) of PCE intraperitoneally (IP) to rats. Liver damage was measured by an increase in serum glutamic oxalacetic transaminase levels (SGOT) and was observed at all doses (Cornish et al., 1973). Ogata and associates observed a decrease in the adenosine triphosphate (ATP) content of liver as well as an increase in the content of lipids and triglycerides after mice were exposed to 800 ppm for 3 hours (Ogata et al., 1968). Elevation of serum glutamic pyruvate transaminase (SGPT) levels in mice was elicited by exposure to 3700 ppm for 9 to 12 hours, as well as by IP administration of 3900 mg/kg (Gehring, 1968). Klaassen and Plaa also measured increased levels of SGPT in mice that received single intraperitoneal doses of ≥ 9 mL/kg (Klaassen and Plaa et al., 1966). These animals had enlarged hepatocytes and slight liver necrosis. A single intraperitoneal dose of 1.23 mL/kg elevated SGPT levels in dogs.

Cornish and Adefuin studied the effects of PCE administered in combination with ethanol (Cornish and Adefuin et al., 1966). A single dose of ethanol was administered by stomach tube (5 g/kg). Rats were then exposed to 4000, 5000, or 10,000 ppm PCE for 6, 4, or 2 hours, respectively. None of these treatments had a statistically significant effect on levels of SGOT, SGPT, or SICD (serum isocitric dehydrogenase).

Carpenter studied the subchronic and chronic inhalation toxicity of PCE in rats (Carpenter et al., 1937). Although no effects were observed in animals treated with 70 ppm PCE (8 hours/day, 5 days/week for 7 months), rats that received 150 exposures of 230 ppm had less glycogen storage than unexposed animals. Exposure to 470 ppm PCE (150 days) caused liver congestion and swelling. Rowe and co-workers exposed guinea pigs to 100 ppm 7 h/d over a period of 17 to 185 days (Rowe et al., 1952). No effects were apparent in animals that received 13 exposures in 17 days. However, when the number of exposures was increased to 132 over 185 days, females had a significant increase in liver weight ($p = 0.01$) and animals of both sexes exhibited lipid accumulation in the liver.

Schumann and associates dosed mice and rats orally with 100, 200, 500, or 1000 mg/kg of PCE daily for 11 days (Schumann et al., 1980). In mice, all dose levels produced hepatocellular swelling, a significant increase in absolute liver weight ($p<0.05$), and a significant decrease in hepatic DNA content ($p<0.05$). All of these changes are indicative of hypertrophy (the enlargement of an organ due to an increase in size of its constituent cells). Mice that received 100 mg/kg of PCE displayed an increase in hepatic DNA synthesis. In contrast to the pathologies that developed in mice, only the highest PCE dose, 1000 mg/kg, induced hepatic toxicity in rats. These animals had a statistically significant increase in relative liver weight ($p<0.05$). A change in the staining affinity of hepatocytes (for hematoxylin and eosin) was also observed. The significance of the latter observation is not known.

Buben and O'Flaherty treated mice by gavage with PCE dosages ranging from 20 to 2000 mg/kg PCE, 5 days/week for 6 weeks (Buben and O'Flaherty et al., 1985). Liver weights and liver triglycerides were significantly greater than those of controls at doses of 100 mg/kg of PCE and above ($p<0.001$). A dose-dependent increase in liver degeneration and karyorrhexis was also observed at PCE doses of 100 mg/kg and greater. Activity of glucose-6-phosphatase (G6P) was inhibited and a significant increase in SGPT occurred at 500, 1000, 1500, and 2000 mg/kg PCE ($p<0.001$). Hepatic DNA content was measured in mice treated with 200 or 1000 mg/kg PCE; animals that received 1000 mg/kg had significantly lower levels of DNA ($p<0.01$).

In an NTP-sponsored study of the effects of PCE on mice and rats, animals were exposed to PCE by inhalation 6 hours/day, 5 days/week for 103 weeks (NTP, 1986). Mice were exposed to 100 or 200 ppm PCE and rats to 200 or 400 ppm. Male and female mice of both exposure groups developed liver degeneration and necrosis. Development of these pathologies appeared to be dose related. The incidence of liver degeneration in male mice was as follows: controls, 2/49 animals; low dose, 8/49; and high dose, 14/50. The observed incidence of liver degeneration in female mice in the control group was 1/49 animals; in the low dose group, 2/50; and in the high dose group, 13/50. The number of male mice exhibiting necrosis in the treatment groups increased with increasing exposure concentrations (i.e., controls, 1/49 animals; low dose, 6/49; and high dose, 15/50). For female mice the incidence of necrosis was: controls, 3/48 animals; low dose, 5/50; and high dose, 9/50. Treated male mice (but not females) had a greater incidence of hepatic nuclear inclusion than controls (i.e., for controls, 2/49 animals; low dose, 5/49; and high dose, 9/50). The statistical significance of these

data was not evaluated. Under the conditions of this study, rats did not develop hepatic lesions in response to exposure to PCE.

Renal Toxicity

Klaassen and Plaa administered PCE to dogs intraperitoneally and measured excretion of phenolsulfonephthalein (PSP), a substance used to test for renal function (Klaassen and Plaa et al., 1967). Control dogs excreted 56% of the PSP within 30 minutes; excretion of less than 39% was considered to be an indicator of kidney dysfunction. Kidney function was significantly affected after a single IP dose of 1.4 mL/kg PCE (statistical significance was not given). Plaa and Larson reported that all mice given a single IP dose of 2.5 mL/kg PCE exhibited swelling of the proximal convoluted tubule, and one animal (of six treated) developed necrosis of the proximal convoluted tubule (Plaa and Larson et al., 1965). Mice that received a single dose of 2.5 or 5.0 mL/kg PCE excreted protein in their urine. The statistical significance of these responses was not reported. Carpenter found that rats given 230 ppm PCE (8 hours/day, 5 days/week) for 21 days developed swelling and congestion of the kidneys (Carpenter et al., 1937). This response was exacerbated when the concentration was increased to 470 ppm PCE. Subchronic exposure of mice and guinea pigs to 400 ppm PCE, 7 hours/day for 169 times in 236 days caused swelling of the tubular epithelium along with an increase in kidney weight (Rowe et al., 1952).

The NCI cancer bioassay of PCE documented a high incidence of toxic nephropathy in both species of rodents and in all dose groups (toxic nephropathy was defined as degenerative changes in the proximal convoluted

tubule, fatty d generation, and necrosis of the tubular epithelium) (NCI, 1977). PCE was administered by gavage. In this study, mice received time-weighted-average (TWA) daily doses of 386 to 1972 mg/kg PCE; toxic nephropathy was observed in 82 to 100% of the animals. Rats received TWA daily doses of 471 to 949 mg/kg PCE; 58 to 94% of these animals developed toxic nephropathy (see Table A-7 for specific data).

A bioassay sponsored by the NTP documented kidney casts, nephrosis, and tubular cell karyomegaly in mice (animals received 100 or 200 ppm of PCE 6 hours/day, 5 days/week for 103 weeks) (NTP, 1986). Casts occurred more frequently in treated male mice than in controls (incidence in controls, 3/49 animals; low dose, 9/49; and high dose, 15/50). The trend in female mice was not clearly dose related (incidence in controls, 4/48 animals; low dose, 4/49; and high dose, 15/50). Nephrosis developed at a greater incidence in treated female mice (control, 5/48 animals; low dose, 14/49, high dose, 25/50). For male mice, the incidence of nephrosis in the controls was 22/49 animals; low dose, 24/49; and high dose, 28/50. Karyomegaly of tubular cells was treatment-related. The incidence of this pathology in male mice was control, 4/49 animals; low dose, 17/49; high dose, 46/50. In female mice, the incidence of nephrosis was 0/48 animals, 16/49, and 38/50 in the controls, low-dose, and high-dose groups, respectively.

The same study reported a dose-related increase of renal tubular cell karyomegaly in rats of both sexes (NTP, 1986). Low-dose animals received 200 ppm of PCE; high-dose animals received 400 ppm (the exposure regime was the same as listed above for mice). The incidence of karyomegaly in male

rats for the corresponding control group was 1/49 animals; low dose, 37/49; and high dose, 47/50. In female rats, the incidence was 0/50 animals, 8/49, and 20/50, respectively. Male rats exhibited a dose-related increase in renal tubular cell hyperplasia (controls, 0/49 animals; low dose, 3/49; and high dose, 5/50). Only one high-dose female rat had renal tubular cell hyperplasia.

Pancreas

Hamada and Peterson studied the effects of PCE on the electrolyte and protein concentration in bile duct-pancreatic fluid (BDPF) (Hamada and Peterson et al., 1977). The actual source of this fluid (bile duct and/or pancreas) is not known. Rats were given a single IP dose of PCE (1.3 mL/kg in corn oil). Animals were then fasted for 24 hours at which time BDPF was collected and analyzed.

The PCE caused a significant increase in BDPF flow, a decrease in concentration of protein in the BDPF, and an increase in the concentration of chloride and potassium ($p<0.05$ for all parameters). The mechanism of enhanced BDPF is not known. Although Hamada and Peterson discussed possible mechanisms that may be analogous to secretion or cholinergic stimulation, they concluded that PCE (and other chlorinated aliphatic hydrocarbons) altered BDPF by an unknown mechanism, and that the toxicological significance of the reported effects is not known (Hamada and Peterson et al., 1977).

Lungs, Skin, and Eyes

Perchloroethylene is an eye and skin irritant. Application of PCE to the eye of rabbits caused abrasion of the epithelium and conjunctivitis. PCE was also extremely irritating when applied topically to the skin of rabbits (Duprat et al., 1976). However, Jakobsen and co-workers saw no visible sign of skin irritation when guinea pigs were exposed to liquid PCE (Jakobsen et al., 1982).

The NCI reported a high incidence of pneumonia in animals used in the bioassay of PCE (NCI, 1977). Sixty-two to 79% of treated rats and 29 to 66% of treated mice developed pneumonia. However, 95 to 100% of control rats and 28 to 35% of control mice also developed pneumonia. Because of the relatively high incidence of pneumonia observed in control animals, PCE probably did not contribute directly to the infection. In a separate study, chronic inhalation of PCE caused a dose-related incidence of passive congestion of the lungs in mice (NTP, 1986).

Reproductive System

The only indication that PCE has any effect on the reproductive system comes from the work of Rowe and fellow researchers (Rowe et al., 1952). Seven male guinea pigs were exposed to 1600 ppm, 7 hours/day for 8 exposures within 10 days. Microscopic examination of tissues revealed slight degenerative changes in the germinal epithelium of the testes. The implication of this observation was not discussed and subsequent studies

have not confirmed the finding. Therefore, it is difficult to evaluate the significance of this report.

Cardiovascular System

Perchloroethylene has been associated with sudden death from cardiac failure (Rowe et al., 1952; Reinhardt et al., 1973). It has been suggested that PCE (as well as a number of other solvents) may sensitize the heart to the effects of endogenously produced epinephrine (Price and Dripps, 1970; Reinhardt et al., 1973). If sensitization occurs, epinephrine-induced stimulation can lead to tachycardia and cardiac failure. This response is apparently precipitated by physical exertion and exposure to high concentrations of this agent.

Kobayashi and associates investigated the action of intravenously administered PCE on cardiac rhythm (Kobayashi et al., 1982). Rabbits were anesthetized with urethane, while cats and dogs were anesthetized with pentobarbital. A mean dose of 10 mg/kg of PCE administered with 0.7 μg/kg of epinephrine produced tachycardia in rabbits (although the most sensitive animals were effected by 5 mg/kg of PCE). Tachycardia also occurred in dogs given a mean dose of 13 mg/kg PCE with 4.2 mg/kg of epinephrine, while doses of 30 to 40 mg/kg PCE decreased left intraventricular pressure. Cats exhibited ventricular arrhythmias after 24 mg/kg of PCE was administered in conjunction with 13 to 14 mg/kg of epinephrine.

Rowe and co-workers speculated that death in some rats exposed to concentrations of 3000 ppm PCE or more in air was caused by cardiac failure;

however, it is p ssible that cardiac failure occurred as a result of extreme CNS depression (Rowe et al., 1952). Reinhardt and colleagues studied the cardiotoxicity of PCE by exposing unanesthetized dogs to 5000 or 10,000 ppm (R inhardt et al., 1973). Arrhythmias and cardiac failure were not observed and was no evidence of sensitization was seen.

The PCE dose levels used in the aforementioned studies are not representative of typical human exposure levels. Furthermore, the work of Kobayashi and associates utilized anesthetized animals, administered PCE intravenously, and used relatively large amounts of epinephrine, none of which readily facilitates extrapolation of results to humans (Kobayashi et al., 1982). The cardiotoxic potential of PCE requires additional experimental work before any conclusions can be drawn.

Central Nervous System

Acute exposure to PCE typically induces CNS depression. Initial depression can progress to loss of consciousness, anesthesia, and respiratory failure with prolonged or massive exposure. Single oral doses of 1623 mg/kg PCE produced reversible CNS effects in cats (Maplestone and Chopra, 1933), while a single dose of 6492 mg/kg caused lethal CNS depression (Lamson et al., 1929). Death from CNS depression resulted from single PCE doses of 4700 mg/kg (rat) and 6492 mg/kg (dog) (Smyth et al., 1969; Lamson et al., 1929). Over a 4-hour period, 2300 ppm PCE caused an impairment of muscular coordination in female rats, which contributed to a loss of 80 percent of avoidance and escape responses. Animals apparently developed some tolerance

to PCE, because this effect did not persist when dosing was continued over a 2-week period (Goldberg et al., 1964).

Rats exposed to 6000 ppm PCE lost consciousness within a few minutes; decreasing the concentration to 3000 ppm required several hours to elicit the same effect (Rowe et al., 1952). The NTP study found that exposure of mice to 2917 ppm for 4 hours was lethal to all animals. Rats appear to be less sensitive to PCE, because a 4-hour exposure to 5163 ppm was required to produce 100 percent mortality (NTP, 1986).

Carpenter studied the effects on rats of chronic exposure to 70, 230, 470, or 7000 ppm of PCE (Carpenter et al., 1937). Although various pathological changes were observed at 230 ppm PCE and above, no CNS effects were reported. Savolainen and co-workers observed a slight decrease in brain RNA content and an increase in nonspecific cholinesterase in rats exposed to 200 ppm PCE (6 hours/day for 4 days) (Savolainen et al., 1977). A one-month study conducted by Honma and co-workers documented a dose-dependent decrease in dopamine content of the striatum in rats exposed to 200, 400, or 800 ppm PCE 12 hours/day (Honma et al., 1980). The decrease was not statistically significant. Norepinephrine content of the hypothalamus and serotonin levels of the cortex and hippocampus increased after exposure to PCE (all three concentrations). None of the increases were statistically significant. A significant decrease in acetylcholine (ACh) levels in the striatum was m asured after exposure to 800 ppm ($p<0.05$). Drowsiness and other symptoms indicative of CNS depression were reported by Rowe and associates after rats were exposed to 1600 ppm PCE 7 hours/day, 5 days/week over a 25 day period (Rowe et al., 1952). At 2500 ppm PCE, 13 exposures within 18 days caused

TABLE 3-1. TERATOLOGY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Concentration or dose	Exposure duration	Exposure period	Effect	Reference
Rat (Sprague-Dawley)	100 ppm	7 h/d	Days 14 to 20 of gestation	No observed fetal or maternal toxicity	Nelson et al., 1980
Rat (Sprague-Dawley)	300 ppm	7 h/d	Days 6 to 15 of gestation	Maternal toxicity: reduction in mean body weight (4 to 5%) Fetal toxicity: slight but significant increase in fetal resorptions (9 of 17 litters)	Schwetz et al., 1975
Mouse (Swiss-Webster)	300 ppm	7 h/d	Days 6 to 15 of gestation	Maternal toxicity: increase in relative liver weight Fetal toxicity: decrease in body weight, delayed ossification of skull bones, split sternebrae, increase in subcutaneous edema	Schwetz et al., 1975
Rat (Sprague-Dawley)	900 ppm	7 h/d	Days 7 to 13 of gestation	Maternal toxicity: decrease in feed consumption and weight Pup toxicity: diminished performance in some behavioral tests	Nelson et al., 1980
Rat (Sprague-Dawley)	900 ppm	7 h/d	Days 14 to 20 of gestation	Maternal toxicity: decrease in feed consumption and weight Pup toxicity: diminished performance on ascent test	Nelson et al., 1980

TABLE 3-1. (Continued)

Species	Concentration or dose	Exposure duration	Exposure period	Effect	Reference
Chicken embryo	5 to 10 mmole/egg	Injected into air space on days 2, 3, and 6 of incubation	Examined 14 d after incubation	Malformed embryos at 10 mmole; Estimated LD50 over 100 mmole	Elovaara et al., 1979

the death of most rats and guinea pigs from CNS depression. Rabbits that received the same treatment displayed signs of CNS depression but did not lose consciousness.

TERATOGENICITY

The teratogenic activity of PCE has been studied in rats (Nelson et al., 1980; Schwetz et al., 1974; Schwetz et al., 1975) and mice (Schwetz et al., 1975). Maternal exposure levels ranged from 100 to 1800 ppm PCE. Although some minor effects were seen in the progeny, PCE is not considered to be a teratogen. A summary of these studies is provided in Table 3-1.

Investigations of the teratogenic and/or developmental effects of PCE have most commonly shown evidence of maternal toxicity, rather than adverse effects on the progeny. Toxicity was evident at 300 ppm (Schwetz et al., 1974; Schwetz et al., 1975) and 900 ppm (Nelson et al., 1980), while maternal death occurred at 1800 ppm (Nelson et al., 1980). Dams exposed to 300 ppm PCE 7 hours/day on days 6 to 15 of gestation had reduced body weights (rats) or an increase in liver weight (mice). The pups of these mice had lower body weights, and there was a slight increase in the number of runts. Some fetuses had subcutaneous edema or delayed ossification of the skull and sternebrae, as well as splits in the sternebrae. These pathologies probably reflect developmental delays and, as such, are considered to be reversible. Developmental delays are believed to result from maternal toxicity rather than from any direct teratogenic activity of PCE (Schwetz et al., 1975). The mechanism of maternal toxicity is unknown, but is thought to involve CNS depression (weight loss) and cytotoxicity

(change in liver morphology). Because fetal health is often a reflection of the health of the mother, maternal toxicity is a significant concern. The loss of maternal weight, most probably due to decreased feed consumption from subclinical effects (ataxia and anesthesia), can have a great impact on the growth and maturation of the fetus. Maternal malnutrition can cause developmental retardation of the fetus (Doull et al., 1980). The hepatotoxicity observed in mice could also have a profound effect on the growth of the fetus. Maternal toxicity is also suspected of causing a small but significant increase in the number of resorptions in treated rats ($p<0.05$) (300 ppm PCE, 7 hours/day) (Schwetz et al., 1975).

Nelson and associates performed a series of behavioral and biochemical tests on the offspring of exposed rats (Nelson et al., 1980). There were no adverse effects to mothers or their pups following exposure of the mothers to 100 ppm of PCE (7 hours/day) on days 14 to 20 of gestation. Exposure at 900 ppm PCE for 7 hours/day during days 7 to 13 of gestation produced significant differences in neuromuscular coordination ($p<0.02$) and wire mesh ascent ($p<0.05$). Exposure at 900 ppm PCE for 7 hours/day during days 14 to 20 of gestation caused diminished performance in the wire-mesh ascent test, but increased the performance in the neuromuscular coordination test. A neurochemical analysis of whole brain (minus cerebellum) was performed on newborn and 21-day old pups. Twenty-one-day-old pups from dams exposed during either period had a significant decrease in acetylcholine ($p<0.05$). A significant decrease in dopamine ($p<0.05$) was measured in 21-day old pups from dams exposed during days 7 to 13 of gestation.

Elovaara and co-workers injected 5 to 100 μmol of PCE into the air space of chicken eggs and studied the gross effects on the embryo (Elovaara et al., 1979). Malformations observed were exteriorization of viscera, as well as skeletal and eye abnormalities. These deformities occurred in six embryos of 61 examined.

Tests conducted in rodents have not clearly demonstrated that PCE is a teratogen. However, there is some evidence that inhalation exposure of pregnant rodents to PCE can induce developmental delays and altered performance in behavioral tests of the offspring.

MUTAGENIC EFFECTS

Short-term assays have been conducted to evaluate the ability of PCE to permanently alter genetic information. Most of the tests of genetic activity have been microbial assays that measured forward or reverse mutations. Chromosomal effects have been studied in cultured mammalian cells.

The ability of short-term assays to detect mutagens is compromised by lack of knowledge of the mechanisms involved, by different sensitivity and predictive ability of each test, and by variations in protocols used by separate labs. Despite these problems, short-term assays provide supportive evidence in the evaluation of a compound's carcinogenic potential.

Microbial Assays

Greim and fellow researchers evaluated the mutagenic activity of PCE (purity >99.9%) in Escherichia coli K12 with and without metabolic activation (S-9) (Greim et al., 1975). The results were negative at four loci tested. Three of these loci are back mutation systems (gal^+, arg^+, and nad^+), while one measures a forward mutation that produces resistance to 5-methyl-DL-tryptophan. Only one PCE concentration was used (0.9 mM), and detailed data were not reported. The data of Greim and colleagues was the only study cited by Fishbein in his review of the mutagenicity of halogenated aliphatics (Greim et al., 1976; Fishbein et al., 1976).

Cerna and Kypenova reported in an abstract that PCE of unspecified purity produced base-pair substitutions and frameshift mutations in Salmonella typhimurium without S-9 (Ames test) (Cerna and Kypenova, 1977). Concentrations of 0.01, 0.1, and 1.0 mg/mL of PCE produced a dose-dependent increase in the number of revertants. This response was significant only in TA100 (5% level of significance), a strain sensitive to base-pair substitutions. In a host mediated assay that used ICR mice and S. typhimurium strains TA1950, TA1951, and TA1952, PCE reportedly caused a significant increase in the number of revertants (level of significance was not given). The doses used were listed as LD_{50} and $1/2LD_{50}$, but exact quantities were not specified. Because no information was provided on the purity of PCE used, revertant counts, or controls, the significance of these data cannot be evaluated.

The results of Bartsch and associates conflict with those of Cerna and Kypenova (Bartsch et al., 1979; Cerna and Kypenova, 1977). Perchloroethylene (99.7% pure) was studied in the Ames test with strain S. typhimurium TA100. Concentrations up to 4×10^{-3} M were not mutagenic in the presence of an S-9 liver fraction from mice pretreated with phenobarbital. Toxicity was observed at concentrations greater than 5×10^{-4} M.

Kringstad and associates evaluated the mutagenic activity of PCE in the Ames test (Kringstad et al., 1981). The PCE (99.0% pure) was tested at a single concentration (0.1 mg/plate) in S. typhimurium, strain TA1535. No source of exogenous metabolic activation (S-9) was used. A slight increase in the number of revertants was observed (31/plate after PCE compared to 19/plate in the ether controls). However, this response was considered negative.

The NTP reported the results of a series of Ames tests on PCE conducted by the Environmental Mutagen Test Development Program (NTP, 1986). Salmonella typhimurium (strains TA98, TA100, TA1535, and TA1537) was incubated with technical-grade PCE in covered test tubes for 20 minutes. The test was conducted both with and without S-9 (S-9 fractions were prepared from the livers of male Sprague-Dawley rats and Syrian hamsters pretreated with Aroclor 1254). The greatest number of revertants was observed in strain TA100 (all doses, both with and without S-9); high doses (333 μg/plate) were t xic to TA1535 and TA1537 in the absence of S-9. However, PCE was judged not to be mutagenic in any of the strains, regardless of the concentration tested.

Callen and associates used Saccharomyces cerevisiae, strain D7, to study the frequency of gene conversion (trp5 and ilv1 loci) and mitotic recombination (ade2 locus) (Callen et al., 1980). The PCE (purity not given) was added directly to a cell suspension (log phase) and incubated in a closed vial for one hour. Samples were centrifuged, resuspended in buffer, and plated on a medium with glucose. Survival decreased as PCE dose increased from 0 to 4.9, 6.6, or 8.2 mM. At 8.2 mM, survival was greatly reduced and assessment of genetic activity was precluded. Exposure to 6.6 mM PCE elicited substantial increases in mitotic recombination (52.6 recombinants per 10^4 survivors versus 3.3 recombinants per 10^4 survivors in controls). The number of gene conversions (trp5) also increased at 6.6 mM (8.3 convertants per 10^5 survivors versus 1.4 x 10^5 convertants per 10^5 survivors in controls). The number of revertants at the ilv1 locus was not measured at this exposure concentration. Fabre has proposed that mitotic recombination and gene conversion may be induced by the same mechanism (Fabre, 1978). If so, the response may have been inaccurately evaluated, because ade2 recombinants were estimated from plates that had been previously used to determine the number of trp5 convertants. Consideration of this possibility as well as a lack of statistical analysis of results limit the strength of evidence presented by Callen and co-workers (Callen et al., 1980). However, mitotic recombination and gene conversion are indicative of interaction of a substance with DNA. Since the increase in frequency of mitotic recombination was pronounced, this response may warrant additional study.

Bronzetti and associates also studied the effect of PCE on the trp5, ade2, and ilv1 loci in S. cerevisiae (Bronzetti et al., 1983). Cells in the stationary phase were exposed for 2 hours to 5, 10, 20, 60, or 85 mM PCE.

All results were negative. The PCE used was 99.5% pure, whereas the purity of that used by Callen and colleagues was not reported (Callen et al., 1980). When comparing the results of these two studies, consideration must be given to the possibility that cells in the stationary phase may be resistant to the mutagenic or toxic action of xenobiotics.

In addition, Bronzetti and fellow researchers conducted an intrasanguineous host-mediated assay that tested the ability of PCE to induce genetic effects in S. cerevisiae (Bronzetti et al., 1983). Yeast were exposed to PCE and its metabolites in the liver, lungs, and kidneys of mice. The PCE did not induce point mutations, mitotic recombination, or mitotic gene conversion.

Drosophila

The NTP reported the results of an assay that tested the ability of PCE to induce sex-linked recessive lethal mutations in Drosophila (NTP, 1986). Males were exposed by injection or by feeding and were mated to a series of untreated females. Neither route of administration produced a statistically significant increase in sex-linked recessive lethal mutations.

TESTS OF DNA OR CHROMOSOMAL DAMAGE

Cerna and Kypenova did not observe any cytogenetic effects in mouse bone marrow cells following single or repeated IP injections of PCE (daily injections for five days) (Cerna and Kypenova et al., 1977). Cells were recovered for analysis 6, 24, or 48 hours after the last injection of PCE. No details were provided regarding doses used or the specific end points

that were studied (the study was published only as an abstract). The NTP published the results of assays for PCE induced chromosomal aberrations and sister chromatid exchanges in Chinese Hamster Ovary (CHO) cells, both with and without S-9 (NTP, 1986). The S-9 fractions were obtained from livers of male rats pretreated with Aroclor 1254. Data were reported in tables only, with no supportive discussion (such as the number of cells scored for each dose level). However, at least three dose levels were used (with and without S-9), as were both positive and negative controls. The PCE had little, if any, cytogenetic effect in either assay.

Perchloroethylene was not mutagenic in L5178Y/TK$^{+/-}$ mouse lymphoma cells, with or without metabolic activation. Cells were treated for 4 hours with 6.25, 12.5, 25.0, 50.0, and 100.0 nL/mL of PCE. Following incubation for 48 hours, cells were plated in medium supplemented with trifluorothymidine for selection of cells mutant at the thymidine kinase (TK) locus. No statistically significant increase in mutation frequency was observed at any dose level (NTP, 1986).

Somatic mutations are thought to occur when a substance or one of its metabolites interacts with DNA. Alkylation of DNA is therefore one possible indicator of genotoxicity. Schumann and co-workers measured binding to hepatic macromolecules of mice after administration of radiolabeled PCE (Schumann et al., 1980). No radioactivity was detected bound to hepatic DNA. The specific activity of the tetrachloro[^{14}C]ethylene used in this study was too low to permit detection of low levels of DNA binding. Therefore, these results do not rule out the possibility of DNA alkylation following exposure to PCE.

Mutagenic Activity of Metabolites

Tetrachloroethylene oxide (PCE oxide) is believed to be the first intermediate formed by microsomal oxidation of PCE. A concentration-dependent mutagenic response was produced by PCE oxide (0.5, 1.3, 2.5, 5.0, and 25.0 mM) in S. typhimurium TA1535 (without metabolic activation) but PCE oxide was not mutagenic to E. coli WP2 uvrA. The mutagenicity of this epoxide was also evaluated in a DNA-repair-deficient strain of E. coli (E. coli pol A 1^-). In the latter assay, genotoxicity is measured by comparing differential growth inhibition of the DNA-polymerase-deficient strain, pol A 1^-, with a polymerase-proficient strain, pol A 1^+. The PCE oxide gave positive results in this test; growth of the pol A 1^- strain was inhibited at all dose levels used (Kline et al., 1982).

Trichloroacetic acid (TCA) is the principal metabolite of PCE excreted in the urine of rodents and humans; trichloroethanol has also been identified as a metabolite of PCE. In an Ames test conducted with metabolic activation, TCA (0.45 mg/plate) and trichloroethanol (7.5 mg/plate) were not mutagenic to S. typhimurium strains TA98 and TA100. There is some indication, however, that trichloroethanol can induce sister-chromatid exchange in cultured human lymphocytes (Gu et al., 1981).

CARCINOGENICITY IN ANIMALS

Two lifetime bioassays have been completed on PCE (NCI, 1977; NTP, 1986). Additionally, three other studies have addressed the question of PCE carcinogenicity (Rampy et al., 1978; Theiss et al., 1977; Van Duuren et al.,

TABLE 3-2. SUMMARY OF TUMOR-INCIDENCE DATA FROM ANIMAL BIOASSAY STUDIES

Study	Species (strain)	Sex	Concentration or dose	Tumor responses Type[a]	Incidence	p-value
NCI, 1977	Mice (B6C3F1)	M	0 mg/kg-d	HC	2/17	NA
			536 mg/kg-d	HC	32/49	$p<0.001$[b]
			1072 mg/kg-d	HC	27/48	$p<0.001$[b]
		F	0	HC	2/20	NA
			386 mg/kg-d	HC	19/48	$p<0.001$[b]
			772 mg/kg-d	HC	19/48	$p<0.001$[b]
NTP, 1986	Mice (B6C3F1)	M	0 ppm	HC	7/49	NA
			100 ppm	HC	25/49	$p<0.001$[b]
			200 ppm	HC	26/50	$p<0.001$[b]
		M	0 ppm	HAC	16/49	NA
			100 ppm	HAC	8/49	NS
			200 ppm	HAC	18/50	NS
		F	0 ppm	HC	1/48	NA
			100 ppm	HC	13/50	$p<0.001$[b]
			200 ppm	HC	36/50	$p<0.001$[b]
			0 ppm	HAC	3/48	NA
			100 ppm	HAC	6/50	NS
			200 ppm	HAC	2/50	NS

TABLE 3-2. (Continued)

Study	Species (strain)	Sex	Concentration or dose	Tumor responses Type[a]	Incidence	p-value
NTP, 1986	Rats (F344/N)	M	0 ppm	MLK	28/50	NA
			200 ppm	MLK	37/50	p = 0.046[c]
			400 ppm	MLK	37/50	p = 0.004[c]
		F	0 ppm	MLK	18/50	NA
			200 ppm	MLK	30/50	p = 0.023[c]
			400 ppm	MLK	29/50	p = 0.053[c]

[a]HC = hepatocellular carcinoma; HAC = hepatocellular adenoma; and MLK = mononuclear cell leukemia.

[b]Probability level, Fisher Exact Test (NCI, 1977; NTP, 1986).

[c]Probability level, Life Table Analysis (NTP, 1986).

NA = not available.

NS = not statistically significant.

resulted in significant increases in malignant neoplasms among the exposed animals.

The National Cancer Institute conducted a study in which B6C3F1 mice and Osborne Mendel rats were administered PCE in corn oil by gavage, 5 days/week for 78 weeks (NCI, 1977). Animals were then observed for 32 weeks (rats) or 12 weeks (mice). Mice were 25 days old at initial treatment; rats were 35 days of age. The time-weighted average daily doses of PCE were 536 and 1072 mg/kg for male mice, 386 and 722 mg/kg for female mice, 471 and 941 mg/kg for male rats, and 474 and 949 mg/kg for female rats.

Perchloroethylene caused a statistically significant increase in the incidence of hepatocellular carcinoma in mice of both sexes and both dosage groups ($p<0.001$) (Table 3.2). The time to first tumor development was considerably shorter in treated mice than in controls. Hepatocellular carcinomas were first detected at weeks 91 and 90 in untreated and vehicle controls respectively. However, in male mice, hepatocellular carcinomas were detected after 27 weeks (low-dose) and 40 weeks (high-dose). The first hepatocellular carcinomas were observed in female mice at week 41 (low-dose) and week 50 (high-dose).

Exposed mice also exhibited a high incidence of toxic nephropathy, a condition that was not observed in controls. Median survival times of mice were inversely related to dose. Control males had median survival times of more than 90 weeks; this decreased to 78 weeks in low-dose males and 43 weeks in high-dose males. The median survival time of control females was

also greater than 90 weeks. Median survival times of low- and high-dose females were 62 and 50 weeks, respectively (NCI, 1977).

Early mortality occurred in all groups of rats dosed with PCE. Half of the high-dose males had died by week 44; half of the high-dose females died by week 66. The median survival time of control animals was 88 to 102 weeks, depending on sex. The National Cancer Institute determined that there was a statistically significant association ($p<0.001$) between increased dosage of PCE and increased mortality (NCI, 1977). The early mortality observed in rats and its statistical association with dose of PCE indicate that the doses given to rats in this bioassay were inappropriately high. Because the optimum dosage was not used and because significant early mortality occurred, these results preclude any conclusions regarding the carcinogenicity of PCE in rats.

Questions have been raised about the purity of PCE used in the NCI mouse and rat bioassays. The PCE was produced by Aldrich Chemical Co. and had a purity of 99%. However, epichlorohydrin (ECH) was apparently used as a stabilizer. It has been suggested that the presence of this contaminant may have directly contributed to tumor induction. The ECH is a direct-acting alkylating agent and is mutagenic (Kucerova et al., 1977; Bridges, 1978). Van Duuren and associates demonstrated that ECH was carcinogenic in mice when injected subcutaneously (Van Duuren et al., 1974). A subsequent study by Laskin and colleagues showed that ECH induced neoplastic lesions of the nasal cavity of rats (Laskin et al., 1980). Most of these tumors were carcinomas of the squamous epithelium. Interestingly, 30-day exposures to 100 ppm ECH produced a much greater incidence of cancer than lifetime

exposures of 30 ppm (exposures were 6 hours/day, 5 days/week). A study by Konishi and co-workers and Kawabata also showed that ECH-fed discontinuously to rats in drinking water at a concentration of 1500 ppm (and at a lifetime TWA dose of approximately 40.2 mg/kg-d) induced a significantly increased incidence of papillomas and squamous cell carcinomas of the forestomach above that of control animals (Konishi et al., 1980; Kawabata, 1981).

The exact quantity of ECH present in the PCE used in the NCI study is not known, but it has been estimated that high-dose male mice received 0.42 mg/kg-d (EPA, 1985a). This represents a small fraction of the dose that elicited squamous cell carcinomas in rats. Furthermore, ECH appears to initiate tumors by a localized tumorigenic reaction at sites where it is in direct contact with tissue, such as nasal or forestomach squamous-cell epithelium (EPA, 1984c). No animal in the NCI bioassay developed tumors at these sites. The ECH is among the weakest of the more than 50 suspect carcinogens evaluated by the EPA Carcinogen Assessment Group, having an estimated upper-bound carcinogenic potency, or effect per unit dose at low doses, to humans of 9.9×10^{-3} $(mg/kg\text{-}d)^{-1}$, based on data indicating increased nasal cavity tumor incidence in rats exposed to ECH via drinking water (EPA, 1984c). Using the methodology of the EPA, the equivalent potency to mice would be $9.9 \times 10^{-3} \times (f_m/f_h)$, where f_m and f_h are the fractions of body weight consumed as water respectively (EPA, 1984c). The potency for ECH to mice is therefore estimated to be 0.058 $(mg/kg\text{-}d)^{-1}$. Using this potency estimate, the highest dosed animals (high-dose male mice) in the NCI bioassays would be expected to incur an increased cancer risk of $(0.42) \times (0.058) = 0.024$, or less than 2.5% (NCI, 1977). Therefore, it is

unlikely that ECH contributed significantly to the observed increased tumor incidence in PCE-exposed mice in the NCI bioassay (NCI, 1977).

Rampy and fellow researchers exposed male and female Sprague-Dawley rats to PCE by inhalation (300 or 600 ppm) 6 hours/day, 5 days/week for 12 months (Rampy et al., 1978). Animals were subsequently observed for 18 months. High-dose males had slightly greater mortality than did controls, but neither sex exhibited an increased incidence of tumors, regardless of dose. Interpretation of this study is limited by the duration of the exposure and by the fact that it was reported only as an abstract.

Theiss and co-workers studied the ability of PCE to induce lung adenomas in A/St male mice (Theiss et al., 1977). Animals 6 to 8 weeks old were given 80, 200, or 400 mg/kg of PCE in tricaprylin (intraperitoneally) three times a week. Each group received 14, 24, or 48 injections. Animals were sacrificed 24 weeks after the first injection and were examined histologically for the presence of pulmonary tumors. Treated animals did not exhibit a significant increase in the average number of lung tumors when compared to controls. The relevance and validity of these test results are of questionable significance, though, as this test has not produced positive results with several known animal carcinogens.

The ability of PCE to initiate and/or promote skin tumors in ICR/Ha Swiss mice was investigated by Van Duuren and associates (Van Duuren et al., 1979). In one group, 163 mg of PCE was applied once to surface skin. Fourteen days after this, phorbol myristate acetate, a promoter, was applied to the same area three times a week for 428 to 576 days. A second group

received 54 mg of PCE by topical application three times a week for 440 to 594 days. The PCE did not show any initiating activity. It also gave negative results in the portion of the experiment that tested its ability to act as a complete carcinogen. It is difficult to interpret these data in relation to the carcinogenic action of PCE because the significance and sensitivity of skin application tests are not thoroughly understood.

The most definitive study of the carcinogenic potential of PCE was conducted by Battelle Pacific Northwest Laboratories for the National Toxicology Program (NTP, 1986). In this experiment, B6C3F1 mice and F344/N rats were exposed to 99.9% pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks. Mice were exposed to concentrations of 0, 100, or 200 ppm; rats were exposed to concentrations of 0, 200, or 400 ppm. Treated male rats had lower survival rates than control animals (controls, 23/50 animals; 200 ppm, 20/50; 400 ppm, 12/50). Survival rates among female rats showed little variation (controls, 23/50 animals; 200 ppm, 21/50; 400 ppm, 24/50). Both exposure concentrations produced significant increases in mononuclear cell leukemia in female rats (incidence in controls, 18/50 animals; in rats receiving 200 ppm, 30/50; and in rats receiving 400 ppm, 29/50). Life Table analysis showed the significance of these increases to be $p = 0.023$ (200 ppm PCE) and $p = 0.053$ (400 ppm PCE). Treated male rats also developed mononuclear cell leukemia in greater numbers than controls (controls, 28/50 animals; 200 ppm, 37/50; 400 ppm, 37/50). Levels of significance (evaluated by Life Table analysis) are $p = 0.046$ (200 ppm PCE) and $p = 0.004$ (400 ppm PCE) (Table 3-2).

Renal tubular-cell adenomas are rare neoplasms with a historical occurrence at Battelle Laboratories of less than one percent (Appendix F, NTP, 1986). Renal tubular-cell adenocarcinomas are even less common, and have not been documented in any NTP studies (NTP, 1986). Male rats (at the 200 and 400 ppm PCE exposure levels) exhibited an increased incidence of both of these neoplasms (see Table 3-3). Although the increases were not statistically significant, they appeared to be dose-related. Tubular-cell hyperplasia was observed in eight treated males but only in one treated female rat. Tubular-cell karyomegaly developed in a majority of male rats but was less common in females.

TABLE 3-3. INCIDENCE OF RENAL TUBULAR CELL ADENOMAS AND ADENOCARCINOMAS IN MALE RATS EXPOSED TO PCE BY INHALATION[a]

	Treatment		
Neoplasm	Control	200 ppm	400 ppm
Tubular cell adenoma	1/49	3/49	2/50
Tubular cell adenocarcinoma	0/49	0/49	2/50
Tubular cell adenoma or adenocarcinoma	1/49	3/49 ($p = 0.259^b$)	4/50 ($p = 0.070^b$)

[a]Data are from NTP, 1986.

[b]P-values are based on Life Table Tests (Appendix E, NTP, 1986).

Brain glioma is a rare tumor of neuroglial cells (the cells that compose the supporting structure of nervous tissue). Brain gliomas were observed in one male control rat and in four male rats that were exposed to 400 ppm PCE (NTP, 1986). This increase was not statistically significant. However, because the historical incidence of these tumors is quite low (0.2% at

Battelle Laboratories), the increased incidence in treated animals in this study is noteworthy.

In the NTP study, the survival of low-dose male mice (after week 74) and of high-dose male mice (after week 75) was significantly lower than controls ($p<0.001$) (NTP, 1986). The survival of high-dose female mice was significantly lower than controls after week 90 ($p<0.001$). Both concentrations of PCE produced a statistically significant increase of hepatocellular carcinomas in treated mice of both sexes ($p<0.001$) (Table 3-2). The incidence of these carcinomas in male mice was as follows: controls, 7/49 animals; low-dose, 25/49; and high-dose, 26/50. The incidence of hepatocellular carcinomas in treated female mice was: controls, 1/48 animals; low-dose, 13/50; and high-dose, 36/50.

Hepatocellular adenomas occurred in both sexes of mice and at both concentrations of PCE (Table 3-2). The incidence of adenomas was not statistically significant. However, the combined incidence of hepatocellular adenomas and hepatocellular carcinomas was significant. In males, the combined incidence was: controls, 16/49 animals; low-dose, 31/49; ($p = 0.002$); and high-dose, 40/50 ($p<0.001$). In females, the incidence of hepatocellular adenomas and carcinomas was: controls, 4/48 animals; low-dose, 17/50 ($p = 0.001$); and high-dose, 38/50 ($p<0.001$).

Summary of Evidence of Carcinogenicity in Animals

The NCI bioassay of PCE found that administration of PCE by gavage was associated with a statistically significant increased incidence ($p<0.001$) of

hepatocellular carcin ma (NCI, 1977). This increase was documented in low- and high-dose PCE-treated B6C3F1 mice of both sexes. A decrease in the time to first tumor development was also observed in treated mice of both sexes and both dose groups. Early mortality in rats prevented an analysis of PCE's carcinogenic potential in this species. The NCI concluded that under the conditions of this study, PCE was a liver carcinogen to B6C3F1 mice of both sexes (NCI, 1977).

In 1979, IARC reviewed the NCI study on PCE as well as the animal carcinogenicity studies of Rampy and associates (1978) and Theiss and colleagues (1977). Only two short-term assays were evaluated (Cerna and Kypenova, 1977; Greim et al., 1975). The IARC determined that there was "limited evidence" that PCE is carcinogenic in mice (IARC, 1979) .

The IARC recently re-evaluated the evidence of carcinogenocity of PCE to animals (IARC, 1987). They concluded that there was sufficient evidence that PCE is carcinogenic to animals (IARC, 1987).

The final report of the NTP inhalation bioassay on PCE was released in 1986 (NTP, 1986). The NTP determined that, under the conditions of this study, there was "clear evidence of carcinogenicity" of PCE for male F344/N rats, "some evidence of carcinogenicity" of PCE for female F344/N rats, and "clear evidence of carcinogenicity" of PCE for both sexes of B6C3F1 mice. In rats, these conclusions were based on an increased incidence of mononuclear cell leukemia in males and females. Male rats also developed renal tubular cell neoplasms (a rare type of tumor). The evaluation of carcinogenicity in mice was based on an increased incidence f hepatoc llular adenoma and

hepatocellular carcinoma in males, and an increased incidence of hepatocellular carcinoma in females.

4. TOXIC EFFECTS IN HUMANS

To assess correctly the health risks from a chemical, consideration of human toxicity data is essential. Unfortunately, information on human toxicity for many substances is limited or is anecdotal in nature. For PCE, however, there have been some controlled inhalation exposure studies to define occupational limits. In addition, epidemiological studies have been conducted to explore the relationship between exposures to PCE vapors and potential health effects. This section presents a brief overview of the health effects of PCE exposures. This discussion is followed by a review of different epidemiological studies dealing with PCE. Finally, human data on the toxic effects of PCE on specific organs and systems are examined.

GENERAL TOXICITY

Acute exposure to PCE can produce skin irritation and burns, as well as irritation of the eyes and respiratory tract. Central nervous system (CNS) depression is the most immediate effect of exposure, but high concentrations can also cause loss of consciousness and respiratory failure. Liver and kidney toxicity can result from single exposures (Stewart et al., 1961a; Stewart, 1969; Hake and Stewart, 1977), but the concentration and duration are typically greater than those that produce transient CNS effects. Chronic occupational exposure to PCE has caused headache, dizziness, hangover, intoxication, diminished cognitive abilities, and a decreased performance in the Romberg and Flanagan Coordination Tests (Stewart et al., 1961b; Stewart et al., 1970; Stewart et al., 1974). Extended exposure to PCE (2 1/2 months to several years) has also promoted changes in kidney and

liver function, cirrhosis, and toxic hepatitis (Coler and Rossmiller, 1953; Meckler and Phelps, 1966; Hake and Stewart, 1977).

In experimental studies, human volunteers have been exposed to PCE by inhalation at various concentrations and for various durations. Because subjects were allowed to leave exposure chambers when they felt discomfort, observed adverse effects have been restricted to the respiratory tract and CNS (Carpenter, 1937; Rowe et al., 1952; Stewart et al., 1961b; Stewart et al., 1970; Stewart et al., 1974; Hake and Stewart, 1977). Accidental exposure to PCE has occurred primarily as a result of its use as an industrial solvent. Although specific exposure levels have not always been determined, concentrations have been high enough to cause liver and kidney dysfunction (Coler and Rossmiller, 1953; Hake and Stewart, 1977; Koppel et al., 1985).

EPIDEMIOLOGIC EVIDENCE FOR CARCINOGENICITY IN HUMANS

Epidemiologic studies of PCE exposure have been reviewed by Reichert and by the EPA (Reichert, 1983; EPA, 1985a). Blair and associates analyzed the death certificates of 330 union laundry and dry-cleaning workers (out of a cohort of 10,000) (Blair et al., 1979). Of 330 decedents, 279 had worked solely in dry-cleaning establishments (while union members). The solvent(s) used by the dry cleaners were not identified. Length of union membership ranged from one to 25 years, with a mean of 13 years. The number of expected deaths from cancer was 67.9 (based on proportionate mortality of the U.S. population) while 87 deaths from cancer were observed. The authors also compared the number of years of union membership with cause of death.

With the exception of nonwhite males, length of union membership was nearly identical for cancer and noncancer deaths. Increased mortality from cancers of the respiratory tract, cervix, and skin was documented ($p<0.05$). When all malignancies were evaluated together, the number of observed deaths was also significantly greater than expected ($p<0.05$). The authors noted that the excess of cervical cancer may be related to the typically low wages and socioeconomic class of this occupational group. Although an excess of liver cancer and leukemia was also observed, these increases were not statistically significant.

The increases in cancer deaths among the study group probably contributed to a lower than expected relative frequency of deaths from other causes. It is noteworthy that death from circulatory disease was significantly lower than expected ($p<0.005$) (Blair et al., 1979). The factors contributing to this phenomenon are not known. Causes of death were not determined separately for laundry and dry-cleaning workers in this study. The actual solvent(s) used were not identified, and smoking history was not documented. The lack of control for smoking proved a significant deficiency of the study because lung cancer was a major contributor to the total number of cancers. Although this study identifies a potential occupational hazard, data provided are not adequate to evaluate the carcinogenic potential of PCE.

Katz and Jowett analyzed the mortality patterns of 671 white female laundry and dry-cleaning workers (Katz and Jowett, 1981). Data were obtained from the death certificates of individuals who died in the period 1966 to 1977. Occupational codes listed on the certificates did not distinguish between the two types of work. Data on the duration of employment were not

available, nor were the investigators able to determine to which solvent(s) the individuals were exposed. Smoking history was not known. Cause-specific proportionate mortality ratios were calculated for 25 causes of death. A significant increase in risk of death from cancer of the kidneys ($p<0.05$) and genitals ($p<0.01$) was documented. An excess risk from skin and bladder cancer was also found; however, neither increase was statistically significant. Individuals in the group under study had a greater risk of death from cancer of the cervix, ischemic (obstructive) heart disease, and diabetes mellitus. However, when the effect(s) of low-wage occupations were accounted for, only the risk for diabetes mellitus remained statistically significant ($p<0.05$).

Other studies of laundry and dry-cleaning workers have also reported an increased risk of death from cervical cancer (Blair et al., 1979; Kaplan, 1980); however, these investigators have not compared mortality data by low-wage occupation. Although not definitive, the findings of Katz and Jowett suggest that factor(s) other than (or in addition to) solvent exposure are important contributors to cervical cancer (Katz and Jowett, 1981).

Kaplan completed a retrospective mortality study of 1597 dry-cleaning workers exposed to PCE for at least one year (prior to 1960) (Kaplan, 1980). By the end of the study period, 1028 of the cohort were alive, 285 had died, and the status of the remaining 254 was not known. Although a considerable effort was made to determine the history of solvent exposure, the solvent history of approximately half of the dry-cleaning establishments was unknown. Of those shops with known solvent history, none had used trichloroethylene; individuals who had worked in shops that had used carbon

tetrachloride were eliminated from the study. However, prior to 1960 (the period of interest in this study), the majority of dry cleaners used petroleum solvents (NIOSH, 1980). In keeping with this information, Kaplan decided that employment in a shop with unknown solvent history probably involved exposure to petroleum solvents. Similarities in the physical properties and physiological effects of gasoline, which has been associated with kidney cancer in rats (Kitchen, 1983), and petroleum solvents suggest that use of these solvents may contribute to an increased risk of cancer. The inability of Kaplan to quantify solvent exposure adds an important confounding variable to the study (Kaplan, 1980). The mean exposure concentration of individuals to PCE was calculated to be 22 ppm for dry-cleaning machine operators and 3.3 ppm for all other jobs. These values are based on a NIOSH survey (NIOSH, 1980) cited by Kaplan (1980).

A Standardized Mortality Ratio (SMR)* was used to compare the number of observed deaths to the number of expected deaths by cause. Kaplan found an elevated SMR (182) for malignant neoplasms of the colon (11 observed deaths, 6.77 to 6.98 expected deaths) (Kaplan, 1980). In discussing this observation, Kaplan pointed out that those individuals of high socioeconomic status are at greater risk for cancer of the colon than individuals of low socioeconomic status (Kaplan, 1980). Because dry-cleaning workers generally receive low wages, the study cohort may have overrepresented individuals of low socioeconomic status, and therefore, included a disproportionate number of individuals who are at low risk for colon cancer. If this risk trend is

* $\text{SMR} = \frac{\text{observed deaths in study population}}{\text{expected deaths in study population}} \times 100$

valid, the elevated SMR reported for colon cancer may actually be an underestimate of PCE risk.

In addition to colon cancer, SMR's for malignant neoplasms of the rectum (158), pancreas (152), respiratory system (140), urinary organs (198), and "other and unspecified sites (major)" (156) were observed (Kaplan, 1980). Although Kaplan did not evaluate SMR's for statistical significance, a review of this study by the EPA included an evaluation of significance of these malignant neoplasms (EPA, 1985a). The SMR's for cancer of the rectum, pancreas, respiratory system, urinary organs, and "other and unspecified sites (major)" were not significant at the $p<0.05$ level. However, cancers of the respiratory system, urinary organs, and "other and unspecified sites" were of borderline significance ($0.10<p<0.05$).

For nonneoplastic diseases, elevated SMR's were reported for diseases of the blood and blood-forming organs (290) and for diseases of the stomach and duodenum (211) as well as hernia and intestinal obstruction (125) (Kaplan 1980). These values are based on data from only two to four individuals and cannot be considered definitive. They do suggest the need for additional study to determine if a relationship does exist between PCE or solvent exposure and these diseases.

Although the relatively small cohort in this study limits conclusions about the carcinogenic potential of PCE, the study (Kaplan, 1980) results suggest a relationship between colon cancer and solvent exposure. Because the NTP study of PCE found hyperplastic and neoplastic changes in the kidneys of treated rats (NTP, 1986), the increase in the SMR from malignant neoplasms

of the urinary organs raises the possibility that occupational exposure to solvents may increase the risk of cancer in these organs. Since petroleum products have also been linked to kidney cancer in rats (Kitchen, 1983), and because it is probable that some of the cohort were exposed to petroleum solvents (as well as to PCE), the possible contribution of PCE to an increased risk of urinary organ cancer cannot be ascertained.

An additional problem in this study was the inability of investigators to collect data on (and thus control for) smoking history. Since smoking is associated with an elevated risk of many types of cancers (including lung and kidney), its contribution to the elevated SMR's reported by Kaplan needs to be evaluated (U.S. DHEW, 1979).

Duh and Asal studied the cause(s) of mortality among 440 laundry and dry-cleaning workers from Oklahoma who died during 1975 to 1981 (Duh and Asal, 1984). This study had the same problem as the studies of Blair and co-workers and Katz and Jowett: smoking histories were not available and separation of the two groups by occupation was not possible (Blair et al., 1979; Katz and Jowett, 1981). Therefore, duration or characterization of individual exposure was not reported. However, Duh and Asal noted that the two groups of workers probably experienced substantially different solvent exposure.

The NIOSH reported that, although 75% of dry-cleaning establishments in the U.S. use PCE, Oklahoma may be unique in that petroleum solvents account for more than 50% of total solvents used (NIOSH, 1980).

A Standardized Mortality Odds Ratio (SMOR)* revealed elevated SMOR's for all digestive diseases (1.5), cirrhosis of the liver (1.3), and homicide (3.8). The SMOR's less than 1.0 were reported for diabetes mellitus (0.7), ischemic (obstructive) heart disease (0.8), emphysema (0.8), and suicide (0.2). A SMOR less than 1.0 suggests that laundry and dry-cleaning workers may be at low risk for these diseases. Analysis of deaths due to cancer showed an increase in the SMOR for cancers of the respiratory system (1.8), lung (1.7), and kidney (3.8). Deaths from breast cancer were considerably less than expected (SMOR = 0.1).

Brown and Kaplan conducted a retrospective, cohort-mortality study of workers employed in the dry-cleaning industry to evaluate the carcinogenic potential from occupational exposure to PCE (Brown and Kaplan, 1987). The study cohort consisted of 1,690 members of four labor unions (located in Oakland, Detroit, Chicago, and New York City). Individuals selected for the study had been employed for at least one year prior to 1960 in dry-cleaning shops using PCE as the primary solvent. Complete solvent-use histories were not known for about half of the shops included in the study. Because petroleum solvents were widely used by dry cleaners prior to 1960, most of the cohort had known or potential exposure to solvents other than PCE (primarily, various types of Stoddard solvents). The investigators also identified a subcohort of 615 workers who had been employed only in establishments where PCE was the primary solvent.

*SMOR was defined by Duh and Asal as a method that compares the number of deaths by specific cause to the number of deaths due to other causes in the exposed population (the odds) to the expected odds derived from a comparison population (Duh and Asal, 1984).

The PCE exposure in shops included in the study was evaluated independently (Ludwig et al., 1983). The geometric mean of time-weighted-average exposures was 22 ppm PCE for machine operators, and approximately 3 ppm for other workers.

Brown and Kaplan calculated person-years-at-risk (PYAR) for each worker (Brown and Kaplan, 1987). The PYAR were then combined into five-year calendar periods and five-year age groups by the life-table-analysis-system (Waxweiler et al., 1983). The PYAR values were also evaluated by length of employment and by time lapsed since first employment in a shop that used PCE. The expected number of deaths was calculated by multiplying PYAR (by age and calendar period) by the U.S. mortality rates. Risk of death due to a specific cause was calculated by means of a SMR.

Among the (main) cohort, the number of observed deaths from all causes (considered together) was less than expected (493 observed, 575.5 expected; SMR = 86) (Brown and Kaplan, 1987). No deaths occurred from liver cancer, although 3.5 were expected. There were also fewer deaths due to diseases of the circulatory system and nervous system (SMR = 70 and 73, respectively). However, observed deaths from all types of neoplasms were higher than expected (142 observed, 122.9 expected; SMR = 116). Elevated SMR's from malignant neoplasms of the intestine (136) and pancreas (172) were documented. Malignant neoplasms of the urinary tract caused a significant excess of deaths (12 observed, 4.7 expected; SMR = 255). Of these urinary tract cancers, kidney cancer caused four deaths (2.0 expected; SMR = 200), while eight deaths from bladder cancer were observed (2.7 expected; SMR = 296). Mortality from calculi of the urinary system (a nonmalignant disease)

was also greater than expected (2.0 observed deaths, 0.3 expected; SMR = 667). Although Brown and Kaplan note that there may be an association between calculi and malignant disease of the urinary tract (Brown and Kaplan, 1987), the association is speculative. An elevated SMR for cancer of the cervix (196) and a decreased SMR due to cancer of the breast (87) were attributed to factors associated with the low socioeconomic status of the cohort (Hoover et al., 1975). The subcohort (workers employed only in shops where PCE was the primary solvent) had only one death from urinary tract cancer (1.3 deaths expected). All deaths from urinary calculi (2) occurred in this group.

In summary, a statistically significant excess of deaths from urinary tract cancer was observed in those workers potentially exposed to both PCE and petroleum solvents. Individuals employed in shops where PCE was the primary solvent did not have an increased risk of mortality from kidney or bladder cancer. Although these findings do not rule out PCE as the causative agent of urinary tract cancer, the data suggest that other factors or agents may have contributed to the development of neoplastic disease.

The possible relationship between exposure to petroleum solvents and kidney cancer has already been noted (Kitchen, 1983). An excess risk of bladder cancer has been associated with cigarette smoking (Matanowski and Elliot, 1981). Brown and Kaplan were not able to document smoking history; however, they calculated the possible effects of smoking on the risk for bladder cancer (based on Axelson, 1978) (Brown and Kaplan, 1987). They concluded that the three-fold increase in bladder cancer among the cohort could not be attributed to smoking.

The currently available epidemiologic studies add limited information to the understanding of the health hazards associated with occupational exposure to PCE. Although there is some indication that use of dry-cleaning solvents poses a health risk, the contribution of individual solvents to the overall problem is far from clear. Until studies are completed that include a thorough analysis and quantification of PCE exposures, epidemiological studies will not be useful for the assessment of the human health risks of PCE.

TOXICITY TO MAJOR ORGANS AND SYSTEMS

Information on human toxicity following exposure to PCE has been obtained from case reports of accidental exposures, as well as from a limited number of experimental studies. Human health effects from short- or long-term exposures are similar to those observed in animals. Perchloroethylene initially affects the CNS, and larger doses cause various degrees of hepatic and renal damage. Table 4-1 summarizes human health effects resulting from experimental inhalation exposures to PCE.

Liver

The earliest reports of PCE-induced liver damage are associated with its use as an anti-helminth in the 1920's and 1930's. Hundreds of thousands of individuals were treated with PCE for hookworm infestations. The PCE was typically given as a single oral dose of 0.12 mL/kg (maximum of 5 mL) (Reichert, 1983). The PCE reportedly produced hepatic necrosis on some occasions. Damage was transient and recovery took place within 1 to 2 weeks

TABLE 4-1. HUMAN HEALTH EFFECTS FROM EXPERIMENTAL INHALATION EXPOSURE TO PCE.

Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
20	5 d/wk for 5 wk	7.5 h/d	No change in EEG[a]	Stewart et al., 1974
75 to 80	Single exposure	1 to 4 min	Slight eye irritation	Stewart et al., 1961b
100	Single exposure	7 h	Headache; sleepiness; transient eye, nose, and throat irritation; abnormal modified Romberg test scores[b]	Stewart et al., 1970
100	5 d/wk for 5 wk	7.5 h/d	Increase in delta-wave activity on EEG[a]	Stewart et al., 1974
100 to 120	Single exposure	4 to 6 min	Soft palate irritation	Stewart et al., 1961b
106	Single exposure	1 h	Transient eye irritation; congestion of frontal sinuses	Rowe et al., 1952
150	5 d/wk for 5 wk	7.5 h/d	Lower scores in Flanagan test[c]	Stewart et al., 1974
200	Single exposure	6 to 30 min	Normal Romberg test scores[b]	Stewart et al., 1961b
216	Single exposure	45 min to 2 h	Eye irritation; sinus congestion; inebriation	Rowe et al., 1952
210 to 244	Single exposure	30 to 187 min	Lightheadedness; difficulty maintaining normal Romberg test[b]	Stewart et al., 1961b

TABLE 4-1. (Continued)

Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
280	Single exposure	2 h	Lightheadedness; eye irritation; sinus congestion; transient nausea	Rowe et al., 1952
475	Single exposure	130 min	Eye irritation; sinus congestion; slight feeling of elation	Carpenter, 1937
600	Single exposure	10 min	Eye and nose irritation; dizziness; diminished motor coordination; some loss of inhibition	Rowe et al., 1952
911	Single exposure	95 min	Lassitude; inebriation; exhilaration; mental fogginess	Carpenter, 1937
1060	Single exposure	1 to 2 min	Eye and upper respiratory tract irritation	Rowe et al., 1952
2000	Single exposure	7.5 min	Exposure terminated because all subjects felt faint	Carpenter, 1937

[a]EEG: electroencephalogram.

[b]Romberg test: measurement of ataxia.

[c]Flanagan test: measurement of coordination.

(Hall and Schillinger, 1925; Lambert, 1933). Meckler and Phelps documented a case in which an individual developed hepatitis after a massive inhalation exposure to PCE (of undetermined concentration) (Meckler and Phelps, 1966). The individual's liver remained enlarged 6 months after the exposure. Interestingly, in a separate case of oral overexposure reported by Koppel and co-workers, an individual did not have any measurable liver or kidney damage after ingestion of 8 to 10 mL of relatively pure PCE. Clinical measurements of organ function that were within normal limits included SGOT, SGPT, alkaline phosphatase, red and white blood-cell counts, and serum creatinine. However, the individual was hospitalized for treatment within 1 hour of ingestion, which probably averted organ damage (Koppel et al., 1985).

Stewart and co-workers have investigated several cases of acute overexposure to PCE that caused liver damage. The earliest report documented the clinical effects of occupational exposure to the vapor of a petroleum-based solvent mixture that contained approximately 50% PCE (Stewart et al., 1961). The individual was exposed to this mixture for about 3.5 hours, which caused a loss of consciousness. Simulation of exposure conditions gave an estimated concentration of 250 ppm, with levels that reached 1000 ppm for the last 30 minutes. Nine days after the incident, urinary urobilinogen and serum bilirubin levels were elevated, an indication of liver impairment. On the 18th day after exposure, a slight elevation of SGPT was measured (Stewart et al., 1961a). In a separate incident reported by Stewart, a worker was overcome by PCE vapors (of unknown concentration) (Stewart, 1969). The exposure lasted about 10 minutes and produced hepatic dysfunction. Clinical measurements of liver function were normal shortly

after exposure. A slight increase in SGOT levels was measured on the third and fourth days following exposure, and urinary urobilinogen levels were elevated on the ninth day. Elevated serum enzymes were also measured by Hake and Stewart after a massive overexposure to PCE (estimates of the exposure concentration were not made) (Hake and Stewart, 1977). The individual was found lying in a pool of PCE, some of which was probably absorbed dermally as well as through the lung. Recovery was complete within 21 days.

Eight of nine firemen exposed to PCE vapors for 3 minutes (unknown concentration) had elevated SGOT levels. Hepatomegaly and splenomegaly were also found in one individual. Normal function was regained within 22 to 63 days (Saland, 1967).

The effects of chronic occupational exposure to PCE vapor were studied in seven individuals exposed for 2 to 6 years (Coler and Rossmiller, 1953). Short-term tests indicated that exposure levels ranged from 232 to 385 ppm. The authors assumed that these measurements were representative of levels that workers were exposed to 8 hours/day, 5 days/week. Of the 7 individuals, 3 had abnormal liver-function tests, and 1 was diagnosed as having cirrhosis.

Kidneys

In animals, kidney damage generally occurs at exposure levels greater than those that cause liver toxicity. This trend seems to hold true for humans as well. Several cases of overexposure great enough to cause loss of

consciousness have not produced measurable kidney damage (Stewart et al., 1961a; Stewart, 1969; Patel et al., 1973; Patel et al., 1977). In 1 case of overexposure (where an individual was unconscious in a pool of PCE for 12 hours), kidney damage was measured by proteinuria and hematuria. These effects lasted for 20 days and for 8 days, respectively (Hake and Stewart, 1977).

Lungs

Pulmonary edema has been documented in only one instance. Exposure to PCE was probably massive (>1500 ppm) because the individual was comatose and required mechanical ventilation upon admission to the hospital. Recovery was complete within 4 days (Patel et al., 1977).

Skin and Eyes

Dermal contact with PCE causes localized irritation; prolonged exposure can cause erythema, first- and second-degree burns, and blistering (Gold, 1969; Stewart et al., 1961b; Hake and Stewart, 1977). The PCE vapor is also irritating to the eyes (Carpenter, 1937; Rowe et al., 1952). Exposure of human volunteers to 106 ppm produced transient eye irritation; this became more pronounced when the concentration was increased to 216 ppm (Rowe et al., 1952). Stewart and colleagues has also reported eye irritation when humans were exposed to 100 ppm for a period of 7 hours (Stewart et al., 1970).

Connective Tissue

Sparrow described a patient who had a connective tissue disorder with similarities to a syndrome observed in vinyl chloride workers (Sparrow, 1977). The individual in question was exposed to PCE vapor during his work at a dry cleaners. No measurements of concentration were reported, but at least once a week (over a 4-year period), exposure was high enough to cause dizziness and sleepiness. The individual displayed pathological changes in the skin of the hands, acrocyanosis, and polymyopathy. Abnormalities in the immune system and in hepatic function (mild hepatitis) were also documented. The patient may have been abnormally sensitive to PCE, perhaps related to an existing abnormality in the immune system. Indications that the individual did have an abnormal immune system are suggested by intermittent alopecia areata (since childhood), vitiligo (an apparently autoimmune condition characterized by destruction of melanocytes), and an absence of immunoglobulin A (IgA). This appears to be a unique case report, whose information is confounded by the abnormal medical history of the individual. Although PCE exposure may have contributed to the disease, it is not clear if PCE was the sole causative agent.

Central Nervous System

Acute exposure to PCE generally causes temporary CNS effects such as dizziness, headache, and confusion. However, massive single exposures can cause loss of consciousness (Patel et al., 1973; Patel et al., 1977; Hake and Stewart, 1977), and have been fatal in at least two instances (Lukaszewski, 1979; Levine et al., 1981). Protracted exposure produces

symptoms similar to those observed after short-term exposure, although the effects apparently persist, even after exposure is terminated.

Rowe and associates did not observe any CNS effects in humans exposed to 106 ppm (single exposure of unspecified duration) (Rowe et al., 1952). Minor CNS effects were produced by 216 ppm (45 minutes to 2 hours), and a 10-minutes exposure to 600 ppm significantly affected motor coordination. Eleven volunteers exposed for a single 7-hour period to 100 ppm experienced headache, dizziness, and somnolence (Stewart, 1970). Three of the 11 had abnormal scores on the Romberg test, which measures ataxia. Tests of coordination, visual inspection, visual acuity, and depth perception were normal. Carpenter noted only minor and transient CNS effects in individuals exposed to 500 ppm for 2 hours (Carpenter, 1937). When the same subjects were exposed to 911 ppm, they complained of lassitude, exhilaration, and inebriation.

In a study conducted by Stewart and co-workers, individuals were exposed to 20 to 150 ppm of PCE, 7.5 hours/day over a 5-week period (Stewart et al., 1974). No alterations in the EEG were noted at 20 ppm, but some aberrant EEG tracings were seen after 100 ppm. A decrease in Flanagan Coordination Test scores was observed following exposure to 150 ppm. In a subsequent experiment, individuals were repeatedly exposed to 0, 25, or 100 ppm of PCE, 5.5 hours/day over 11 week (Stewart et al., 1977). CNS effects were observed by measuring the subjects' response on the Romberg, Michigan Hand-Eye Coordination, and Flanagan Coordination Tests, and on the EEG. In contrast to the 1970 study, exposure to 100 ppm did not produce abnormal

scores on the Romberg Test. PCE at 100 ppm did cause a significant decrease in Flanagan Coordination Test scores.

Coler and Rossmiller documented subjective complaints of malaise, dizziness, headache, lightheadedness, and intoxication in individuals regularly exposed to concentrations of 232 to 385 ppm PCE (Coler and Rossmiller, 1953). Gold described a case history of an individual exposed to PCE vapors, 6 to 7 days a week for 3 years (Gold, 1969). The individual was hospitalized after exhibiting confusion, disorientation, agitation, and an inability to concentrate. A neurological examination revealed a normal EEG. However, his performance on psychological tests that required concentration was "poor", and he showed "marked confusion." These problems persisted over a 12-month follow-up period, although there was no further exposure to PCE (the individual was lost to follow up at this time). Gold concluded that there was suggestive evidence of both cerebral and cortical damage, and basal ganglia involvement (Gold, 1969). However, it was not possible to obtain conclusive evidence of any neurological damage. Gregersen and colleagues examined 65 Danish workers exposed to various organic solvents for neurotoxic effects (Gregersen et al., 1984). Although only 15% of the cohort were exposed to PCE (approximately 100 ppm), the results are intriguing. Individuals were examined for intelligence, given a neuropsychological exam, and were subjected to a number of neuropsychological tests. The authors concluded that solvent exposure was correlated with acute neurotoxic symptoms, as well as longer-lasting symptoms of intellectual impairment. A relationship between exposure and signs of peripheral neuropathy was also observed.

McMullen reported on a case in which an individual was exposed to PCE vapor (500 ppm) for an undetermined period of time (McMullen, 1976). CNS depression was observed; the effects were described as resembling alcohol intoxication. No clinical measurements of sensory or organ function were made, but the individual apparently recovered within 6 hours.

Reproductive System

No studies have addressed the question of whether exposure to PCE affects the human reproductive system. At present, there is no evidence of human reproductive toxicity from PCE exposure.

Cardiovascular System

Some organic solvents have been associated with cardiac arrest due to ventricular fibrillation. It is thought that these compounds sensitize the heart to epinephrine-induced arrhythmias. There is suggestive evidence that PCE has this effect in animals (see Section 3), and there is one report of PCE-induced cardiac arrhythmias in humans. Abedin and associates observed that occupational exposure to PCE probably caused dizziness and premature ventricular contractions in one case (Abedin et al., 1980). Although PCE may not have been the only factor in this response, removal from exposure to PCE alleviated the symptoms.

TERATOGENIC EFFECTS

There is no published information on the teratogenicity of PCE in humans.

MUTAGENIC EFFECTS

Ikeda and co-workers examined lymphocytes from individuals exposed to PCE for 3 months to 18 years (Ikeda et al., 1980). Chromosomal aberrations, sister-chromatid exchanges, and alterations of the mitotic index were the cytogenetic effects studied. The exposure level in 1 group of workers was 92 ppm (geometric mean), while a second group was exposed to 10 to 40 ppm (the authors did not give TWA exposure concentrations). Although a control group was included, the criteria used to select and/or match controls was not reported. Exposed individuals did not have a significantly greater frequency of chromosomal aberrations or sister-chromatid exchanges, nor were there any substantial differences in the mitotic index.

Trichloroethanol is a metabolite of PCE isolated from the urine of humans. Gu and associates reported a slight increase in the number of sister-chromatid exchanges per cell in human lymphocytes exposed to 178 mg/L of trichloroethanol (Gu et al., 1981). Neither of these studies is adequate to assess the mutagenic potential of PCE and its metabolites in humans.

SUMMARY OF EVIDENCE OF HUMAN CARCINOGENICITY

Evaluation of the carcinogenic potential of a chemical is based on the results of short-term assays of mutagenesis, pharmacological data (e.g., distribution and metabolism), lifetime animal bioassays, and epidemiological evidence. Several agencies and groups have developed systems of classification for evaluating evidence on the carcinogenic activity of a substance. The International Agency for Research on Cancer (IARC) separates

strength of evidence of carcinogenic activity into 4 groups: sufficient evidence, limited evidence, inadequate evidence, and no evidence of carcinogenicity (IARC, 1982). Inclusion in any of these categories is based on data from short-term assays, as well as animal and human studies (if available).

The EPA uses the same groupings, but places a substance in one or the other category solely on the basis of animal bioassay data (EPA, 1984a). To assess overall evidence of carcinogenic potential to humans, 6 additional categories are used: group A - Human Carcinogen, group B - Probable Human Carcinogen (further separated into B1 and B2), group C - Possible Human Carcinogen, group D - Not Classified (due to inadequate animal evidence), and group E - No Evidence of Carcinogenicity for Humans (EPA, 1984a).

In the absence of sound epidemiological data, the greatest weight of evidence in a carcinogen assessment is typically given to the results of lifetime animal bioassays. The criteria employed in analysis of bioassay data include an increase in the incidence of tumors in treated animals over those noted in controls, a decrease in latency (time to tumor development) development of rare tumors, and an increase in the number of tumors in individual animals.

In 1982 and 1987, the IARC evaluated available information on PCE and determined that there was "inadequate" evidence to conclude that PCE is carcinogenic to humans (IARC, 1982). An analysis of animal data gave sufficient evidence of carcinogenicity (IARC, 1987); evidence for any activity of PCE in short-term tests was "inadequate" to judge its

carcinogenic potential (IARC, 1982). The EPA Health Assessment Document for Tetrachloroethylene (Perchloroethylene) has also analyzed the evidence of carcinogenicity of PCE (EPA, 1985a). This evaluation included an extensive review of short-term test results, data from animal tests, and several epidemiological studies. The EPA concluded that the evidence for the carcinogenicity of PCE in animals is "limited," and that the epidemiological data were inconclusive. Perchloroethylene was placed in group C, a possible human carcinogen (EPA, 1985a).

It should be noted however, that since these 2 analyses were published, other epidemiologic and animal study results have become available. It is possible that a subsequent evaluation by either the EPA or IARC would result in a different conclusion.

5. QUANTIFICATION OF PCE'S CARCINOGENIC POTENCY

The term carcinogenic "potency" is used herein to mean the quantitative increase in tumorigenic risk per unit dose for very low exposure levels. Risks are predicted using the "linearized" multistage dose-response extrapolation model that has been generally used for cancer risk assessment by the California Department of Health Services (CDHS, 1985) and the U.S. Environmental Protection Agency (EPA) (EPA, 1985b; Anderson et al., 1983).

The following carcinogenic potency assessment proceeds in 5 steps: (1) selection of those cancer bioassay data sets suitable for dose-response assessment; (2) determination of the empirical relationship between applied dose and cancer risk for each data set selected; (3) determination of the relationship between administered dose and the amount of PCE metabolized for animals and humans; (4) expression of carcinogenic potency in terms of rate of metabolite formation; and (5) expression of carcinogenic potency in terms of estimated human applied dose, taking PCE metabolism into account.

SELECTION OF BIOASSAY DATA INDICATIVE OF PCE CARCINOGENICITY

The bioassays used in this potency assessment are the National Cancer Institute (NCI) study of mice exposed to PCE by gavage (NCI, 1977) and the recent National Toxicology Program (NTP) studies of mice and rats exposed to PCE by inhalation (NTP, 1986). The EPA used the gavage study as the basis of a carcinogenic potency assessment in 1985 (EPA, 1985a) and used the inhalation study to update this assessment in 1986 (EPA, 1986). In each of these studies PCE caused a significantly increased tumor incidence (see Section 3). These

bioassay data sets are used here because they represent the only long-term exposure studies with well-defined, exposure-response data that indicate a positive carcinogenic response for PCE in animals. Human epidemiological data suitable for dose-response assessment are not available.

Brief reviews of the administered dose and associated tumor response for the NCI gavage study with mice and for the NTP inhalation studies with rats and mice are given below. This information is summarized in Table 5-1, along with other information derived later, which also is tabulated here for convenience. From the doses (D) administered in those bioassays corresponding lifetime, time-weighted average (TWA) applied doses (A), are derived using certain standard assumptions (noted below).

As discussed in Section 2 PCE is extensively metabolized in mammals. The metabolites (rather than PCE) have been suggested to be responsible for almost all acute, chronic, and carcinogenic effects (e.g., Pegg et al., 1979; Schumann et al., 1980). Postulated toxic metabolites of PCE that have been identified include trichloroacetyl chloride, trichloroacetic acid, and trichloroethanol; the formation of the reactive epoxide tetrachloroethylene oxide is thought to be the first step in the metabolism of PCE (Bouse et al. 1975; Greim et al., 1975). Other minor metabolites have also been identified and/or proposed. If a reactive metabolite is indeed responsible for the carcinogenic effects of PCE, then the total metabolized dose may be useful as a surrogate measure of the actual delivered dose. Since the metabolized dose is likely to be smaller than the administered dose, using the metabolized dose to calculate cancer potency would result in a higher potency value than would the administered dose. Using available data, carcinogenic potencies have been

TABLE 5-1. DOSE-RESPONSE DATA FOR SELECTED CANCER BIOASSAYS

Study species (strain)	Sex and weight (kg)	Administered dose or conc., D	TWA Applied dose, A. (mg/kg-d)	Tumor	
				Type	Incidence[a]
NCI, 1977		0	0		2/20
Mice	Male	536[b]	215.0[d]	hepatocellular carcinoma	32/48
(B6C3F1)	0.030	1072[b]	430.1[d]		27/45
		0	0		0/20
	Female	386[b]	154.9[d]	hepatocellular carcinoma	19/48
	0.025	772[b]	309.7[d]		19/45
NTP, 1986		0	0		7/49
Mice	Male	100[c]	146.6[e]	hepatocellular carcinoma	25/47
(B6C3F1)	0.037	200[c]	293.2[e]		26/50
		0	0		1/44
	Female	100[c]	153.9[e]	hepatocellular carcinoma	13/42
	0.032	200[c]	307.8[e]		36/47
		0	0		16/49
	Male	100[c]	146.6[e]	hepatocellular adenoma/carcinoma	31/47
	0.037	200[c]	293.2[e]		40/50

TABLE 5-1. DOSE-RESPONSE DATA FOR SELECTED CANCER BIOASSAYS

Study species (strain)	Sex and weight (kg)	Administered dose or conc., D	TWA Applied dose, A. (mg/kg-d)	Tumor	
				Type	Incidence[a]
		0	0		4/44
	Female	100[c]	153.9[e]	hepatocellular adenoma/carcinoma	17/42
	0.032	200[c]	307.8[e]		38/47
NTP, 1986		0	0		28/50
Rats	Male	200[c]	143.0[f]	mononuclear-cell leukemia	37/48
(F344/N)	0.44	400[c]	286.0[f]		37/50
		0	0		18/49
	Female	200[c]	159.0[f]	mononuclear-cell leukemia	30/50
	0.32	400[c]	318.1[f]		29/50

[a]Tumor-incidence denominator excludes animals dying before the occurence of the first corresponding tumor type observed in each study.

[b]Average administered daily gavage dose, D, in mg/kg-d, for a 5 d/wk exposure over 78 wk of a 90-wk bioassay.

[c]Average administered inhalation exposure in ppm 6 h/d, 5 d/wk over 2-years.

[d]Time-weighted average (TWA) dose: $A = D\ (5/7) \times (78/90)\ (90/104)^3$ (following Anderson et al. 1983).

[e]Total respired dose averaged over time: $A = D\ (6/24)\ (5/7)\ (0.0345)(\text{body weight}/0.025)^{2/3}$ (6.78 mg PCE/m^3 ppm).

[f]Total respired dose averaged over time: $A = D\ (6/24)\ (5/7)\ (0.105)\ (\text{body weight}/0.113)^{2/3}$ (6.78 mg PCE/m^3-ppm)/body weight (following Anderson et al. 1983).

estimated on the basis of metabolized dose (denoted M), in addition to those based on the administered dose or "applied" dose (denoted A) (EPA, 1985a, 1985b, and 1985c; EPA Draft, 1986; CDHS, 1985). From pharmacokinetic data an empirical relationship was obtained between administered dose and the total metabolized dose.

PHARMACOKINETIC ANALYSES

In two previous risk assessments, EPA calculated the metabolized dose (M) as a function of the administered dose (D) for the NCI and NTP bioassay data using a simple steady-state pharmacokinetic (SSPK) approach (EPA, 1985a; EPA Draft, 1986). In using this approach the EPA did not take into account: (1) bioassay duration relative to expected lifespan; (2) male/female animal weight differences; (3) the treatment of species-specific data on metabolic elimination pathways; (4) the scaling of certain kinetic parameters across species; and (5) the treatment of available human metabolic data. Therefore, a reanalysis of the relevant pharmacokinetic data was undertaken as part of the current potency assessment for PCE. This reanalysis, however, relied on the same basic SSPK approach that EPA used. The SSPK approach presented here and used by the EPA is fairly crude, primarily because much of the available metabolic data were not gathered under steady-state physiological conditions at the very low levels of anticipated human exposure.

Physiologically-based pharmacokinetics (PB PK) is a relatively new form of pharmacokinetic modeling designed to consider physiological processes, biochemical kinetics, and tissue levels of the chemical (or its metabolites) under investigation, based on available biological data. This approach

represents the body by compartments, into and out of which compounds are transferred by diffusion and blood flow. This aids in cross-species comparison of metabolizing enzymes, metabolism pathways, organ volume and blood flow, absorption and distribution phenomena, differences in body size and composition, transport characteristics, and differences in the relative routes of detoxification and excretion. Preliminary results from PB-PK models of PCE metabolism for bioassay and environmental contexts are available (EPA Draft, 1986; Reitz and Nolan, 1986). Although a detailed description of a PB-PK approach is beyond the scope of the present analysis, results using such an approach along with results obtained using the simpler approaches are presented here.

The use of metabolized, rather than applied, dose adds and/or emphasizes several uncertainties relevant to the analysis of the experimental dose response data, including: uncertainty in identifying the active carcinogenic species; uncertainty in parameter estimates based on experimental animal data; uncertainty involved in extrapolating kinetic constants between species; uncertainty in some key constants estimated for humans based on limited human metabolism data; uncertainty in the application of the non-steady state PB-PK model (which purportedly adjusts variables to steady-state conditions); uncertainty in the detection of all human PCE metabolites; uncertainty in the relative metabolic rates at environmental exposure levels; and uncertainty regarding the extent to which inter-individual variability relates to pharmacokinetic parameters, particularly for humans. The problem of inter-individual variability is, of course, common to many problems in predictive regulatory toxicology, not just pharmacokinetic analysis. For risk assessments using toxic endpoints other than carcinogenesis, this is generally

dealt with by incorporating a safety factor. With regard to the other sources of uncertainty mentioned, an attempt is made here and in other reports (EPA, 1985a, 1985b, and 1985c; EPA Draft, 1986) to assess available metabolism data for internal consistency.

The alternative to using estimates of metabolized PCE dose in this analysis is to rely on the applied dose. This latter approach would not consider possible interspecies differences in: 1) absorption of the administered dose; 2) both the qualitative and quantitative metabolism of the PCE; and 3) relative rates of detoxification. However, the applied dose approach can be adjusted for absorption differences. The decision to use the applied dose or the metabolized dose model involves a trade-off between the additional parameter uncertainties associated with a physiologically-based pharmacokinetic model and a potential systematic error associated with an applied dose model. The optimum approach hinges on scientific/policy judgments concerning the quality of data underlying (1) identification of carcinogenic mechanism of PCE and (2) pharmacokinetic parameter estimates. The problems and benefits associated with both approaches are discussed below for the different bioassays.

METHODOLOGY

Evaluation Of Cancer Potency

To calculate potential risks associated with PCE exposure, the staff of CDHS used a linearized multistage model, which provides a reasonably health-protective risk estimate due to its property of being linear at low exposure levels. The lifetime probability of developing a tumor (p) induced by a

average daily intake of chemical (d) is often assumed to be (CDHS, 1985; Anderson et al., 1983):

$$p(d) = 1\text{-}\exp\text{-}(q_0 + q_1 d + q_2 d^2 + \ldots + q_j d^j)$$

with constraints $q_i > 0$ for all i.

The q_i are parameters of the model which are taken to be constants and are estimated by maximum likelihood techniques from the data. The parameter q_0 represents the background lifetime incidence of the tumor. The q_1 value or some upper bound is often called the cancer potency, since for small doses it is the ratio of excess lifetime cancer risk to the average daily dose received. For the present discussion, cancer potency will be defined as q_1^*, the upper 95% confidence bound of q_1, as estimated by maximum likelihood techniques. When the dose is given in mg/kg-d, the parameters q_1 and q_1^* are given in units $(mg/kg\text{-}d)^{-1}$. Details of the estimation procedure are given in Crump, Guess and Deal (1977). To estimate potency in animals (q_{animal}) from experiments of duration Te, rather than the natural lifespan of the animal (T), it is assumed that cancer incidence increases with the third power of age:

$$q_{animal} = q_1^* \times (T/Te)^3$$

Following Gold et al. (1984) and the EPA (Anderson et al., 1983), the natural lifespan of mice and rats is assumed to be two years, so that for experiments lasting Te weeks in these rodents:

$$q_{animal} = q_1^* \times (104/Te)^3.$$

To estimate risk at low doses or exposure levels, the potency value is multiplied by the average daily dose.

Interspecies Scaling

Once a potency value is estimated in animals using one of the techniques described above, human potency can be estimated. As described in the California risk assessment guidelines (CDHS, 1985), a dose in units of milligram per unit surface area is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Under this assumption, scaling to the estimated human potency (q_{human}) can be achieved by multiplying the animal potency value (q_{animal}) by the ratio of human (bw_h) to animal body weights (bw_a) raised to the one-third power when animal potency is expressed in units $(mg/kg\text{-}d)^{-1}$:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}.$$

Body weights are typically assumed to be 70 kg for humans, 0.35 kg for rats and 0.030 kg for mice, but each experiment should be interpreted with respect to the actual weight recorded during the bioassay.

Dose Adjustments

Several adjustments need to be made to the experimental exposures to calculate the lifetime daily exposure levels. Thus, for inhalation exposures, the reported dose must be multiplied by:

H/24: where H is the hours of exposure per day. This converts the exposure period to a time weighted average for 24 hours daily continuous exposure.

D/7: where D is the number of days exposed per week. This converts the dosing schedule to a time weighted average for a seven day/week continuous exposure.

Le/L: where Le is the length of the experiment and L is the lifespan of the animal (the longer of Le or 24 months). This converts the experimental protocol to a continuous lifetime exposure.

NCI (1977) Mouse Study: Gavage

Applied Dose and Tumor Incidence

In the NCI study, PCE in corn oil was administered to male and female B6C3F1 mice, beginning at about 5 weeks of age, by gastric intubation for 5 days/wk for 78-weeks, followed by 12 additional weeks of pre-sacrifice observation (NCI 1977). Incidence of hepatocellular carcinomas increased with dose for both males and females (see earlier discussion in Section 3). Table 5-1 gives the average administered daily dose, D, for the male and female vehicle control, low- and high-dose groups along with corresponding tumor incidence data (see EPA, 1985a). Note that D is the time-weighted average (TWA) dose (in units of mg/kg). In table 5-1, in contrast to Table 3-2 tumor-incidence data are given as the number of tumors found in animals which survived at least until the appearance of the first carcinoma in each study (which appeared at week 24 for

female mice and at week 41 for male mice in the NCI study). The mortality-adjusted incidence data are used here in preference to unadjusted incidence data to partially correct for the influence of competing mortality risks.

Metabolized Dose

The pharmacokinetic data of Buben and O'Flaherty (1985) for PCE metabolism in mice were used to calculate the metabolized dose from the applied dose. In this study, PCE metabolism was examined in 3- to 5-month-old, male Swiss-Cox mice during subchronic administration of PCE by gavage in corn oil for 5 days/week for 6 weeks, exposure conditions similar to those of the NCI study. Seven different animal groups received dose levels ranging from 20 to 2000 mg/kg. Metabolism was estimated by measuring the daily excretion of the sole urinary metabolite detected, trichloroacetic acid (TCA). Dose-dependent metabolism was observed to be described by the Michaelis-Menten equation:

$$M_u = \frac{D\ V_{max,u}}{D + K_m} \qquad (5\text{-}1)$$

where

M_u = TWA yield of urinary metabolite, mg/kg-d;

D = TWA daily administered dose, mg/kg-d;

$V_{max,u}$ = apparent maximum rate of urinary metabolite production, mg/kg-d; and

K_m = apparent Michaelis constant, mg/kg-d.

The value of M_u is essentially equivalent to the dose rate in mg PCE metabolized, since the molecular weights of PCE and TCA differ by less than

1.5%. In the Buben and O'Flaherty study, $V_{max,u}$ was estimated to be 136 mg/kg-d, while K_m was estimated to be 660 mg/kg-d (Buben and O'Flaherty, 1985).

If for different species the dose estimated from the urinary metabolites, M_u, were a constant proportion of total metabolized dose (which we shall denote as M), then it would make no difference whether M or M_u were used to derive a relationship between cancer risk and applied dose, D. But this proportion does not appear to be constant for different species. In B6C3F1 mice, for example, the mass-balance metabolic study by Schumann and co-workers reported that the total amount of PCE metabolites found after either a 6-hour inhalation at 10 ppm or a single, oral dose of 500 mg/kg of radiolabeled PCE, were 80.0% and 82.3% of the administered dose, respectively, in the form of urinary metabolites (Schumann et al., 1980). These results were based on the assumption that metabolism was complete by 72 hours post-exposure and that cagewash radioactivity was attributable solely to urine content. For Sprague-Dawley rats, a metabolic study by Pegg and associates found that urinary metabolites comprised only 58.9% and 57.1% of the total PCE metabolized after exposures of 10 ppm for 6 hours and 1 mg/kg by injection, respectively, of radiolabeled PCE (and only 49.9% and 45.7% after the higher exposures of 600 ppm for 6 hours and 500 mg/kg by injection, respectively) (Pegg et al., 1979). Since both studies assumed complete metabolism by 72 hours post-exposure, the estimates of M would be decreased to a greater extent for rats than for mice. Thus, these two studies indicate that M_u was a greater fraction of M for the mice than for the rats. In addition, M_u was found to decrease with an increase in dose for rats.

Based on the proportion M_u/M indicated by Schumann et al. (1980), and the relationship between applied dose and urinary metabolite production indicated by Buben and O'Flaherty (1985), M_u and $V_{max,u}$ in mice are assumed to be 80% of M and V_{max}. Thus, the parameter V_{max} (which allows us to estimate the total amount of PCE metabolized) is 170 mg/kg-d (= 136/0.80, using the $V_{max,u}$ estimated by Buben and O'Flaherty (1985). This assumes that PCE metabolism is quantitatively similar for B6C3F1 and Swiss-Cox mice. A single, oral dose of 500 mg/kg of PCE administered to B6C3F1 mice was found by Schumann et al. (1980) to yield an average metabolized dose of 85.02 mg/kg. This is 16% greater than the value of 73.26 mg/kg predicted by Equation 5-1 using a $V_{max,u}$ estimate of 170 mg/kg. Using a $V_{max,u}$ of 136 mg/kg yields an average metabolized dose of 58.6 mg/kg. These results did not agree with the PCE metabolism data obtained by Mitoma et al. (1985) for groups of four male 4-6 week-old B6C3F1 mice. Mitoma and co-workers reported that only 22 to 37% of radiolabeled gavage doses (900 and 225 mg/kg, respectively) administered after 4 weeks of similar, daily, non-labeled dosing, was metabolized. Fitting the Michaelis-Menten equations (5-4 and 5-5 below) to these two data points results in parameter estimates of V_{max} = 366 mg/kg and K_m = 765 mg/kg.

The advantage of using the data from Mitoma and associates in estimating Michaelis-Menten metabolic parameters is that the same strain of mouse and a similar exposure protocol were used in the 1977 NCI mouse bioassay (Mitoma et al., 1985; NCI, 1977). The drawbacks, on the other hand, are (1) that the mice studied by Mitoma and colleagues were quite young and therefore perhaps not representative of mice in the 90-week NCI bioassay, (2) the metabolite recovery period used by Mitoma and co-workers was only 48 hours,

and (3) total radioactivity recovered by Mitoma and associates accounted for only about 80% of the radiolabeled PCE administered. For these reasons the data from Mitoma and colleagues (1985) on PCE was not considered accurate enough for use in the calculation of a metabolized dose. However, it should be kept in mind that, for mice administered comparable dose levels, a 3- to 4-fold difference in the rate of PCE metabolism has been reported (22 to 82%). This leads to a two-fold difference in the calculated V_{max} (170 mg/kg-d to 366 mg/kg-d) in mice.

For gavage studies the apparent K_m is unaffected by the transformation from M_u to M (see Equation 5-5 below). Under the assumptions stated above, it is possible to relate administered dose to the metabolized dose for the 1977 NCI mouse bioassay using the equation

$$M = \frac{1}{0.80} \cdot \frac{D\ V_{max,u}}{D + K_m} \qquad (5\text{-}2)$$

To convert M to a lifetime TWA, equation 5-2 needs to be adjusted for the specific exposure scenario being conside i.

The EPA assumed that cumulative age-specific cancer rates increase as th third power of age (EPA, 1980; Anderson et al., 1983). Thus, given a bioassay duration of L_e and a natural test-species lifespan of L, the cancer potency value calculated using a multistage-risk-extrapolation model would be increased by the factor $(L/L_e)^3$ (EPA, 1980; Anderson et al., 1983). Equivalently, the lifetime TWA dose that would yield the corrected potency value would be the actual bioassay TWA dose multiplied by the factor $(L_e/L)^3$. In the 1977 NCI study, for example, the mice used were 5 weeks

old at start, and their age at the end of the bioassay was 95 weeks; the L_e value used was 90 weeks (NCI, 1977). The median survival time for (control) mice was 104 weeks, i.e., L = 104 wk. For the NCI (1977) data, a partial lifetime-exposure-correction factor of $(90/104)^3$ was used. This is close to the value of $(95/108)^3$, which reflects the actual age at bioassay termination and assumes an experimental lifespan for B6C3F1 mice of about 25 months. The EPA used this approach to derive potencies for trichloroethylene (EPA, 1985b), but this approach was not used by EPA to derive a potency value for PCE carcinogenicity (EPA, 1985a; EPA Draft, 1986).

Thus, the daily metabolite doses (M) in the NCI (1977) study were derived from corresponding values of applied dose, D, using the following modification of Equation 5-2:

$$M = \frac{D\ V_{max}}{D + K_m} \times \frac{5}{7} \times \frac{78}{90} \times \left[\frac{90}{104}\right]^3, \qquad (5\text{-}3)$$

where M and D are in units mg/kg-d, V_{max} and K_m were assumed to be 170 mg/kg-d and 660 mg/kg-d, respectively.

NTP (1986) Rat Study: Inhalation

In the 1986 NTP study, groups of fifty 8- to 9-week-old male and female F344/N rats were exposed to PCE by inhalation at 0, 200, or 400 ppm for 6 hours/day, 5 days/week over 2 years (NTP, 1986). The exposure concentration values for males and females appear in Table 5-1, along with the

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TABLE 5-2.

METABOLIZED DOSE CALCULATIONS FOR SELECTED CANCER DATA SETS

Study species (strain)	Sex and weight (g)	Experimental applied dose or conc., D[a]	Average Daily Metabolized Dose (M) in mg/kg-d: LLNL[b]	EPA equivalent[c]	EPA equivalent PB-PK[d]	Reitz and Nolan equivalent PB-PK[e]
NCI, 1977		0 mg/kg	0	0	--	--
Mice	Male	536 mg/kg	30.6	30.6	--	--
(B6C3F1)	0.030	1072 mg/kg	42.2	42.2	--	--
		0 mg/kg	0	0	--	--
	Female	386 mg/kg	25.2	25.2	--	--
	0.025	772 mg/kg	36.8	36.8	--	--
NTP, 1986		0 ppm	0	0	0	0
Mice	Male	100 ppm	43.3	35.0	13.5	65.4
(B6C3F1)	0.037	200 ppm	61.4	53.1	19.5	93.8
		0 ppm	0	0	0	0
	Female	100 ppm	46.7	35.0	13.5	67.5
	0.032	200 ppm	65.8	53.1	19.5	96.9
NTP, 1986		0 ppm	0	0	0	--
Rats	Male	200 ppm	11.8	15.7	14.9	--
(F344/N)	0.44	400 ppm	17.2	21.2	18.6	--
		0 ppm	0	0	0	--
	Female	200 ppm	14.0	15.7	14.9	--
	0.32	400 ppm	20.0	21.2	18.6	--

[a] For the NCI study, average administered daily gavage dose, D, in mg/kg-d, for a 5 d/wk exposure over 78 wk of a 90-wk bioassay; for the NTP study, average administered inhalation exposure in ppm for a 6 h/d, 5 d/wk exposure over a 2-y bioassay.

[b] LLNL refers to the Lawrence Livermore National Labs' approach used herein.

[c] Here $M = M^* \; W/F$, where M* is the "estimate of dose metabolized", which for NCI study is given in Table 9-9 of EPA (1985a) and the NTP study given in Table 4-3 of EPA (1986). W is $(78/90)(5/7)(90/104)^{\frac{3}{4}}$ for mice in the NCI study, and W is (5/7) for mice and rats in the NTP study. F equals 0.80 and 0.54 for mice and rats, respectively.

[d] These values for the NTP mouse and rat studies are derived from information in Tables A-4 and A-3, respectively, in EPA (1986). Metabolized doses appear to be low for mice (by a factor of about 3) due to the underestimated mouse alveolar ventilation rate (EPA, 1986; see p. 4-15 and p. A-17).

[e] Derived from the values for amount metabolized ("AM" in mg/day) given on page 6 of Reitz and Nolan (1986).

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corresponding incidence of mononuclear-cell leukemia (MLK), the only tumor type observed to be significantly increased in rats at either the low or high dose levels. Again, the incidence values in the denominators appearing in Table 5-1 represent animals surviving at least until the appearance of the first MLK (which was at week 53 for males and at week 60 for females (NTP, 1986)).

The amount of PCE metabolized in the NTP study can be estimated by fitting the Michaelis-Menten equation to the data obtained from the metabolism study in Sprague-Dawley (SD) rats conducted by Pegg et al. (1979). This assumes F344 and SD rats metabolize PCE similarly. In the Pegg and associates study, rats exposed via inhalation to 10 or 600 ppm of radiolabeled PCE for 6 hours were found to have metabolized a total of 1.87 and 36.4 mg/kg of PCE, respectively, by 72 hours post exposure. Of these totals, 1.10 (or 59%) and 18.2 (or 50%) mg/kg, respectively, were in the form of urinary metabolites. Thus, both urinary and total PCE metabolite production reportedly demonstrated saturable kinetics that may be represented by Equation 5-1. When only 2 dose-response points, say D_1, M_1 and D_2, M_2, are available, as in the data from Pegg et al., the corresponding Michaelis-Menten parameter estimates are completely specified by the following equations:

$$V_{max} = \frac{D_2 - D_1}{\frac{D_2}{M_2} - \frac{D_1}{M_1}} \quad \text{and} \qquad (5\text{-}4)$$

$$K_m = \frac{M_2 - M_1}{\frac{M_1}{D_1} - \frac{M_2}{D_2}} \qquad (5\text{-}5)$$

Thus, V_{max} and K_m are estimated to be 24.6 mg/kg and 214 ppm based on the urinary metabolite data for a 6-hour exposure to PCE, and 53.0 mg/kg and 273 ppm based on the corresponding total metabolite data (Pegg et al., 1979). In its updated PCE potency assessment, the EPA used the former values based on urinary metabolism to derive the total metabolized doses for the NTP (1986) rat inhalation study (EPA Draft, 1986). The CDHS estimates of V_{max} and K_m are based on the total amount of metabolites generated by rats inhaling PCE as measured by Pegg et al. (1979). The V_{max} values expressed above in mg/kg of metabolites produced following a single 6-hour exposure were also used to estimate corresponding steady-state values (in mg/kg-d) for a repeated exposure of 6 hours/day.

Before estimating the rate of metabolite formation for the 1986 NTP rat bioassay, adjustments must be made to account for the interrupted exposure pattern (5 days/week) used in the NTP (1986) rat inhalation study, and to account for the fact that the rats used by Pegg et al. (1979) were lighter in weight compared to those used in the NTP study. The weight differences can be expected to result in corresponding differences in metabolic capacity. The approach used by Lawrence Livermore National Labs (and used herein) takes into account these differences in animal weight.

In the context of pharmacokinetic modeling, physiological parameters such as maximum enzymatic reaction rates and related metabolic clearance rates are generally assumed to vary with basal metabolic rate in proportion to body surface area (or, approximately, to body weight raised to the two-thirds power), rather than to body weight per se (Gehring et al., 1978; Dedrick and Bischoff, 1980; Anderson et al., 1980; Andersen et al., 1980; Calabrese,

1983; Ramsey and Andersen, 1984; EPA, 1985a; EPA Draft, 1986; NAS, 1986). Accordingly, given an estimated V_{max} in mg/hour for an animal of weight w_1, the corresponding predicted value for animals of weight w_2 would be $V_{max}(w_2/w_1)^{2/3}$ or, for V_{max} expressed in mg/kg-hour, $V_{max}(w_1/w_2)^{1/3}$. That is, a heavier animal would be expected to metabolize less per unit body weight than a lighter one in a given amount of time.

In contrast, the value of the Michaelis-Menton constant, K_m, for a given compound is generally assumed to be independent of body size (in the absence of data indicating otherwise) when this constant is expressed as the reactant concentration in units mg/L blood (Ramsey and Andersen, 1984; EPA Draft, 1986; NAS, 1986). Since blood weight is proportional to body weight for animals of widely varying weights (Adolph, 1949; Dedrick and Bischoff, 1980), the independence of K_m and body size should also be expected to hold for K_m values expressed in terms of mg/kg body weight. Under this assumption, however, apparent K_m values expressed in terms of an inhaled air concentration (e.g., ppm), as opposed to a blood concentration, would not be expected to be constant for animals of widely varying size unless pharmacokinetic steady-state conditions applied. Upon initial exposure or after an exposure of short duration (relative to the half-life of metabolism/elimination), the maximum rate at which an inhaled toxicant reaches an organ is related to the rate of pulmonary uptake. Since weight-normalized breathing volume decreases as body weight increases, an apparent inhalational K_m in ppm for animals of a given weight is expected to be higher for heavier animals (Anderson et al., 1980). That is, the heavier the animal the higher the air concentration required to achieve a specified target organ concentration (corresponding to the actual K_m).

Respiration rate is observed to be proportional to body surface area (or, approximately, to body weight to the two-thirds power) (Guyton, 1947; Adolph, 1949; EPA, 1980b; Anderson et al., 1983; Calabrese, 1983). Accordingly, for brief, nonsteady-state and/or discontinuous exposure scenarios such as those present in the Pegg et al. (1979) and Schumann et al. (1980) metabolic studies and (to a certain extent) in the 1977 NCI and the 1986 NTP bioassays, the assumed corresponding predicted value of Km for animals of weight, w_2, would be $K_m\ (w_2/w_1)^{1/3}$ ppm, given an estimated apparent inhalational K_m in ppm for an animal of weight, w_1. Under this assumption, lifetime TWA equivalent values for total PCE metabolized dose, M, in the 1986 NTP rat study is derived from corresponding values of applied dose, D, using the following modification of Equation 5-3:

$$M = \frac{D\ V_{max} \left[\frac{w_1}{w_2}\right]^{1/3}}{D + K_m \left[\frac{w_2}{w_1}\right]^{1/3}} \times \frac{5}{7} \qquad (5\text{-}6)$$

where M is in mg/kg-d and D is in ppm, V_{max} is 52.982 mg/kg-d and K_m is 273.32 ppm, and in which w_1 and w_2 are the weights of the Pegg et al. (1979) rats (0.25 kg) and the 1986 NTP rats (0.44 or 0.32 kg), respectively. Values of D and M derived from Equation 5-6 for the 1986 NTP bioassays for male and female rats are listed in Table 5-2, along with corresponding tumor-incidence data.

NTP (1986) Mouse Study: Inhalation

In the 1986 NTP study, groups of fifty 8- to 9-week-old male and female B6C3F1 mice were exposed to PCE by inhalation at 0, 100, or 200 ppm for 6

hours/day, 5 days/week over 2 years (NTP, 1986). These exposure concentrations appear in Table 5-1, along with the corresponding incidence data for hepatocellular carcinoma (HC) and hepatocellular adenoma or carcinoma (HAC), the only tumor types observed to be significantly increased in the mice at either the low- or high-dose levels. Again, the incidence-rate denominators appearing in Table 5-1 represent animals surviving at least until the appearance of the first HC (which was at week 60 for males and week 67 for females; cf. NTP, 1986). Since one female mouse was missexed in the control group, the tumor-incidence-rate denominator used for that group appearing in Table 5-1 is 44 (NTP, 1986). In a draft form of its updated carcinogenic risk assessment for PCE, the EPA used a denominator value of 46 for the control female mice (EPA Draft, 1986). The latter value is not consistent with the data published by the NTP (1986).

Lifetime TWA values for the total metabolized dose (M) of PCE for the 1986 NTP mouse bioassay are derived from Equation 5-6. The mouse data of Schumann et al. (1980) on PCE metabolism following inhalation or injection provide insufficient information for estimating V_{max} and K_m using Equation 5-6, because only one exposure level was used for each route. The value of V_{max} for the total amount of metabolites formed was assumed to be 170 mg/kg-d, estimated from the PCE oral administration data of Buben and O'Flaherty (1985). The value of K_m was estimated from the rat inhalation data of Pegg et al. (1979) and was calculated to be 126 ppm ($= 273.32 \times (w_1/0.25 \text{ kg})^{1/3}$) where w_1 represents the body weight of one mouse and 0.25 kg is the approximate weight of one rat in the study by Pegg et al. (1979). The values for mice of differing weights were estimated using Equation 5-6, where w_1 and w_2 are the weights of the mice from the Schumann et al. study

(0.0245 kg) and the 1986 NTP mice (0.037 or 0.032 kg). One of the assumptions made in using this approach is that (lacking evidence to the contrary), there are no differences in the metabolism of PCE between oral and inhalation exposure. Thus, after scaling for differences in body size, it is possible to estimate the V_{max} and K_m for PCE metabolism based on both a mouse oral study and a rat inhalation study.

The Schumann et al. (1980) data on metabolism following PCE inhalation by mice for 6 hours at 10 ppm may be used to check the estimates of V_{max} and K_m. They found that a total of 14.5 mg/kg PCE was metabolized by mice within 72 hours after being exposed to 10 ppm PCE for 6 hours. The 14.5 mg/kg PCE value is 16% greater than the predicted value of 12.5 mg/kg using Equation 5-6 with a D of 10 ppm, a V_{max} of 170 mg/kg, and a K_m of 126 ppm. For this case w_2 and w_1 are equivalent and the factor 5/7 relating to the NTP exposure scenario is deleted.

Results of Metabolized Dose Calculations

Metabolized PCE doses calculated here by Lawrence Livermore National Labs (LLNL) are summarized and compared in Table 5-2 to values calculated by the EPA (1985a; 1986) and by Reitz and Nolan (1986) using alternative approaches to metabolic analysis. Their values have been adjusted to correspond to a lifetime TWA total metabolized dose.

For the NTP inhalation study, the metabolized doses estimated for mice in either exposure group range 5-fold. However, the actual range may be smaller, due to an underestimate of the mouse alveolar ventilation rate by

the EPA (1986), which would reduce the estimate of the amount of PCE metabolized (Table 5-2). This range of a factor of 5 indicate the magnitude of some of the uncertainties involved in the modeling and parameter selection from limited data.

CARCINOGENIC POTENCY EXTRAPOLATION BASED ON ANIMAL BIOASSAY DATA

Carcinogenic "potency" refers to a quantitative expression of increased tumorigenic response per unit dose at very low dose levels. The following carcinogenic potency assessment is based on a quantitative analysis of animal bioassay data sets, assuming that PCE is carcinogenic to both animals and humans at low environmental dose levels. The rationale for using this assumption for PCE is well-established and is discussed in detail elsewhere (EPA, 1980; Anderson et al., 1983; CDHS, 1985). Arguments against using this assumption for PCE focus on the possibility that the carcinogenicity of PCE in bioassays conducted at high doses may be caused primarily by increased cellular and/or subcellular proliferation (i.e., by tumor promotion or some epigenetic mechanism, rather than by initiation or some genotoxic mechanism), and that associated dose-response relationships contain a threshold below which carcinogenic effects do not occur (e.g., Schumann et al., 1980; Stott et al., 1982; Buben and O'Flaherty, 1985; Elcombe et al., 1985; Green and Prout, 1985; Prout et al., 1985; Mirsalis et al., 1985).

Low-dose potency extrapolation from dichotomous tumor-response information in selected animal-bioassay data sets was performed as described by Crump

and Watson (1979) to numerically fit parameters q_i of the multistage dose-response extrapolation model:

$$\text{Probability of Cancer} = R = 1 - e^{-\sum_{i=1}^{g} q_i d^i} \quad \text{with } q_i \geq 0 \text{ for all } i. \qquad (5\text{-}7)$$

in which g is the number of exposed groups in the bioassay, and d is the dose level at which the risk function is evaluated. Following EPA, (1980), Anderson et al. (1983) and CDHS (1985), q_1 or some upper statistical confidence bound is defined as the low-dose "potency" parameter since at low doses an estimated extra risk may be obtained by multiplying q_1 by the dose. The input to this program for each data set consisted of the values for total lifetime TWA applied dose, A, or metabolized dose, M, (in mg/kg-d) and corresponding tumor incidence data given in Table 5-1. For each data set GLOBAL79 was used to calculate a maximum likelihood estimate (MLE) and a one-tailed 95% upper confidence limit (UCL) for the linear parameter q_1. The MLE estimates of q_1 that relate A and M to predicted tumor risk are denoted $q_1(A)$ and $q_1(M)$, respectively, and the corresponding UCL estimates are denoted $q_1^*(A)$ and $q_1^*(M)$, respectively. When dose is given in units of mg/kg-d, the units of q_1 and q_1^* are $(mg/kg\text{-}d)^{-1}$. Calculated values of $q_1(A)$, $q_1^*(A)$, $q_1(M)$ and $q_1^*(M)$ corresponding to each of the 8 bioassay data sets considered here are given in Table 5-3.

The male and female rat potency values of 0.064 and 0.04 $(mg/kg\text{-}d)^{-1}$ calculated from the 1986 NTP rat-leukemia data are somewhat larger than those calculated from both the 1977 NCI and the 1986 NTP mouse data. The maximum potency value of 0.064 $(mg/kg\text{-}d)^{-1}$ is about 9 times larger than the

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smallest calculated potency value of 0.0073 $(mg/kg\text{-}d)^{-1}$ derived from HC incidence data for female mice in the 1986 NTP bioassay. In contrast, the calculated UCL potency values corresponding to the applied dose approach ($q_1^*(A)$) span only a 2-fold range (0.0026 to 0.0064 $(mg/kg\text{-}d)^{-1}$). Thus, the metabolized dose tends to indicate a different sensitivity between rats and mice while the applied dose indicates a more similar susceptibility to the carcinogenicity of PCE.

Time-to-tumor data are readily available for the NTP mouse and rat bioassay data, as well as for the NCI mouse bioassay data. Thus, it is possible to use a more complex, time-dependent version of the multistage model that takes into account the observed differential survival of control and exposed bioassay groups. In the NTP bioassays, survival was only slightly decreased in the PCE-exposed groups, so the multistage time-to-tumor model is not used as the basis for potency extrapolation in the present analysis. However, for comparative purposes a time-dependent version of the multistage model, WEIBULL82 (Howe and Crump, 1983; Crump and Howe, 1984) was used to derive potency estimates from the NCI and NTP bioassay data. These potency values are given in the last two columns of Table 5-3. Note that the time-dependent potency values are similar to values based on the time-independent form of the multistage model (also shown in Table 5-3). These time-dependent values differ from time-independent values by no more than a factor of 1.5. The largest potency value, 0.071 $(mg/kg/day)^{-1}$ for MLK in male rats, represents an increase of about 11% over the corresponding q_1^*.

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TABLE 5-3

CANCER POTENCIES ESTIMATED FROM SELECTED DATA SETS

Data Set	Administered Dose		Metabolized Dose: Time-Independent Analysis		Metabolized Dose: Time-Dependent Analysis	
	MLE $q_1(A)$	95% UCL $q_1^*(A)$	MLE $q_1(M)$	95% UCL $q_1^*(M)$	MLE $q_1(M)$	95% UCL $q_1^*(M)$
Oral NCI (1977) B6C3F1 Mice						
Male - Hepatocellular Carcinoma	0.0046	0.0064	0.024	0.032	-----	-----
Female - Hepatocellular Carcinoma	0.0023	0.0030	0.017	0.022	-----	-----
Inhalation NTP (1986) B6C3F1 Mice						
Male - Hepatocellular carcinoma	0.0025	0.0035	0.011	0.015	0.012	0.022
Female - Hepatocellular carcinoma	0	0.0028	0	0.0073	0	0.0072
Male - Hepatocellular adenoma/ carcinoma	0.0043	0.0059	0.0062	0.024	0.0032	0.026
Female - Hepatocellular adenoma/ carcinoma	0.00044	0.0039	0	0.0098	0.0088	0.012
NTP (1986) F344/N Rats						
Male - Mononuclear-cell leukemia	0.0022	0.0040	0.037	0.064	0.043	0.071
Female - Mononuclear-cell leukemia	0.0015	0.0026	0.024	0.040	0.024	0.040

MLE = maximum-likelihood estimate; 95% UCL = one-tailed 95% upper confidence limit.

CARCINOGENIC POTENCY IN TERMS OF HUMAN APPLIED DOSE

Assuming that the above calculated values of $q_1^*(M)$ are adequate to approximate expected tumor incidence among animals subjected to very low levels of effective dose M, three issues need to be addressed: first, the application these calculated potency values across exposure routes; second, the extrapolation of potency from animals to humans; and third, determination of the relationship between applied dose, D, and metabolized dose, M, for humans. Each of these issues will be addressed in turn.

Exposure Route

Various physiological processes, such as the "first pass effect" involving liver-mediated activation or detoxification, may result in differing values of metabolized dose, given the same applied dose but administered via different exposure routes. If biotransformation of PCE to a reactive metabolite is solely responsible for the carcinogenic effects of PCE, the actual exposure route and administered dose may not be as important as the determination of the metabolized dose. Different routes of exposure can allow differing amounts of PCE to reach the sites of metabolism or the target tissues, and thus effect the calculation of the metabolized dose. In this document it is assumed that a given dose of PCE is equipotent regardless of exposure route, as long as the distribution of this dose among susceptible target tissues is not affected by the exposure route. Comparison of the potency estimates for both the applied dose and the metabolized dose for the mouse gavage study and the mouse inhalation study indicate that the route of exposure may not be an important factor for PCE

(Table 5-3) (NCI, 1977; NTP, 1986). However, for the purposes of risk assessment of inhaled PCE, the range of the inhalation studies will be used.

Interspecies Dose Equivalence

Following the suggestion of Mantel and Schneiderman, the EPA and the California Department of Health Services assume that mg/(surface area) is an equivalent measure of lifetime TWA dose between species for carcinogens (Mantel and Schneiderman, 1975; EPA, 1980b, 1984a; Anderson et al., 1983; CDHS, 1985). Specifically, for purposes of carcinogen-risk assessment, the EPA assumes that a TWA lifetime dose (expressed as a dose rate in units of $mg/kg^{2/3}$) is equivalent between species, since surface area is roughly proportional to the 2/3rd power of body weight. Given this assumption and a lifetime metabolized dose rate for an animal of M_a mg/kg-d, then the equivalent human TWA dose rate would be M_a/f, where the dose-equivalence factor f is here given by

$$f = \left[\frac{W_a}{W_h}\right]^{1/3} \qquad (5\text{-}8)$$

in which W_h and W_a are the weights of humans (generally assumed to be 70 kg) and the test animal, respectively.

In the absence of definitive empirical data, however, it is simply not known whether a mg/(surface area) or a mg/kg interspecies dose-extrapolation assumption better reflects reality in the context of extrapolating tumor-response data in animals to anticipated response in humans. Existing data

do not rule out either approach. For comparative purposes extrapolation of potency values from animals to humans is here carried out using both a dose per body weight (BW) and a dose per body surface area (SA) extrapolation method.

Human Metabolism

To estimate the carcinogenic potency of PCE in humans from $q_1^*(M)$, additional assumptions need to be made regarding human metabolism. The assumptions and extrapolations reveal additional uncertainties to the potency calculation when the metabolized dose is used.

Several studies have examined the metabolism of PCE in humans following a controlled inhalation exposure to this compound. As discussed in Section 2, several PCE metabolites have been identified in human urine, the major one being trichloroacetic acid (TCA). There is a possibility that other metabolic products of PCE in humans have not been identified. Some human exposure studies have sought to identify total urinary trichloro-compounds produced after inhalation exposure to PCE using a nonspecific, Fujiwara-reaction analytical method (e.g., Ikeda and Imamura, 1973), but the actual products measured by this technique are in doubt (EPA, 1985a). The studies used here to estimate the extent of human PCE metabolism consist of four relatively recent studies that quantified only the cumulative amount of TCA produced for an observation period less than one estimated half-life (typically about 3 days), during and after a controlled PCE inhalation exposure (Ogata et al., 1971; Fernandez et al., 1976; Monster et al., 1979; Bolanowska and Golacka, 1972).

Before reviewing the above studies, three issues concerning how the results of these studies may be used to estimate the degree to which PCE in humans is metabolized during a steady-state (continuous) exposure will be discussed. These issues are: the excretion half-life of PCE in humans, estimation of total PCE metabolism and use of continuous versus peak exposures.

Excretion Half-life in Humans

The first of these issues involves the decay half-life of urinary metabolite formation. That is, the time required for half of the TCA formed from PCE metabolism to be excreted in the urine. Because the metabolism rate of PCE in humans is very slow, it is unlikely that the studies discussed herein were actually able to quantitatively determine the total amount of PCE metabolized following exposure. (Exposure time, t, for each of the studies discussed is listed in Table 5-4.). To extrapolate from the existing data, the remaining TCA produced after the end of urine collection had to be approximated. This was done by integrating the TCA production rate as a function of time from the termination of collection to time equals infinity, where this function is assumed to represent a simple first-order decay process. This is the same assumption used by the EPA (EPA, 1985a; EPA 1986) in assessing the results of the Bolanowska and Golacka (1972) human-exposure study. The EPA assumed a half-life for urinary TCA excretion of 100 hours, apparently based on a presumed empirical range of approximately 65 to 144 hours for this process (EPA, 1985a, where the TCA decay half-life is stated to be 144 hours). The lower end of this range is derived from studies indicating a terminal decline in TCA excretion with a half-life of

from 65 to 90 hours in volunteers exposed to 72 and 144 ppm PCE for 4 hours (Monster et al., 1979). The upper value of 144 hours is derived from the study of Ikeda and Imamura (1973) as the mean of measured total urinary trichloro-compound decay half-lives of 13 subjects occupationally exposed to PCE, where the observed range was reported to be 123 to 190 hours. In this study, however, TCA itself was not measured, but total trichloro-compounds were measured using the nonspecific type of Fujiwara reaction method whose dependability has been questioned (EPA, 1985a). The values based on the studies by Monster and co-workers indicate that the rate of PCE release from adipose tissue, the most highly retentive tissue type for PCE, is an exponentially decaying function of time with a half-life of about 71.5 hours (Monster et al., 1979; Guberan and Fernandez, 1974). Thus, a value of 100 hours may overestimate the expected late-stage decay half-life of TCA excretion in humans. Accordingly, for the purpose of the metabolized dose analysis performed herein, a value of 75 hours was used as the presumed approximate late-stage TCA excretion half-life for humans.

Urinary Metabolites as a Fraction of Total Metabolites

The second issue addresses the uncertainties of estimating total metabolism of PCE strictly from TCA measurements. It involves developing the relationship in humans of total PCE metabolized to urinary metabolites, and estimating the proportion of TCA metabolites excreted in the urine as compared to total elimination by all routes. For the purposes of this analysis it was assumed that 58% of the metabolized dose was found in the form of urinary TCA following low levels of exposure to PCE. The value of 58% is the average fraction of total metabolites found in the form of

TABLE 5-4.

COMPARISON OF HUMAN PCE METABOLISM AFTER INHALATION EXPOSURES

	Administered Dose				Urinary metabolite[a]		Estimated total metabolites[b]				
Study	Exposure period (h)	Concentration (ppm)	Urine collection (h)	Inspired Dose[c] (mg)	U(T) (mg)	U(E) (mg)	M_t (mg)	M_6 mg/kg	M_p mg/kg	P[d]	P_{corr}[e]
Ogata et al., 1971 (n=4)	3	87	67	594.6	4.3	8.6	14.8	0.42	0.38	2.5	3.3
Fernandez et al., 1976 (n=2)	8	150	72	2734	24.6	35.4	61.0	0.65	0.63	2.2	3.5
Monster et al., 1979 (n=6)	4	72	70	656.1	6.0	10.5	18.1	0.35	0.31	2.8	4.0
Monster et al., 1979 (n=6)	4	144	70	1312	11.0	20.0	34.5	0.67	0.60	2.6	3.8
Bolanowska and Golacka, 1972 (n=2)	6	56.4	23.5	771.1	3.5	14	24	0.34	0.25	3.1	3.8
Weighted mean (weight = n, the sum of n = 20)										2.6	3.7
S.D. of mean										±0.05	±0.06
99% Upper (2-tailed) confidence limit of mean (df=19)										2.8	3.9

[a] U(T) = observed cumulative urinary metabolite (trichloroacetic acid only) production by any time T after exposure. See text for derivation of U(T) values. U(E) = estimated total urinary metabolites if collection period were extended to infinity.

[b] Estimated total metabolites produced if the monitoring period were extended so time = infinity.

M_t = total amount of metabolites formed.

M_6 = amount of metabolites formed in 6 hrs.

M_p = predicted total metabolite dose produced if the collection period were extended to infinity, and assuming that $M = D\,V_{max}/(D + K_m)$, where V_{max} = 8.099 mg/kg and K_m = 273.32 ppm.

[c] Assumes an alveolar ventilation rate of 5.6 L/min = 2.016 m^3/6·h, and 6.78 mg PCE/m^3 per ppm.

[d] P = the percent of respired dose that is metabolized.

[e] P_{corr} = where P is corrected to reflect a steady-state, low level exposure. The correction factor is based on equation 5-9.

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TABLE 5-5.

PREDICTED UPPER 95% UPPER CONFIDENCE LIMITS ON POTENCY (MG/KG-D) SUMMARY (ASSUMING HUMANS METABOLIZE 4% OF ABSORBED PCE).

Study species strain	Tumor type[a]	Sex and weight (kg)	Metabolized dose[b] - q_1^*(M) BW[d]	Metabolized dose[b] - q_1^*(M) SA[e]	Human applied dose[c] - q_1^*(A) BW[d]	Human applied dose[c] - q_1^*(A) SA[e]
NCI, 1977 Mice B6C3F1	HC	M 0.030	0.032	0.42	0.0013	0.017
		F 0.025	0.022	0.31	0.00089	0.012
NTP, 1986 Mice B6C3F1	HC	M 0.037	0.015	0.19	0.00060	0.0074
		F 0.032	0.0073	0.095	0.00029	0.0038
NTP, 1986 Mice B6C3F1	HAC	M 0.037	0.024	0.30	0.00096	0.012
		F 0.032	0.0098	0.13	0.00039	0.0051
NTP, 1986 Rats F344/N	MLK	M 0.44	0.064	0.35	0.0026	0.014
		F 0.32	0.040	0.24	0.0016	0.0096

[a] HC = hepatocellular carcinoma, HAC = hepatocellular adenoma or carcinoma, MLK = mononuclear-cell leukemia.

[b] Human equivalent lifetime, time-weighted-average metabolized dose, M, in mg/kg-d.

[c] Human equivalent lifetime, time-weighted-average applied dose, D, in mg/kg-d, is here assumed to be equal to M/0.04 when D is very small; thus, $q_1(D) = 0.04q_1(M)$ for very small D.

[d] BW = Body Weight inter-species dose extrapolation method; equivalent doses assumed to be in mg/kg, so $M_{human} = M_{animal}$.

[e] SA = Surface Area interspecies dose extrapolation method: equivalent doses assumed to be in $mg/kg^{2/3}$, so $M_{human} = M_{animal}[(\text{animal weight})/70\ kg]^{1/3}$.

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urinary metabolites produced by rats exposed to 1 mg/kg PCE by intubation (yielding 57.1% urinary metabolites) or 10 ppm PCE for 6 hours (yielding 58.9% urinary metabolites), in the study by Pegg et al. (1979). Rat, as opposed to mouse, data are used as the basis for this assumption only because of the greater similarity in body weight between rats and humans. However, this assumption may greatly underestimate the fraction of PCE metabolized in humans. Since humans produce lower levels of trichloro urinary metabolites than do rats, they may produce more nonurinary metabolites or more urinary metabolites that are not trichloro- compounds. As indicated in studies below and in Section 2, only TCA has been used to estimate urinary excretion of PCE metabolites. The production of other urinary metabolites in humans, although documented, has not been adequately investigated as to their relative importance in the metabolism of PCE.

Continuous Versus Peak Exposures

The third and final issue concerns the assumptions about a continuous human-exposure scenario. Results of the human studies considered below were compared to predictions of PCE metabolism based on extrapolation from the data on PCE metabolism in rats exposed to 10 or 600 ppm PCE for 6 hours (Pegg et al., 1979), using the assumptions made in Equation 5-6. The V_{max} calculated from this rat study was 53.0 mg/kg. Using Equation 5-6, the equivalent human V_{max} would be the latter value multiplied by $(0.25/70)^{1/3}$, or 8.10 mg/kg for a 6-hour exposure to PCE. Similarly, the corresponding rat inhalational apparent K_m value of 273 ppm would be divided by $(0.25/70)^{1/3}$ to yield an equivalent (initial-exposure) human Michaelis-Menten constant of 1790 ppm. Using these parameter values, the predicted

metabolized dose, M (in mg/kg), as a function of applied dose, D (in ppm), is presented in Table 5-4 for each of the various studies considered below.

The brief exposure periods used in the human experiments were conducted at relatively high concentrations compared to the average ambient concentrations of PCE identified in air. At lower doses, a greater percent of the dose is likely to be metabolized. Using the Michaelis-Menten relationship, the maximal metabolized dose per unit applied dose occurs as D approaches 0 in the equation $M = D(V_{max}/K_m)$. Thus, an estimate of the maximum factor by which the ratio M/D is increased at very low doses is given by

$$\lim_{D \to 0} \frac{M_0}{M} = \frac{\left[D \dfrac{V_{max}}{K_m} \right]}{\left[\dfrac{D \; V_{max}}{D + K_m} \right]} = 1 + \frac{D}{K_m}. \qquad (5\text{-}9)$$

This factor is used in Table 5-4 to adjust the percent, P, of respired dose, I, that is metabolized to yield a new percentage value, P_{corr}, which is corrected to reflect the steady-state, very low-level exposure conditions that relate to the human environmental exposure scenario being modeled. In this factor, K_m was assumed to be 273 ppm, based on the Pegg and associates (1979) metabolism data (this value was not adjusted upward to account for initial rapid uptake prior to steady-state, since P_{corr} is meant to reflect steady-state exposure conditions).

Having addressed these issues and assumptions regarding human metabolism, the four studies used for calculating the rate and extent of human PCE metabolism will now be reviewed.

Ogata and Co-workers (1971)

Urinary excretion of TCA was measured by Ogata and co-workers in four volunteers exposed to 87 ppm PCE for 3 hours (Ogata et al., 1971). From the graphical information presented in this study, the amount of TCA excreted over the 67-hour collection period was calculated from the area under the time versus TCA excretion-rate curve, and found to be about 4.3 mg. This value is presumed to be excess excretion over background, but a pre-exposure TCA excretion rate was not provided in this study. At 67 hours, the observed excretion rate was about 0.040 mg/hour, so that remaining excretion from that time on is estimated to be (0.040 mg/hour x 75 hours)/ln(2) = 4.3 mg. Total metabolized dose, M_3, (assuming that urinary metabolites in humans represent 58% of total metabolites, as was seen in the rat study by Pegg et al., 1979), from this 3-hour exposure was (4.3 + 4.3)/0.58 = 14.8 mg, which when multiplied by (6/3) yields an approximate equivalent 6-hour metabolized dose, M_6, of 0.42 mg/kg (assuming a 70-kg average subject weight).

Fernandez and Co-workers (1976)

Urinary excretion of TCA was measured by Fernandez and colleagues in two volunteers exposed to 150 ppm PCE for 8 hours (Fernandez et al., 1976). This study reported an average total TCA excretion of 24.6 mg over the 72-hour collection period applied. Urine was not collected during the exposure period, thus the total metabolites produced were underestimated. During the period from 48 to 72 hours post-exposure the reported TCA excretions for the 2 subjects were 3.63 and 3.70 mg, equivalent to an average excretion rate of

about 0.15 mg/hour. It was estimated from the data that by 72 hours the average excretion rate had declined to about 0.10 mg/hour, so that remaining excretion from that time on is estimated to be (0.10 mg/hour x 75 hours)/ln(2) = 10.8 mg. Total metabolized dose, M_8, (assuming a proportion similar to rats), from this 8-hour exposure was (24.6 + 10.8)/0.58 = 61.0 mg, which multiplied by (6/8) yields an approximate equivalent 6-hour metabolized dose, M_6, of 0.65 mg/kg (again assuming a 70-kg average subject weight).

Monster and Co-workers (1979)

Urinary excretion of TCA in the Monster and colleagues study was measured in six volunteers at rest exposed to 72 ppm PCE for 8 hours and again in these same volunteers at a later date exposed at rest to 144 ppm PCE for 4 hours (Monster et al., 1979). (Data from this study that were obtained from volunteers subjected to physical activity routines are not used for the present analysis). From the published graphical urinary excretion information, it was estimated that average total TCA excretions of 6.0 and 11.0 mg were observed among the 72 ppm and 144 ppm exposure groups, respectively, over the 70-hour collection period applied. (It appears that urine was not collected during the exposure period. These estimates take into account the background 0.025 mg/h TCA excretion rate observed in this study.) During the 24-hour period from 46 to 70 hours post-exposure, the reported TCA excretions were about 1.0 and 2.0 mg (and fairly constant over the period 22- to 70-hours post-exposure) for the 72 ppm and 144 ppm exposure groups, equivalent to average terminal excretion rates of about 0.042 and 0.083 mg/hour. Thus, the corresponding remaining excretions from

70 hours on are estimated to be (0.042 mg/hour x 75 hours)/ln(2) = 4.8 mg and (0.083 mg/hour x 75 hours)/ln(2) = 9.0 mg, respectively. Corresponding total metabolized doses, M_4, from these 4-hour exposures are (6.0 + 4.5)/0.58 = 18.1 mg and (11.0 + 9.0)/0.58 = 34.5 mg, respectively, which multiplied by (6/4) yields corresponding approximate equivalent 6-hour metabolized doses, M_6, of 0.35 and 0.67 mg/kg (using the reported average subject weight of 77 kg).

Bolanowska and Golacka (1972)

In evaluating the human metabolism study of Bolanowska and Golacka (1972), the EPA assumed that five subjects were exposed to 390 mg/m^3 PCE for 6 hours and were followed for 20 hours; the EPA did not take into account the background TCA excretion rates observed in the study. Actually, urinary excretion of TCA was measured from only 2 volunteers exposed to 391 and 374 mg/m^3 PCE for 6 hours (interspersed with two 30-minutes "rest" periods). Urine from these subjects was collected for a total of 22 and 25 hours, respectively, including the exposure time. Background TCA excretion rates for the two subjects are given as approximately 0.035 and 0.010 mg/h. Taking these background rates into consideration, it is estimated from the graphical urinary excretion information given in this study that average total TCA excretions of 2.3 and 4.7 mg were observed from these subjects over the (approximately) 23.5-hour average collection period. During the final hours of urine collection, excretion rates for these subjects were approximately 0.045 and 0.15 mg/hour (where 0.15 mg/hour represented a weighted average of 9 hours at 0.14 mg/hour followed by 3 hours at 0.19 mg/hour). Thus, the corresponding remaining excretions from about 24 hours

on are estimated to be (0.045 mg/hour x 75 hours)/ln(2) = 4.9 mg and (0.15 mg/hour x 75 hours)/ln(2) = 16.2 mg. Corresponding total metabolized doses, M_6, from these 6-hour exposures are thus 12 mg ((2.3 + 4.9)/0.58) and 36 mg ((4.7 + 16.2)/0.58), yielding an average value of about 0.34 mg/kg for this study (assuming an average subject weight of 70 kg).

Metabolic Parameters Estimated from Different Human Data Sets

Table 5-4 summarizes the metabolic data obtained from the studies discussed herein and presents comparisons between the predicted and the observed total metabolite dose for each experiment. The internal consistency of the general approach used in the metabolic analyses is supported by the observation that the predicted total metabolite doses for a 6-hour exposure to PCE for humans are quite similar to the corresponding empirically derived values, M_6, as shown in Table 5-4 (correlation coefficient $r = 0.99$, degrees of freedom = 3, $p \leq 0.01$).

To calculate the average percentage, P, of PCE metabolized on the basis of the studies considered here, the inspired dose I had to be estimated from the PCE concentrations specified in these studies. Although PCE retention values were given in the Ogata et al. (1971) study, the basis for their calculations was not provided. Fernandez and associates used an estimated alveolar ventilation rate of 5.6 L/minute (equivalent to 340 L/hour or approximately 4.8 L/kg-hour for a 70 kg person) in their calculation of retained dose, a value close to those currently used in proposed PB-PK models for human metabolism (Fernandez et al., 1976; EPA Draft, 1986; NAS, 1986). The 5.6 L/minute value is also close to the effective value used by

Monster and co-workers, who assumed that alveolar retention was approximately equal to 60% of the minute volume (which averaged 10 ± 1.8 L/minute among their 6 subjects) (Monster et al., 1979).

To calculate inspired dose, I, in mg as a function of applied concentration in ppm for the purpose of the present analysis, the alveolar ventilation rate of 5.6 L/minute is assumed, and 1 ppm PCE = 6.78 mg/m^3. This 5.6 L/minute estimate has been used in several pharmacokinetic models, but underestimates the average breathing rate of humans (20 L/minute) by almost 3-fold. The resulting values of P for the 5 data sets range from about 2 to 3%, with a weighted average of 2.6%, where the values of n, the number of people studied in each experiment, are the weights (see Table 5-4). On the basis of the predictive model adjusted for continuous human exposure discussed above, corrected values, P_{corr}, for the average percent PCE metabolized range from about 3 to 4%, with a weighted average of 3.7%. The upper 99% confidence limit on the average P_{corr} was calculated to be approximately 4%, assuming a normal error distribution of the mean and 19 degrees of freedom associated with the sample estimate (i.e., 20 persons studied, minus one). The UCL was approximated in this way because needed data for each individual studied could not be obtained for most of the studies considered. The calculated UCL value of 4% is also equal to the highest value of P_{corr} calculated here, derived from the study of Monster et al. (1979).

It should be emphasized here that these results are based on relatively brief experimental exposures to relatively high concentrations of PCE in air. Linear extrapolation of animal studies from high experimental exposure

concentrations to low ambient concentrations suggests that essentially 100% of the PCE may be metabolized at ambient levels by mice and rats. At ambient levels humans would be expected to metabolize PCE to a much greater extent than that reported in brief, high exposure studies. The Pegg and associates inhalation (and oral) studies showed that for rats metabolism increases with decreasing PCE exposure (Pegg et al., 1979). In these studies, rats were exposed to either 10 or 600 ppm PCE for 6 hours. With a 60-fold decrease in concentration, there was a 2.7-fold increase in percent PCE metabolized. These acute exposure experiments were conducted at concentrations 10,000- to 100,000-fold greater than ambient levels (0.001 ppm). Assuming an inverse linear relationship between percent metabolism and concentration, rats and mice would be predicted to metabolize essentially 100% of the PCE at concentrations below 0.1 ppm. Similar estimates can also be made for humans by applying the relationship of percent metabolism and concentration established for rats. The fraction of applied dose metabolized in humans, based on measured urinary trichloro compounds is estimated to be 4%, based on human experiments where exposure concentrations averaged 102 ppm. This exposure concentration is 100,000 times greater than ambient levels. Using the same linear relationship between metabolism and exposure conditions described above, extrapolating from the limited human exposure data to ambient PCE concentrations implies that humans would be expected to metabolize more than 60% of the PCE absorbed. This 15-fold increase in the expected extent of PCE metabolism at ambient concentrations indicates some uncertainty in the use of the PCE pharmacokinetic data for risk assessment.

Using a PB-PK modeling approach, Bogen and McKone estimated that the maximum plausible rate of PCE metabolism in humans at steady-state for a given, extremely low PCE concentration (C_{in}) in air is a physiologically defined fraction (f_m^{**}) of the alveolar input rate, $C_{in}Q_a$ mg/hour, where Q_a is the alveolar ventilation rate in L/hour (Bogen and McKone, 1987). This fraction is defined by

$$f_m^{**} = \left[\frac{Q_a/Q_l}{P_b} + 1\right]^{-1} \qquad (5\text{-}10)$$

in which Q_l is the blood flow to liver (metabolizing) tissue in L/hour and P_b is the PCE blood/air partition coefficient for humans. This relationship reportedly holds for continuous, steady-state infusion by other exposure pathways as well. Note that Equation 5-10 assumes that the rate of PCE metabolism becomes infinite as PCE concentration in air approaches zero. Using the parameter specifications of $Q_a = 3.8Q_l$ and $P_b = 10.5$ taken from recent studies of PCE pharmacokinetics (Reitz and Nolan, 1986; Ward et al., 1987), it follows that for PCE, $f_m^{**} = 73\%$. Thus, the physiological upper bound on metabolism of inspired PCE is predicted to be near 73%, i.e., 0.7 $C_{in}Q_a$ at any given extremely low concentration C_{in}. Using a PB-PK approach and an analysis of the data of Ikeda and co-workers and Ohtsuki and colleagues on PCE metabolism among occupationally exposed humans, it was estimated that the actual fraction of PCE metabolized at steady-state for extremely low levels of PCE absorption (by any route) is likely to be between 2% and 50% (Ikeda et al., 1972; Ohtsuki et al., 1983; Bogen and McKone, 1987). This conclusion is consistent with predictions of other investigators who used dynamic PB-PK modeling (EPA Draft, 1986; Hattis et al., 1987).

PCE Carcinogenic Potency as a Function of Human Applied Dose (Taking PCE Metabolism Into Account)

To estimate the carcinogenic potency of PCE in humans for a given steady-state applied dose (in mg/kg-day) administered by ingestion or inhalation, the value of 4% derived above was used as the fraction of applied dose that is metabolized in humans. Under this assumption, extrapolated potency is reexpressed in Table 5-5 as a function of human applied dose for each bioassay data set considered here under both the body weight (BW) and surface area (SA) assumptions for extrapolating equipotent doses between species.

Using the BW approach, the calculated values of $q_1^*(M)$ (based on animal bioassay data) can be directly as estimates of human carcinogenic potency. That is, by this approach, a human metabolized dose in mg/kg has equal tumorigenic potency compared to an animal metabolized dose in mg/kg, regardless of body weight differences. Accordingly, the values of $q_1^*(M)$ appearing in Table 5-3 are repeated in Table 5-5, which summarizes the predicted tumorigenic potency of PCE to humans as calculated in this analysis based on the 8 bioassay data sets considered here. Corresponding values of $q_1^*(M)$ based on the SA approach are also listed in Table 5-5. The latter values range from 0.095 to 0.42 $(mg/kg\text{-}d)^{-1}$ (a 4.4-fold range) and so are somewhat more homogeneous than the $q_1^*(M)$ values based on the BW approach. The range of $q_1^*(M)$ values is reduced by a factor of about 2 substituting the SA for the BW approach (but note that the tumor incidences in control rats were much higher than those for mice, which influences potency calculations with the model used here). Using the SA approach, the

maximum $q_1^*(M)$ value is 0.42 $(mg/kg\text{-}d)^{-1}$ based on HC incidence in male mice in the 1977 NCI bioassay. This value is about 6.6 times greater than the largest value obtained using the BW approach.

Table 5-6 compares the 95% UCL potencies from Table 5-5 with corresponding values based on different approaches to calculating dose than the SSPK approach used to generate the potency values appearing in Table 5-5.

In interpreting the values presented in Table 5-6, 4 points should be kept in mind.

1) The EPA approach to the NCI bioassay data implies that following ingestion humans metabolize PCE similar to mice (the "EPAI" method in Table 5-6), whereas following inhalation exposure humans are assumed to metabolize a somewhat lesser amount of PCE than mice or rats (the "EPAR" method in Table 5-6) (EPA 1985a; NCI, 1977).

2) All approaches based on the use of metabolic data involving respiratory exposure to PCE (namely, the "EPAR", "EPPK", "RNPK", and "SSPK" methods referred to in Table 5-6) were adjusted to reflect a single assumption regarding human alveolar respiration. The alveolar ventilation rate (AVR), assumed here to be 5.6 L/minute, is the same value used by the "SSPK" method and explained above in the subsection dealing with the comparison of human PCE metabolism after inhalation. For reference, it is noted that the actual AVR's

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TABLE 5-6.

TUMORIGENIC POTENCY OF PCE: SUMMARY OF VALUES BASED ON DIFFERENT APPROACHES TO DOSE CALCULATION.

Study/ Species/ Sex	Tumor type[a]	Calc. method[b]	95% UCL potency[c] values: As a function of metabolized dose[d] (M) q_1^*(M) in (mg M/kg-d)$^{-1}$ BW[f]	As a function of metabolized dose[d] (M) q_1^*(M) in (mg M/kg-d)$^{-1}$ SA[g]	As a function of human applied dose[e] (A): q_1^*(D) (mg D/kg-d)$^{-1}$ BW[f]	As a function of human applied dose[e] (A): q_1^*(D) (mg D/kg-d)$^{-1}$ SA[g]
NCI, 1977 Mouse Male	HC	SSPK	0.032	0.42	0.0013	0.017
		EPAI	0.032	0.42	0.0064	0.085
		EPAR	0.032	0.42	0.00066	0.0088
		APPL	--	--	0.0064	0.085
Mouse Female	HC	SSPK	0.022	0.31	0.00089	0.012
		EPAI	0.022	0.31	0.0044	0.062
		EPAR	0.022	0.31	0.00046	0.0064
		APPL	--	--	0.0030	0.042
NTP, 1986 Mouse Male	HC	SSPK	0.015	0.19	0.00060	0.0074
		EPAR	0.018	0.22	0.00037	0.0046
		EPPK	0.048	0.59	0.0047	0.058
		RNPK	0.0099	0.12	0.00040	0.0049
		APPL	--	--	0.0035	0.043
Mouse Female	HC	SSPK	0.0073	0.095	0.00029	0.0038
		EPAR	0.0093	0.12	0.00019	0.0025
		EPPK	0.025	0.32	0.0024	0.031
		RNPK	0.0050	0.064	0.00020	0.0026
		APPL	--	--	0.0028	0.036
Mouse Male	HAC	SSPK	0.024	0.30	0.00096	0.012
		EPAR	0.029	0.36	0.00060	0.0074
		EPPK	0.077	0.95	0.0075	0.093
		RNPK	0.016	0.20	0.00064	0.0079
		APPL	--	--	0.0059	0.073
Mouse Female	HAC	SSPK	0.0098	0.13	0.00039	0.0051
		EPAR	0.013	0.17	0.00026	0.0034
		EPPK	0.033	0.43	0.0033	0.042
		RNPK	0.0067	0.087	0.00027	0.0035
		APPL	--	--	0.0039	0.051

TABLE 5-6. (Continued)

Study/ Species/ Sex	Tumor type[a]	Calc. method[b]	95% UCL potency[c] values: As a function of metabolized dose[d] (M) q_1^*(M) in (mg M/kg-d)$^{-1}$ BW[f]	As a function of metabolized dose[d] (M) q_1^*(M) in (mg M/kg-d)$^{-1}$ SA[g]	As a function of human applied dose[e] (D): q_1^*(D) (mg D/kg-d)$^{-1}$ BW[f]	As a function of human applied dose[e] (D): q_1^*(D) (mg D/kg-d)$^{-1}$ SA[g]
Rat Male	MLK	SSPK	0.064	0.35	0.0026	0.014
		EPAR	0.051	0.28	0.0016	0.0085
		EPPK	0.057	0.31	0.0056	0.030
		APPL	--	--	0.0040	0.022
Rat Female	MLK	SSPK	0.040	0.24	0.0016	0.0096
		EPAR	0.037	0.22	0.0011	0.0068
		EPPK	0.041	0.25	0.0040	0.024
		APPL	--	--	0.0026	0.016

[a] HC = hepatocellular carcinoma, HAC = hepatocellular adenoma or carcinoma. MLK = mononuclear-cell leukemia.

[b] Methods of calculation used are as follows (see text for more detailed discussion):
SSPK = simple steady-state pharmacokinetic method, corresponding values taken from Table 5-5.
EPAI = EPA-equivalent ingestion method: assumes that M = 20% of ingested PCE is metabolized
EPAR = EPA-equivalent respiratory method; assumes that for humans M = 0.0207A or M = 0.0306A for potencies based on mouse or rat data, respectively, and the alveolar ventilation rate (AVR) is 5.6 L/min.
RNPK = Reitz & Nolan-equivalent PB-PK method; assumes that for humans M = 0.04A and AVR = 5.6 L/min.
EPPK = EPA-equivalent PB-PK method; assumes that for humans M = 0.0977A and AVR = 5.6 L/min.
APPL = applied dose method; corresponding values taken from Table 7-1, where they are labelled q_1^*(A).

[c] 95% UCL = one-tailed 95% upper confidence limit.

[d] Human equivalent lifetime, time-weighted-average metabolized dose, M, in mg/kg-d, defined as a function of D as described above.

[e] Human equivalent lifetime, time-weighted-average applied dose, D (or A, in the context of the APPL method described above).

[f] BW = Body weight inter-species dose extrapolation method; equivalent doses assumed to be in mg/kg, so $M_{human} = M_{animal}$

[g] SA = Surface Area interspecies dose extrapolation method; equivalent doses assumed to be in mg/kg$^{2/3}$, so $M_{human} = M_{animal}[(\text{animal weight})/70\ \text{kg}]^{1/3}$.

used in the "EPPK" and "RNPK" approaches were 3.42 L/minute and 5.80 L/minute, respectively. No assumption regarding AVR was incorporated into the "EPAR" method, since that approach extrapolated directly from experimental human metabolic data to predicted risk based on animal-bioassay data for which metabolized doses were calculated (EPA 1985a). Standardization using the 5.6 L/minute AVR assumption was undertaken for the purpose of presenting meaningful comparisons in Table 5-6. It is emphasized that it would be incorrect to use any of the potency values associated with any of the respiratory methods just discussed (viz., the "EPAR", "EPPK", "RNPK", or "SSPK" methods) with an AVR (or other respiratory volume clearance rate) not equal to 5.6 L/minute.

3) Both the "EPAI" and "EPAR" methods were adjusted in the context of the 1977 NCI bioassay data sets to incorporate the partial lifetime factor of $(104/90)^3$ used in the "SSPK" method, again to facilitate a meaningful comparison of alternative potency calculations.

4) If the assumption is made that humans (and animals) metabolize some fraction, f_m (besides the 4% value assumed in this analysis), of all respired or ingested PCE at very low levels of applied PCE dose, the appropriate upper-limit potency value to use would be calculated as $q_1^*(D) = f_m q_1^*(M)$ based on the values of $q_1^*(M)$ in Table 5-6. Such alternative

assumptions are plausible, given that there are no animal or human experimental data that specifically address the issue of what fraction of an extremely small applied PCE dose (e.g., continuous exposure to one ppb in air) is metabolized.

A total of 112 alternative potency values appear in Table 5-6, with 48 values representing potency expressions, $q_1^*(M)$, in terms of metabolized dose and 64 values representing potency expressions, $q_1^*(D)$, in terms of applied dose (or PCE potentially available for uptake). The $q_1^*(M)$ values range from 0.0050 to 0.42 (mg M/kg-d)$^{-1}$, or an 84-fold range, and the $q_1^*(D)$ values range from 0.00019 to 0.085 (mg D/kg-d)$^{-1}$, or a 447-fold range. Clearly then, the model, study, route of exposure, and tumor type taken to calculate the appropriate dose in dose-response assessment is a significant factor in cancer-risk extrapolation.

Recommendation

The staff of CDHS recommends that the metabolized PCE dose not be used in the recommended range of risks for several reasons. The metabolized dose adjustment does not reduce the uncertainty of the final potency values primarily due to poor characterization of PCE metabolism in humans. The dose calculation uncertainties must be considered in addition to the general uncertainties of low dose extrapolation. The current data available on the quantity of PCE metabolized by different pathways across species remains uncertain. This uncertainty is evident in the very large range of the potencies estimated using different pharmacokinetic techniques. To summarize, the following concerns remain: 1) The metabolized dose

calculated by several methods, produces a 5-fold range of doses in male mice (19.5 mg/kg-day to 93.8 mg/kg-day, as shown in Table 5-2) corresponding to a greater than 10-fold range in human potency estimates for the same tumor site (see Table 5-6). 2) The metabolized dose approach assumes that the metabolic pathway leading to the production of the carcinogenic metabolite has been identified, but a cause-effect relationship has not been clearly established for any proposed pathway. 3) The metabolism of PCE in humans has not been clearly defined. Studies on metabolism have detected small amounts of two metabolites in urine. In humans, metabolism that produces urinary trichloro compounds accounts only for 1-2% of the administered dose following exposure to high concentrations, whereas 60-80% of the PCE inhaled is excreted unchanged through the lungs during the exposure. This implies that 20-40% of the absorbed PCE is stored (presumably in adipose tissue) and is slowly released over time. However, the high storage capacity of PCE in adipose tissue requires approximately 125 hours to reach steady-state equilibrium in adipose tissue upon continuous exposure. The slow release of PCE from adipose tissue results in a half-life in adipose tissue of approximately 91 hours. The difficulty in tracing the fate of these residual amounts of PCE has prevented the construction of a mass balance relationship between PCE absorbed and the PCE metabolized or exhaled unmetabolized by the lungs from human experiments. The residual PCE could be metabolized by the trichloro pathway over time, or by an unrecognized pathway producing metabolites such as CO_2 and oxalic acid that could not be easily recognized as products of metabolism without using radiolabeled compounds.

Uncertainty remains concerning the extent to which PCE is metabolized in animals and humans. Quantitative mass-balance studies of PCE metabolism during chronic (radiolabeled) PCE exposure conditions are available only for mice via ip-injection and drinking water exposure routes, while quantitative studies of urinary PCE-metabolite yield in chronically exposed mice are also available for the gavage exposure route. Such studies are not available for mice using an inhalation exposure route or for any exposure route using rats. This information necessitates the use of approximations of metabolized dose based on acute PCE exposures to interpret the results of chronic animal bioassays using inhalation exposures. In the context of extrapolating animal bioassay results to human risk predictions, further uncertainty arises from the current lack of any metabolic data on humans exposed to PCE under well-controlled, long-term experimental conditions (e.g., continuous exposures lasting more than 1 week) -- a data gap that is likely to persist. Even the interpretation of available data on PCE metabolism in experimentally exposed humans is uncertain, since these studies measured the production of only certain metabolities, rather than the total amount of metabolites produced.

Data on the amount of PCE metabolized at ambient concentrations (less than 1 ppb) are not available. However, several studies indicate that PCE metabolism increases as the concentration decreases. Extrapolation of metabolism rates to ambient levels indicates that up to 100% of the PCE may be metabolized by mice and rats. Humans may metabolize more than 60% at ambient levels compared to the 4% level estimated in the human studies. Pharmacokinetic models generally assume that PCE is metabolized at the same rate at different concentrations unless an ambient absorption factor is

added. 5) Pharmacokinetic models do not account for individual differences in metabolism and storage. A high variability of body burden of PCE was found for different people tested (Guberan and Fernandez, 1974; Hake and Stewart, 1977; Stewart et al., 1970). The body burden was found to depend on such factors as age, sex, exercise or workload, body mass and adipose tissue mass, pulmonary dysfunctional states, and individual differences in the intrinsic capacity to metabolize PCE. The pathways of PCE metabolism are speculative at present, but it is known that cytochrome P-450 is involved. The presence and basal activity of the enzyme class of cytochrome P-450 are determined genetically, but such systems are also readily altered by components of the diet. Certain phenolic food additives such as BHA and BHT, for example, influence enzyme levels involved in the detoxication and conjugation as well as the activation in animals. Epidemiologic evidence relating enzyme induction to components of human diet are not available at this time, but such induction is likely. Thus, although there is no definitive evidence, a large variability in metabolism in humans appears likely, but cannot be accounted for in the calculation of the metabolized dose other than through the incorporation of generic safety factors. None of the available pharmacokinetic models has incorporated a safety factor to account for variability in humans due to dietary or genetic predisposition. 6) Chronic studies in mice and occupational studies in humans indicate that mice and humans have similar sensitivity to PCE, so the 50-fold species difference suggested by some of the metabolized dose calculations do not appear justified. Thus, it is premature to use the metabolized dose in current estimations of human risk to PCE.

For the low-dose risk assessment, the multistage model was used to estimate cancer potency. A time dependent analysis was found to result in values slightly larger. The surface area correction factor was used to adjust animal exposure data to a human exposure scenario. Thus as shown in Table 5-6, the suggested carcinogenic risk potency range is 0.016 to 0.073 (mg/kg per day)$^{-1}$. Using the assumption of a 70 kg individual breathing 20 m^3/day, and the conversion factor of 1 ppm = 6.89 mg/m^3, potency can be converted as follows:

$$0.016\ (mg/kg\text{-}day)^{-1} \times 6.89\ ((mg/m^3)/ppm) \times 20\ (m^3/day) \div 70\ kg$$
$$= 0.031/ppm = 31 \times 10^{-6}/ppb$$

and

$$0.073\ (mg/kg\text{-}day)^{-1} \times 6.89\ ((mg/m^3/ppm) \times 20\ (m^3/day) \div 70\ kg$$
$$= 0.144/ppm = 144 \times 10^{-6}/ppb.$$

Based on the data of both rats and mice from the 1986 NTP study, it was estimated that the upper 95% confidence interval range of risks indicates that 31 to 144 excess cancer cases may result in every million individuals exposed over their lifetime to 1 ppb (6.78 $\mu g/m^3$) PCE. Based on the same data, the unit risk for a lifetime continuous exposure to 1 $\mu g/m^3$ of PCE is estimated to be between 5 and 21 x 10^{-6}. The calculations represent the upper range of plausible excess cancer risk: the actual risk, which cannot be estimated, may be insiginificant. The potency based on a metabolized dose method suggested by EPA (1986) for the upperbound risk due to lifetime exposure to 1 $\mu g/m^3$ of PCE in air ranges from 2.9 x 10^{-7} to 9.5 x 10^{-7}. However, EPA reported that the complete range of potencies for all methods and dose-tumor incidence data evaluated for 1 $\mu g/m^3$ of PCE in air was 2.9 x 10^{-7} to 1.1 x 10^{-5} (EPA 1986). Based on the CDHS potency evaluation of the

annual average of 0.43 ppb of PCE in the South Coast Air Basin and assuming that there are approximately 10 million residents in that area, an excess number of additional lifetime cancer cases of 133 to 619 might result from PCE exposure. Based on these findings, CDHS concludes that at ambient concentrations, PCE may cause or contribute to an increase in mortality or serious illness due to the induction of cancer and thus pose a hazard to human health.

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APPENDIX A

DOSE-RESPONSE INFORMATION FOR ACUTE, SUBCHRONIC, AND CHRONIC TOXICITY IN ANIMALS (EXCLUDING TERATOGENIC, MUTAGENIC, AND CARCINOGENIC EFFECTS)

Animal dose-response data should be evaluated together with applicable human data to establish safe exposure limits for PCE to prevent acute, subchronic and certain (specifically, noncarcinogenic and nonmutagenic) chronic toxicological endpoints. Here, dose-response data are reviewed according to exposure period (e.g., acute, subchronic, and chronic), route of exposure, and species for different toxic effects to major body organs and systems in animals.

Acute Exposures

Most of the studies reviewed did not clearly identify a no-observed-adverse-effect level (NOAEL) for acute exposures. At the upper bound of acute, oral toxicity, LD50 values range from 3005 mg/kg to over 10,000 mg/kg (rats). Representative LD50 values are presented in Table A-1. Other acute responses to oral and inhalation exposures of PCE are shown in Tables A-2 and A-3, respectively. Even at doses as low as 10 mg/kg, ventricular arrhythmias were observed in rabbits, and cardiovascular effects were noted in dogs at an average dose of 13 mg/kg. Table A-4 summarizes the acute responses to intravenous (IV) and intraperitoneal (IP) administrations. It is difficult to evaluate these studies with regard to their implications for predicted human toxicity because neither the doses nor the routes of administration are typical of human exposure.

Subchronic and Chronic Exposures

Carpenter and Rowe and co-workers conducted studies that identified subchronic and chronic exposure levels in the rat and guinea pig at which no effects were observed (Carpenter, 1937; Rowe et al., 1952). Carpenter exposed rats to 70 ppm of PCE 8 hours/day, 5 days/week for 7 months (Carpenter, 1937). Blood samples were analyzed for glucose and calcium. Periodic counts of white cells, polymorphonuclear neutrophil leukocytes, lymphocytes, and eosinophils were made. Urine was evaluated for bilirubin and albumin. In all instances, values were within normal limits. At the end of the exposure period, animals were sacrificed and examined for histological and/or pathological changes. No damage to organs or to the peripheral and central nervous systems were observed.

Rowe and associates exposed female guinea pigs to 100 ppm of PCE 7 hours/day for a total of 13 exposures in 17 days (Rowe et al., 1952). Animals were observed for changes in behavior, appearance, growth, mortality, and final body weight. Tissues were also examined microscopically. No evidence of adverse effects was reported. However, a separate group of guinea pigs that were administered PCE by the same dose regime 132 times over 185 days displayed some evidence of toxicity. Females had a significant increase in liver weight ($p = 0.01$), and animals of both sexes had some abnormal deposition of fat in the liver.

A recently completed bioassay of PCE used 100 ppm as the lowest concentration administered to mice (6 hours/day, 5 days/week for 103 weeks) (NTP, 1986). Although th- results h-ve been discussed previously (see

Section 4), it is important to note that numerous adverse effects were observed. Therefore, it appears that 70 ppm may be a NOAEL for inhalation exposure of rats (based on the 1937 Carpenter study), but NOAELS for mice and guinea pigs have not been identified.

Hayes and co-workers studied the subchronic toxicity of PCE administered in the drinking water of rats (Hayes et al., 1986). Animals received 14, 400, or 1400 mg/kg-d in water daily, for 90 days. The primary effect was a significant decrease in body weight of high-dose males and of females given 400 to 1400 mg/kg-d ($p<0.05$). Although a loss of body fluids was not considered to be a factor in the lowered body weights, the actual cause of weight loss was not determined. Blood and serum were analyzed for a number of parameters. The only consistent effect was a significant elevation ($p<0.05$) of 5'-nucleotidase in high-dose animals of both sexes, as well as in males that received 400 mg/kg-d. The authors suggest that this may be indicative of cholestasis (suppression of bile flow). However, no other serum indicators of hepatotoxicity were observed. A dose-dependent increase in liver and kidney/body weight ratios was found, but no statistical difference in liver and kidney/brain weight ratios occurred. No adverse hematological or pathological effects were noted in low-dose animals (14 mg/kg-d). The observed NOAEL in rats for ingestion of PCE in drinking water is 14 mg/kg. Tables A-5, A-6, A-7, and A-8 summarize the responses to subchronic and chronic administration of PCE.

TABLE A-1. MEAN LETHAL DOSES (LD50) OF TETRACHLOROETHYLENE TO LABORATORY ANIMALS

Route	Species	Dose (mg/kg)	Reference
IP[a]	Rat (female)	3005	Hayes et al., 1986
IP	Dog	3400	Klaassen and Plaa, 1967
IP	Rat (male)	3835	Hayes et al., 1986
Oral	Rat	3980 to 4680	Withey and Hall, 1975
IP	Mouse	4700	Klaassen and Plaa, 1966
Oral	Mouse	6400 to 8000	Von Oettingen, 1964
Oral	Mouse	8115	Wenzel and Gibson, 1951
Oral	Mouse	8571	Dybing and Dybing, 1946
Oral	Rat	8850	Lewis and Sweet, 1984
Oral	Rat	13,000	Smyth et al., 1969

[a]Intraperitoneal administration.

TABLE A-2. ACUTE ORAL TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Dose (mg/kg)	Effect	Reference
Cat	812	No observed effects	Maplestone and Chopra, 1933
Cat	1623	Drowsiness; unsteadiness	Maplestone and Chopra, 1933
Rabbit	2158	50% Increase in serum lipoprotein; transient elevation in serum-enzyme activities	Fujii, 1975
Rat	4700	Death	Smyth et al., 1969
	6492 to 8115	Death in 2 to 9 h	Lamson et al., 1929
Dog	6492	Death in 5 h	Lamson et al., 1929
Cat	6492	Death in 36 h	Lamson et al., 1929
Rabbit	8115	Death in 17 to 24 h	Lamson et al., 1929

TABLE A-3. ACUTE INHALATION TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Concentration (ppm)	Exposure period	Effect	Reference
Mouse	200	4 h	Moderate fatty infiltration of liver	Kylin et al., 1963
Mouse	400	4 h	Moderate to massive fatty infiltration of liver	Kylin et al., 1963
Mouse	800		Decrease in hepatic ATP levels; increase in total hepatic lipids and triglycerides	Ogata et al., 1968
Mouse	1600	4 h	Massive fatty infiltration of liver; statistically significant increase in liver fat content	Kylin et al., 1963
Rat	2000	Various exposure durations	CNS depression; loss of consciousness; possible cardiac failure; respiratory failure	Rowe et al., 1952
Rat	2300	4 h	Ataxia; 80% loss of avoidance and escape response	Goldberg et al., 1964
Mouse	2917	4 h	100% Mortality	NTP, 1986
Rat	3000	"Several hours"	Loss of consciousness	Rowe et al., 1952
Mouse	3700	24 min	Anesthesia	Gehring, 1968
Mouse	3700	470 min	Liver dysfunction	Gehring, 1968
Rat	5163	4 h	100% Mortality	NTP, 1986
Dog	9900		Narcosis	Lamson et al., 1929

TABLE A-4. ACUTE INTRAVENOUS (IV) AND INTRAPERITONEAL (IP) TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Dose	Route of administration[a]	Effect	Reference
Dog	13 mg/kg (mean dose)	IV (animals were anesthetized with pentobarbital)	Depression of myocardium; increased vulnerability of ventricles to epinephrine-induced arrhythmias; ventricular arrhythmias	Kobayashi et al., 1982
Rabbit	10 mg/kg (mean dose)	IV (animals were anesthetized with urethane)	Increased vulnerability of myocardium to tachycardia	Kobayashi et al., 1982
Dog	20 to 40 mg/kg	IV	Significant depression rate of rise of left intraventricular pressure	Kobayashi et al., 1982
Rat	1.3 mL/kg	IP	Increase in BDPF[b]; increase in Cl-, K+, decrease in protein in BDPF	Hamada and Peterson, 1977
Rat	0.3 to 2.0 mL/kg	IP	20 to 440% Increase, SGOT[c]	Cornish et al., 1973
Dog	1200 mg/kg	IP	Increased SGPT[d], 50% of animals	Klaassen and Plaa, 1967
Dog	2300mg/kg	IP	Increased retention PSP[e], 50% of animals	Klaassen and Plaa, 1967
Mouse	3900 mg/kg	IP	ED_{50}; elevation of SGPT	Gehring, 1968

TABLE A-4. (Continued)

Species	Dose (mg/kg)	Route of administration	Effect	Reference
Mouse	2.5 mL/kg	IP	Necrosis and swelling proximal convoluted tubule	Plaa and Larson, 1965
Mouse	4700 mg/kg	IP	Enlargement of hepatocytes; cellular infiltration and vacuolation; slight hepatic necrosis; slight necrosis convoluted tubule	Klaassen and Plaa, 1966

[a]IV = Intravenous injection; IP = intraperitoneal injection.
[b]BDPF: Bile duct-pancreatic flow.
[c]SGOT: Serum glutamic oxalacetic transaminase.
[d]SGPT: Serum glutamic pyruvate transaminase.
[e]PSP: Phenosulfonephthalein.

TABLE A-5. SUBCHRONIC ORAL TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Dose (mg/kg)	Dose regime	Effect	Reference
Rat	14	Daily for 90 d	No observed adverse effects	Hayes et al., 1986
Mouse	100,250,1000, 1500 or 2000	5 d/wk for 6 wk	Significant increase absolute liver weight[a]; significant increase liver triglycerides[a]	Buben and O'Flaherty, 1985
Mouse	100,250,500 or 1000	Daily for 11 d	Significant elevation in absolute liver weights[a]; hepatocellular swelling[a]; significant decrease of hepatic DNA content per gram of liver[a]; dose-related increase of hepatic DNA synthesis (1000 mg/kg)	Schumann et al., 1980
Rat	100,250,500 or 1000	Daily for 11 d	Significant elevation of liver weight (1000 mg/kg group only); minimal hepatic changes (1000 mg/kg group only)	Schumann et al., 1980
Mouse	100,200,500,1000, 1500 or 2000	5 d/wk for 6 wk	Dose-dependent increase in liver degeneration and karyorrhexis	Buben and O'Flaherty, 1985
Dog	300		Degenerative changes of liver; extensive atrophy of liver	Hall and Schillinger, 1925

TABLE A-5. (Continued)

Species	Dose (mg/kg)	Dose regime	Effect	Reference
Rat	400	Daily for 90 d	Significant decrease in body weight (females); significant increase in 5'-nucleotidase (males)	Hayes et al., 1986
Mouse	500,1000,1500, or 2000	5 d/wk for 6 wk	Significant decrease in G6P[a-b]; significant increase in SGPT[a-c]	Buben and O'Flaherty, 1985
Mouse	1000	5 d/wk for 6 wk	Significant decrease in hepatic DNA content (indicative of hypertrophy)	Buben and O'Flaherty, 1985
Rat	1400	Daily for 90 d	Significant decrease in body weight (both sexes); significant increase in 5'-nucleotidase (both sexes)	Hayes et al., 1986

[a]All dose levels.
[b]G6P: Glucose 6 phosphatase.
[c]SGPT: Serum glutamic pyruvate transaminase.

TABLE A-6. SUBCHRONIC INHALATION TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
Guinea pig (females)	100	13 exposures in 17 d	7 h/d	No observed effects	Rowe et al., 1952
Guinea pig	100	132 exposures in 185 d	7 h/d	Significant increase in liver weight (female); fat deposition in liver	Rowe et al., 1952
Rat	200	4 exposures in 4 d	6 h/d	Decreased RNA content of brain; increased nonspecific cholinesterase activity; behavioral changes	Savolainen et al., 1977
Rat	230	5 d/wk 21 exposures	8 h/d	Granular swelling and congestion of kidneys	Carpenter, 1937
Mouse	200 to 1600	Daily for 3 d	8 h/d	Inhibition of growth; increase in mortality	Schumacher et al., 1962
Rat	400	130 exposures in 183 d	7 h/d	No observed effects in mortality	Rowe et al., 1952
Rat	800	Daily for 1 month	12 h/d	Significant decrease in ACh[a]	Honma et al., 1980
Rat	1600	8 exposures in 10 d	7 h/d	Slight degeneration of germinal epithelium of testes; increase in liver weights; moderate fatty degeneration of liver	Rowe et al., 1952

TABLE A-6. (Continued)

Species	Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
Rabbit	2211	6 d/wk for 45 d	4 h/d	Significant decrease in rate of glomerular filtration; decrease of renal tubular capacity	Brancaccio et al., 1971
Guinea pig	2500	18 exposures in 24 d	7 h/d	High mortality; loss of equilibrium, coordination, and strength; rapid weight loss; increase in liver and kidney weights; fatty degeneration of liver; swelling of tubular epithelium	Rowe et al., 1952
Rabbit	2500	28 exposures in 39 d	7 h/d	Slight hepatic degeneration; CNS depression to point of helplessness	Rowe et al., 1952
Rat	2500	13 exposures in 18 d	7 h/d	CNS depression with loss of consciousness; 90% lethality	Rowe et al., 1952

[a]ACh: acetylcholine.

TABLE A-7. CHRONIC ORAL TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS (Noncarcinogenic effects only)

Species[a]	Dose[b] (mg/kg)	Dose regime	Exposure frequency	Effect	Reference
Mouse (female)	386[c]	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 62); toxic nephropathy (96%)	NCI, 1977
Rat (male)	471	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 72); toxic nephropathy (88%)	NCI, 1977
Rat (female)	474	5 d/wk, for 78 wk	Daily	Early mortality (50% mortality by wk 74); toxic nephropathy (58%)	NCI, 1977
Mouse (male)	536[b]	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 78); toxic nephropathy (82%))	NCI, 1977
Mouse (female)	772[b]	5 d wk for 78 wk	Daily	Early mortality (50% mortality by wk 50); toxic nephropathy (100%)	NCI, 1977
Rat (male)	941	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 44); toxic nephropathy (94%)	NCI, 1977
Rat (female)	949	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 66); toxic nephropathy (76%)	NCI, 1977

TABLE A-7. (Continued)

Species	Dose[a] (mg/kg)	Dose regime	Exposure frequency	Effect	Reference
Mouse (male)	1072[b]	5 d/wk for 78 wk	Daily	Early mortality (50% mortality by wk 43); toxic nephropathy (94%)	NCI, 1977

[a]Each dose group initially had 50 animals.
[b]All values are time-weighted average doses.
[c]These dose levels are associated with an increased incidence of cancer in experimental animals. See Section 5 for additional information.

TABLE A-8. CHRONIC INHALATION TOXICITY OF TETRACHLOROETHYLENE TO ANIMALS

Species	Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
Rabbit	15	7 to 11 months	3 to 4 h/d	Reduction in agglutinin formation	Mazza, 1972
Rat	70	5 d/wk for 7 months	8 h/d	No observed effects	Carpenter, 1937
Mouse	100	5 d/wk for 103 wk	6 h/d	Significantly lower survival than controls (after wk 74); increased incidence of liver degeneration and liver necrosis	NTP, 1986
Mouse (females)	100	5 d/wk for 103 wk	6 h/d	Increased incidence of nephrosis	NTP, 1986
Guinea pig	200	158 exposures in 220 d	7 h/d	Significant depression of growth; increase in liver and kidney weight; slight to moderate fatty degeneration of liver	Rowe et al., 1952
Mouse	200	5 d/wk for 103 wk	6 h/d	Significantly lower survival than controls (after wk 78); increased incidence of liver degeneration, liver necrosis, and nephrosis	NTP, 1986
Rat	230	5 d/wk for 7 months (150 exposures)	8 h/d	Granular swelling of the liver; decrease in glycogen storage	Carpenter, 1937
Rat (males)	400	5 d/wk for 103 wk	6 h/d	Decreased survival (after wk 82)	NTP, 1986

TABLE A-8. (Continued)

Species	Concentration (ppm)	Dose regime	Exposure period	Effect	Reference
Mouse	400	169 exposures in 236 d	7 h/d	Increase in kidney weight; swelling of tubular epithelium	Rowe et al., 1952
Guinea pig	400	169 exposures in 236 d	7 h/d	Significant depression of growth; increase in liver and kidney weights; moderate fatty degeneration and slight cirrhosis of liver	Rowe et al., 1952
Rabbit	400	159 exposures in 220 d	7 h/d	No observed effects	Rowe et al., 1952
Monkey	400	179 exposures in 250 d	7 h/d	No observed effects	Rowe et al., 1952
Rat	470	5 d/wk for 7 months 150 exposures	8 h/d	Liver congestion and cloudy swelling; increased secretion, cloudy swelling and desquamation of kidney; congestion and increased pigmentation spleen	Carpenter, 1937
Rat	600	5 d/wk for 12 months	6 h/d	Increase in mortality	Leong et al., 1975
Rat	600	5 d/wk for 12 months	6 h/d	Increase in mortality (males only); inflammation of kidney cells; nephrosis	Rampy et al., 1978

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