DRAFT

Do not cite or quote

External Review
Draft No. 1
April 1979

HEALTH ASSESSMENT DOCUMENT FOR TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implication.

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Environmental Criteria and Assessment Office
Research Triangle Park, North Carolina 27711

DRAFT

Do not cite or quote

External Review
Draft No. 1
April 1979

HEALTH ASSESSMENT DOCUMENT FOR TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

by

Mark M. Greenberg and Jean C. Parker

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implication.

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Environmental Criteria and Assessment Office
Research Triangle Park, North Carolina 27711

PREFACE

This Health Assessment of Tetrachloroethylene was prepared at the request of the Office of Air Quality Planning and Standards (OAQPS) to evaluate the carcinogenic and toxicological potential of this ambient air pollutant.

While this assessment constitutes a comprehensive review and evaluation of current scientific knowledge, the references cited do not constitute a complete bibliography.

ABSTRACT

Tetrachloroethylene, also called perchloroethylene (PERC), is emitted into the atmosphere in significant quantities as a result of evaporative losses. Although background concentrations in the ambient air are less than 1 part per billion, much higher concentrations have been observed in and around urban centers ($\leq$10 parts per billion). Tetrachloroethylene is rapidly destroyed by photo-oxidative mechanisms in the troposphere and yields phosgene, which has been identified as a secondary anthropogenic pollutant of concern. There is data based on animal studies that suggest that tetrachloroethylene is a potential human carcinogen.

Toxicological effects of tetrachloroethylene in animals and humans include adverse effects on liver, kidney, and other organs. In humans, toxicological effects observed were associated with tetrachloroethylene concentrations in the parts per million range; ambient concentrations, on the other hand, have been reported at 10 parts per billion or less.

Due to its solubility in adipose and lean tissue, tetrachloroethylene would be expected to accumulate in the body with chronic exposure. Preliminary evidence in humans suggests that tetrachloroethylene is concentrated in breast milk and can be transmitted to nursing infants. Pharmacokinetic data indicate that tetrachloroethylene stored in the body is released slowly and is completely eliminated only after two weeks or more following exposure.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

The U.S. Environmental Protection Agency project manager for this health assessment was Mark M. Greenberg.

Acknowledgment is made to those individuals who contributed to the review of this document, in particular:

Dr. I. W. F. Davidson, Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Winston-Salem, North Carolina

Dr. Benjamin L. Van Duuren, Professor of Environmental Medicine, New York University Medical Center, New York, New York.

Dr. Hanwant Bir Singh, Senior Chemical Engineer, Atmospheric Sciences Laboratory, SRI International, Menlo Park, California.

Dr. Norbert P. Page, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

Dr. Richard J. Bull, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, Ohio.

Dr. George W. Wahl, Jr., Professor of Chemistry, North Carolina State University, Raleigh, North Carolina.

Dr. Bruce W. Gay, Jr., Environmental Sciences Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina.

Dr. Joseph H. Roycroft, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina.

AUTHORS AND REVIEWERS

Principal Authors

Mark M. Greenberg, Environmental Criteria and Assessment Office (ECAO), U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

Dr. Jean C. Parker, ECAO, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

Principal Reviewers

Dr. I. W. F. Davidson, Consultant, Bowman Gray School of Medicine, Winston-Salem, North Carolina

Dr. Lawrence Fishbein, National Center for Toxicological Research (Arkansas)

Dr. Hanwant Bir Singh, Consultant, SRI International, Menlo Park, California

Dr. Bruce W. Gay, Jr., U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

Dr. Benjamin L. Van Duuren, Consultant, New York University Medical Center, New York

Dr. Norbert P. Page, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY REVIEW COMMITTEE

Jack L. Arthur, Office of Toxic Substances, EPA, Washington, D.C.

Dr. Richard J. Bull, Health Effects Research Laboratory, EPA, Cincinnatti.

Gary F. Evans, Environmental Monitoring and Support Laboratory, EPA, Research Triangle Park.

Dr. Bruce W. Gay, Jr., Environmental Sciences Research Laboratory, EPA, Research Triangle Park.

Mark M. Greenberg, Environmental Criteria and Assessment Office, EPA, Research Triangle Park.

Ken Greer, Office of Air Quality Planning and Standards, EPA, Research Triangle Park.

Chuck Kleeberg, Office of Air Quality Planning and Standards, EPA, Research Triangle Park.

Gary McCutchen, Office of Air Quality Planning and Standards, EPA, Research Triangle Park.

Dr. Norbert P. Page, Office of Toxic Substances, EPA, Washington, D.C.

Dr. Jean C. Parker, Environmental Criteria and Assessment Office, EPA, Research Triangle Park.

Dr. Joseph H. Roycroft, Health Effects Research Laboratory, EPA, Research Triangle Park.

John H. Smith, Office of Toxic Substances, EPA, Washington, D.C.

Dr. George W. Wahl, NSSU, Consultant (Office of Air Quality Planning and Standards, EPA, Research Triangle Park).

1. SUMMARY AND CONCLUSIONS

Tetrachloroethylene, also called perchloroethylene (PERC), is a solvent widely used in the cleaning of textile fabrics and in the degreasing of metals. For the past decade the U.S. production of PERC has remained relatively steady at approximately 300,000 metric tons per year. Significant amounts of PERC are imported and exported annually.

A highly sensitive and convenient analytical system used to measure PERC concentrations in ambient air/water is gas/liquid chromatography with electron capture detection. This system has a detection limit on the order of a few parts per trillion (ppt).

It is estimated that between 80 and 95 percent of the PERC used in the United States, principally from processes used to dry clean fabrics, is evaporated to the atmosphere. There are no known natural sources of PERC. Ambient air and water measurements indicate that PERC is found in a variety of urban and nonurban areas of the United States and in other regions of the world. Based on available data, an average concentration of approximately 1 ppb (0.007 mg/m^3) (v/v) would be expected for some large urban centers. Short-term peak levels as high as 9.5 ppb (0.065 mg/m^3) have been detected in New York City during a 24-hour diurnal cycle.

Ambient air concentrations are greatly influenced by the tropospheric reactivity of PERC, residence time in the troposphere (approximately 21 weeks), urban-nonurban transport, and sources and extent of emissions.

Background levels of PERC, as measured over oceanic areas, at "clean air" sites, and at elevations exceeding 1,000 meters above sea level, indicate that typical concentrations are less than 50 ppt.

In chamber studies simulating tropospheric conditions, PERC has been shown to be susceptible to attack by hydroxyl free radicals. Reaction of PERC with hydroxyl radicals is the principal mechanism by which PERC is scavenged from the atmosphere. The residence time of PERC in the troposphere is, in part, dependent on the concentration of hydroxyl radicals in ambient air. An increase in the concentration of hydroxyl radicals in ambient air will reduce the troposphere residence time of PERC. This scavenging mechanism for PERC results in the transformation of PERC to phosgene, a secondary anthropogenic pollutant of concern.

Tetrachloroethylene has been detected in both natural and municipal waters in various geographical areas of the United States. It has been found in the drinking water of many municipalities at a level of approximately 1 microgram per liter (µg/liter).

While no direct evidence of bioaccumulation of PERC in the food chain is evident, tissues of various marine species of fish, invertebrates, algae, and mammals have been found to contain PERC. Species continuously exposed to PERC in natural waters would be expected to accumulate the halocarbon in their tissues. Limited studies suggest that PERC may be toxic to marine and fresh-water organisms. In addition, reduction in the photosynthetic capabilities of algae may result from PERC exposure. The ecological consequences of these effects are unknown at present.

The results of mammalian studies indicate that PERC exerts a spectrum of toxicological effects. The principal effect of acute inhalation of PERC in animals is depression of the central nervous system. Large acute doses (1,500 to 2,000 ppm; 10,174 to 13,566 mg/m^3) result in cardiovascular and

respiratory effects and death attributed to primary cardiac standstill and respiratory arrest. Tetrachloroethylene has a "degreasing" effect on the skin and is a primary skin irritant. Direct contact can cause burns, blistering, and erythema.

The liver and the kidney are chief target organs of PERC exposure in animals. Fatty liver, liver enlargement, abnormal liver function tests as well as kidney damage, especially in the renal tubule, have been attributed to PERC exposure. However, these toxicities may not all be manifested, especially at lower levels. Thus, latent toxic effects on the liver, kidney, and nervous system have been demonstrated, but the degree and dose relationships of these effects are unclear. Other effects of PERC exposure in laboratory animals include lung damage, depressed antibody synthesis cardiovascular effects, and depressed growth.

Some evidence exists which suggests that PERC has teratogenic potential. The results of mutagenicity testing of PERC in microbial systems are conflicting. However, malignant transformation of mammalian cells has been observed. At least one long-term animal toxicity study has demonstrated that PERC is carcinogenic in laboratory animals. Further research is needed in both these areas. Some studies are currently under way (see Appendix A).

The patterns of use of PERC indicate that vapor inhalation is the predominant mode by which individuals in the general population may be exposed. It should be emphasized that background concentrations and concentrations in the ambient air near urban centers are several orders of magnitude lower than concentrations associated with adverse health effects. Indeed, the products of the photooxidation of PERC may represent a greater hazard.

Knowledge of the effects of PERC in humans has been principally derived from clinical evaluations of individuals occupationally and/or accidentally exposed to vapor concentrations of PERC in the parts per million range. In many cases, the exposure concentration and duration were unknown or roughly estimated. In humans, the adverse effects of PERC primarily involve the central nervous system, liver, and kidney. In most cases studied, these effects are reversible upon cessation of exposure.

The initial effects of vapor inhalation by man are symptomatic of depression of the central nervous system: dizziness, weakness, fatigue, trembling of the eyelids and fingers, excessive sweating, and muscular incoordination. Effects on the liver and kidney have been evidenced by abnormal alterations of various liver and kidney function parameters. Abnormalities frequently appear in the postexposure period.

There are indications that PERC may be concentrated in breast milk after brief (<60 minutes), repeated exposures of nursing mothers to the halocarbon. Transmittance of PERC to breast-fed infants has been demonstrated to result in damage to the neonatal liver. Damage was reversible upon cessation of breast feeding.

The metabolism of PERC in humans is not well understood. The available evidence, drawn largely from animal studies, suggests that PERC may be metabolized to tetrachloroethylene epoxide, a highly reactive, transitory intermediate, having carcinogenic potential. The disposition and fate of PERC in the body indicates that, in contrast to the congener trichloroethylene, 80 to 98 percent of PERC inhaled is excreted unchanged in the breath; generally, less than 2 percent is excreted in the urine in the form of the major metabolite, trichloroacetic acid. Absorption and elimination

of PERC through the skin appears to be a route of only minor concern in terms of the normal usage of, or exposure to, the halocarbon.

Because of its high solubility in lipid-rich tissues, PERC is stored in the body for long periods after inhalation. It has been demonstrated that 2 weeks or more are necessary to completely clear PERC from the body.

Concern for the carcinogenic potential of PERC is, in part, based on its structural similarity to vinyl chloride and other chlorinated olefin compounds known to be carcinogenic. Also, malignant transformation of mammalian cells to tumor-producing cells, upon exposure to PERC, has been observed in a highly sensitive in vitro cell system. These results indicate that PERC has a carcinogenic potential. In addition, a long-term animal study reported by the National Cancer Institute has documented carcinogenicity in laboratory mice. Preliminary results from another study [yet to be published] suggest a possible carcinogenic potential of PERC when applied to the skin of mice. Although other major studies have been initiated, there is, at present, no additional evidence associating PERC exposure with carcinogenicity. There are no known epidemiological results associating PERC exposure with cancer in humans. The potential of PERC in producing these effects in humans, however, must be considered.

2. INTRODUCTION

Tetrachloroethylene (PERC), is one member of a family of unsaturated, chlorinated compounds. Other common names/acronyms are perchloroethylene, Perk, PER, and PCE. Its trade names or synonyms include: Carbon dichloride, Perclene, Perclene-D, Tetrachloroethene, Perchlor, Perchlor HDC, Dee-Solv, Dow-Per, Percosolv, Tetravec, and 1,1,2,2,-tetrachloroethylene.

Concern that PERC may be a carcinogen was expressed by the U.S. Environmental Protection Agency (EPA) Carcinogen Assessment Group in a preliminary health risk assessment report published April 17, 1978. Tetrachloroethylene is the subject of several reviews currently in preparation or recently published. These include: An Assessment of the Need for Limitations on Trichlorethylene, Methyl Chloroform, and Perchloroethylene (Office of Toxic Substances, Dr. Stan Mazaleski, Project Officer); Human Health Effects: Tetrachloroethylene (EPA-Cincinnati, Dr. Richard J. Bull); Chlorinated Hydrocarbon Toxicity (Consumer Product Safety Commission, Dr. T. D. C. Kuch, Project Officer); Air Pollution Assessment of Tetrachloroethylene (MITRE Corporation, 1976); Occupational Exposure to Tetrachloroethylene (National Institute of Occupational Safety and Health, NIOSH, July 1976).

Tetrachloroethylene is released into ambient air as a result of evaporative losses during production, storage, and/or use. It is not known to be derived from natural sources. In the troposphere it is photochemically reactive and is removed by scavenging mechanisms. Concentrations in ambient air are highly dependent on strategies used to control emissions and on the transport and transformation processes in the troposphere.

The scientific data base for tetrachloroethylene is limited with reference to effects on humans. The epidemiology and known effects of tetrachloroethylene have been derived from studies involving individuals occupationally or accidentally exposed to the halocarbon. During such exposures, the concentrations associated with adverse effects on human health were either unknown or far in excess of concentrations measured in ambient tropospheric air. Controlled exposure studies have principally been directed toward elucidating the pharmacokinetic parameters of tetrachloroethylene exposure.

The current Occupational Safety and Health Administration (OSHA) standard for occupational exposure to tetrachloroethylene in the workplace is 100 ppm (678 mg/m^3) over a 10-hour workday, 40-hour workweek. In July 1976, NIOSH recommended an exposure limit of 50 ppm (339 mg/m3). Neither of these limits were based on findings other than toxicity. In the NIOSH Current Intelligence Bulletin #20 (January 20, 1978), it was recommended that PERC be treated in the workplace as if it were a human carcinogen. This interim recommendation was issued until the carcinogenic potential of PERC in the workplace was fully evaluated.

The role of PERC as a primary or additive contributor to human carcinogenesis represents the most serious aspect concerning human health. Efforts to determine the effect of ambient air exposures on human health are complicated by several factors. As with any pollutant, PERC comprises only a small portion of a complex array of pollutants in ambient air. Adverse effects may result from exposure to PERC, to a mix of the halocarbon and other pollutants or to the products of atmospheric interactions of PERC and other compounds. Since epidemiological studies have not been able to assess

adequately the overall impact of PERC on human health, it has been necessary to rely greatly on animal studies to derive indications of potential harmful effects. While animal data cannot always be extrapolated to humans, indications of probable or likely effects among animal species increase confidence that similar effects may occur in humans.

This document is intended to provide an evaluation of the current scientific literature concerning PERC. It is believed that the literature has been comprehensively reviewed through March 1979, and major publications relevant to the topics covered are included in the references cited. Information pertaining to analytical methods, sources and emissions, atmospheric transport, transformation and fate, ambient concentrations, and ecological effects have been included to place the health-related effects of PERC in perspective.

3. CHEMICAL AND PHYSICAL PROPERTIES/ANALYTICAL METHODOLOGY

3.1 CHEMICAL AND PHYSICAL PROPERTIES

Tetrachloroethylene, also called PERC, (1,1,2,2,-tetrachloroethylene or perchloroethylene) is a colorless, clear, heavy liquid with a chloroform-like odor. It has a molecular weight of 165.85 and is relatively insoluble in water.[1] It may be used as a solvent for many organic substances and is industrially important as a solvent in the dry cleaning of fabrics and in the degreasing of metals. Its CAS registry number is 127184.

Tetrachlorethylene has been reported to be photochemically active (Chapter 5) and, depending on conditions, may yield ozone, phosgene, carbon tetrachloride, trichloroacetyl chloride, formic acid, and other compounds. When in contact with water for prolonged periods, PERC slowly decomposes to yield trichloroacetic acid and hydrochloric acid. Upon prolonged storage in light it slowly decomposes to trichloroacetyl chloride and phosgene by autooxidation.[2] At 700°C, it decomposes in contact with activated charcoal to hexachloroethane and hexachlorobenzene.[3] Tetrachloroethylene has a boiling point of 121.2°C at 760 mm Hg. It has a vapor pressure of 14 torr at 20°C.

Tetrachloroethylene is subject to free radical attack by many species, e.g., the chlorine free radical (Cl·) and the hydroxyl free radical (·OH). The hydroxyl free radical reaction represents the principal pathway by which PERC is scavenged from the atmosphere.

The chemical reactivity of PERC has been discussed by Bonse and Henschler.[4] By virtue of the electron-inductive effect of the chlorine

atoms, electron density about the ethylene bond of PERC is reduced. This effect, in combination with a steric protective effect afforded by the chlorine atoms, provides increased stability against electrophilic attack. This has been demonstrated in PERC's rate of reaction with ozone. Compared to ethylene and less-substituted chlorination hydrocarbons, PERC has a low rate of reaction.[5]

3.2 ANALYTICAL METHODOLOGY

To detect the extremely low levels of PERC in ambient air (Chapter 6), sophisticated analytical techniques have been employed. The most generally useful method for detection and analysis of PERC is the gas chromatograph-electron capture (GC-EC) technique which has a lower limit on the order of a few parts per trillion (ppt).

The utility of the system, over others such as gas chromatography-mass spectrometry (GC-MS), is that it can be used in the field to provide quasi-continuous measurements by intermittent sampling (every 15 to 20 minutes).

3.2.1 Gas Chromatography-Electron Capture

The electron capture detector (ECD) analyzes the gaseous effluent of the gas chromatograph (GC) by sensing a variation in the amount of solute (e.g., PERC) passing through it. When used as a concentration detector, it produces a current proportional to the amount of PERC per unit volume of carrier gas (e.g., N_2). The ECD is specific in that chlorinated hydrocarbons may be quantitated while non-halogenated hydrocarbons are not detected. Thus, high background levels due to hydrocarbons in ambient air samples do not interfere with measurements of PERC.

In the detector, PERC "captures" free electrons produced by bombardment of the carrier gas with β^- particles, generated by a radioactive

source. The extent to which a solute "captures" the free electrons is significantly influenced by (1) the flow rate of the carrier gas, (2) the voltage applied to the detector, (3) the energy of the electrons, and (4) the inherent capability of the solute to attract the electrons. The net result of the complex mechanisms is the removal of electrons from the gaseous mixture with substitution by negative ions of greater mass.

The measured effect is a net decrease in ion current since the negative ions produced recombine with positive ions 10^5 to 10^8 times faster than the recombination of free electrons and positive ions.[5] The solute concentration can be calculated directly from the number of electrons absorbed. According to Pellizzari,[6] the theoretical detection limit is near 3.3×10^{-16} mole.

The ionization efficiency of PERC is approximately 70 percent using two ECD's in series, such as described by Lillian and Singh.[7] Once known for the GC-EC operating conditions, the ionization efficiency can be used to calculate the amount of PERC in a sample coulometrically, according to the equation:

$$\text{Coulombs} = 96{,}400\ pQ$$

Where p = ionization efficiency

and Q = moles of compound

The accuracy associated with GC-EC measurements of compounds having ionization efficiencies exceeding 50 percent is 75 percent or greater.[7] In a comparison of GC-EC with GC-MS, Cronn et al.[8] judged GC-EC to be superior in reproducibility. Although PERC was not among four halocarbon standards measured by GC-EC, the coefficients of variation ranged from 1.4 to 4.3 percent. Of 11 halocarbon standards (PERC not among them) measured by

GC-MS, coefficients of variation ranged from 4 to 19 percent. A coefficient of variation of 8.3 percent was reported by Rasmussen et al.[9] for PERC upon evaluation of the precision of a freezeout concentration technique in conjunction with analysis by GC-EC (also section 3.2.3).

A close agreement between the levels of PERC and other halocarbons detected by GC-EC and those by GC-MS, on the same ambient air samples, was obtained by Russell and Shadoff.[10] Using GC-EC, a concentration of 40 ppt (0.3×10^{-3} mg/m^3) PERC was determined; with GC-MS, 50 ppt (0.34×10^{-3} mg/m^3) was measured. Similar agreements were observed in comparison of the methods with methyl chloroform, trichloroethylene, carbon tetrachloride, and chloroform.

Calibrations of the gas chromatograph have been made using permeation tubes,[11,12] standard multiple dilutions of pure material,[13] or detector tubes using sorbents.[14] Detector tubes are designed for measurement in the ppm range.[14]

The utility of the GC-EC system applies to measurements of PERC in water samples as well as ambient air.

3.2.1.1 Sources of Error

3.2.1.1.1 Collection on Sorbents. In the GC analysis of ambient air containing organic vapors such as PERC, several sources of error are possible. When using charcoal as a collection sorbent for vapors, the amount of water in the air may be so great that organic vapors will not be trapped. Solvents other than the one of interest may displace one or more from the charcoal because of differences in polarity.[14] When similar retention times on the GC column are suspected or material is lost on the column, column conditions (packing, temperature) must be changed. The ionization efficiency in

electron capture detectors and retention time can be used to confirm the identification of the compound.

The use of solid sorbents, including charcoal, has been evaluated by Melcher et al.[15] Solid sorbents are convenient to use in collecting and concentrating trace organics in ambient air. While specific information on PERC was not offered, the general use and characterization of this method was discussed.

3.2.1.1.2 Electron Capture Detector. The presence of water and O_2 in EC detectors may cause erroneous results for some compounds being analyzed. Oxygen can be eliminated during pre-concentration techniques (section 3.2.3) while water can be removed through the use of drying tubes.[10]

3.2.1.1.3 In-Situ Monitoring. Many of the problems associated with collection on sorbents can be eliminated or reduced by in situ monitoring and analysis. Ambient air or water samples can be analyzed at the monitoring site by direct injection into a GC-EC system.

3.2.2 Other Methods

Other methods that could be used to detect and measure PERC levels in ambient air include (1) GC-MS, (2) long-path infrared spectroscopy (LPIRS), (3) infrared solar spectroscopy, and (4) CO_2 laser. The GC-MS system cannot be used in the field. The maximum sensitivity is approximately 5 ppt (v/v). It identifies compounds by their characteristic mass spectra, whereas the GC-EC relies on the retention time for compound identification. LPIRS requires concentrations on the order of 10^{-8} (v/v) and the infrared solar method appears to be principally useful in stratospheric measurements. The measurements of Schnell and Fischer[16] with a CO_2 laser indicate that the sensitivity of this procedure for PERC is 1.1 ppb.

3.2.3 Sampling Of Ambient Air

Common approaches used to sample ambient air for trace gas analysis include:[17]

1. Pump-pressure samples: A mechanical pump is used to fill a stainless steel or glass container to a positive pressure relative to the surrounding atmosphere. This approach can provide a sample size adequate for GC-EC analysis.
2. Ambient pressure samples. An evacuated chamber is opened and allowed to fill until it has reached ambient pressure at the sampling location. If filling is conducted at high altitude, the pressure in the container may easily become contaminated when returned to ground level.
3. Adsorption on molecular sieves, activated charcoal or other materials. A variety of sorbents have been tested for use with PERC. Sorbent materials used successfully with PERC include Carbowax 400, Tenax GC, and activated charcoal.
4. Cryogenic samples. Air is pumped into a container, liquefied, and a partial vacuum is created which allows more air to enter. This method allows for the collection of several thousand liters of air.

A convenient approach to obtain cryogenic samples of PERC is to pump air through a loop at cryogenic temperatures. Tetrachloroethylene remains behind while other gases (oxygen, nitrogen) are passed through.

A freeze-out concentration method was employed by Rasmussen et al.[9] to determine atmospheric levels of PERC in the presence of other trace vapors. The detection limit was reported at 0.2 ppt (1.36×10^{-6} mg/m^3) for 500 ml

aliquots of ambient air samples measured by GC-EC. The precision of analysis was 8.3 percent. Standards were prepared by static dilutions in helium. During this procedure, the oven of the GC was cooled to -10°C. When freezeout is complete, the loop containing the concentrated air sample is immersed in heated water, and the carrier gas sweeps the contents of the sample loop onto the column.

3.2.4 Sampling Considerations In Human Studies

In chamber studies, various analytical methods and techniques are used. Measurement of PERC vapors in chamber air are obtained by sampling the general chamber air, exclusive of the breathing zone. This may or may not be representative of the amount of PERC inhaled by test subjects in the chamber, since breathing-zone air may contain quite different concentrations. When volunteers are external to the chamber and breathe chamber vapors through a mask equipped with a one-way valve, differences between PERC concentration in the general chamber air and in the breathing zone are precluded.

Sampling of exhaled breath commonly is accomplished by use of Saran bags or glass pipettes. Temperature and storage time before subsequent analysis are factors to be considered in obtaining accurate data. Some of these considerations are discussed below.

3.2.4.1 Glass Sampling Tubes--Evaluation of glass sampling tubes was recently made by Pasquini.[18] Both breath and air samples of PERC were collected in glass tubes obtained from Stewart and co-workers (Chapter 9). Serial alveolar breath samples, obtained using a 30-second breath holding technique, were collected from two healthy male adults who had inhaled PERC from a breathing chamber. Concentrations were analyzed by a gas chromatograph

equipped with a flame ionization detector. Analysis of vapor retention over 169 hours indicated that glass tubes can be acceptable containers for breath samples if precautions are taken. Moisture, temperature, and tube surface and condition can greatly alter vapor retention.

In tubes filled with breath samples taken at room temperature and also stored at room temperature, the mean percent loss of PERC was 64.8 ± 9.4.

In experiments conducted with trichloroethylene, it was found that tubes stored at 37°C evidenced higher vapor retention rates. If samples of breath were exhaled into tubes at 37°C, water vapor would not condense from the sample. Additional experiments with trichloroethylene indicated that siliconized tubes showed a lower solvent decay than non-siliconized tubes.

Partitioning of PERC between the vapor and liquid states appears to be a reasonable explanation to account for the vapor retention loss.

Pasquini concluded that the breath sampling technique cannot successfully measure a solvent concentration in a breath sample unless the above considerations are utilized. Condensation of water is a major factor when analyzing decay of the solvent in the breath container. When these variables are ignored, erroneous results in the solvent concentration data of breath samples can be expected. The overall accuracy and precision of this study were not reported.

3.2.4.2 Saran and Teflon® Containers. Saran bags as storage containers for PERC vapors have been evaluated by Desbaumas and Imhoff.[19] Although it was concluded that Saran can be an acceptable container, the diffusion rate of PERC was appreciable over a 24-hour storage period. Storage temperature was not reported. The diffusion curve for PERC is shown in Figure 3-1. Analyses were performed by flame ionization detection.

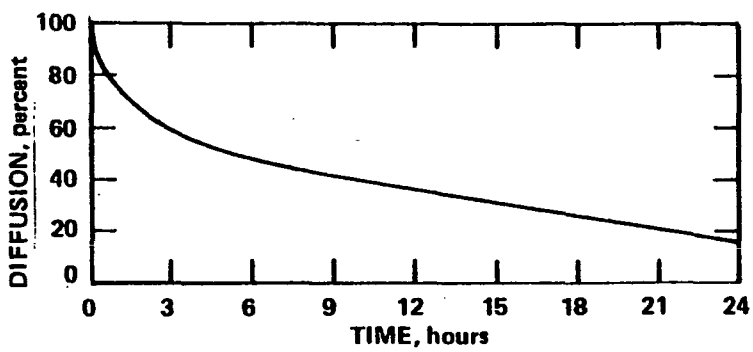


Figure 3-1. Diffusion curve for tetrachloroethylene from Saran containers.19

Teflon® containers were judged by Drasche et al.[20] to be more suitable than Saran bags even though losses of PERC due to adherence to Teflon® surfaces were appreciable. Within the first 30 minutes after introduction of a mixture (relative humidity = 45 percent) of benzene, trichloroethylene, and PERC into a Teflon® bag, vapor concentrations of each dropped 40 to 60 percent. However, upon heating the bag to 100°C for 30 minutes after the mixture had been stored for 44 hours at 25°C, concentrations rose to the initial values.

3.2.5 Calibration

According to a recent National Academy of Sciences report,[13] there are no calibration standards for PERC.

Singh et al.[11] reported that multiple dilution of pure materials at ppt levels is tedious and inaccurate; surface sorption and heterogenous reactions are predominant factors leading to inaccuracies. Permeation tubes, while satisfactory for many halocarbons in establishing primary standards, were judged unsatisfactory for PERC.[11] The permeation rate at the 95 percent confidence limit was 64.8 ± 26.1 nanograms/minute. While PERC permeation tubes were observed to perform satisfactorily for short time periods, errors of less than 10 percent were difficult to obtain.

3.2.6 Standard Methods

The analytical method, 5335, suggested by NIOSH[14] for organic solvents in air utilizes adsorption on charcoal followed by desorption with carbon disulfide. The resulting effluent is analyzed by gas chromatography. This method is recommended for the range 96 to 405 ppm (655 to 2,749 mg/m^3). The coefficient of variation is 0.052.

With the method, interferences are minimal and those that do occur can be eliminated by altering chromatographic conditions.

A disadvantage is that the charcoal may be overloaded, thus limiting the amount of sample that can be collected.

3.3 SUMMARY

An analytical approach which affords high sensitivity, precision comparable to GC-MS, and a capability for *in situ* monitoring of low concentrations of tetrachloroethylene in ambient air/water samples is the gas chromatograph-electron capture detector. With this system, the lower detection limit is on the order of a few parts per trillion (v/v). It is specific for chlorinated hydrocarbons; interferences as a result of the use of solid sorbents to trap vapors are eliminated or reduced. This approach makes it possible to determine concentrations of tetrachloroethylene coulometrically.

3.4 REFERENCES FOR CHAPTER 3

1. Handbook of Chemistry and Physics, 57th Edition, CRC Publishing Co., Cleveland, Ohio, 1976.

2. Hardie, D. W. F. "Chlorocarbons and Chlorohydrocarbons" The Encyclopedia of Chemical Technology, second edition, 1966. p. 195-203.

3. Gonikberg, M. G., V. M. Zhulin, and V. P. Butuzor. Bull. Acad. Sci. USSR. Dir. Chem. Sci. 739: 1956 (English transl).

4. Bonse, G., and H. Henschler. Chemical reactivity, biotransformation, and toxicity of polychlorinated aliphatic compounds. CRC Crit. Rev. Toxicol. 4(4):395-409, 1976.

5. Williamson, D. G., and R. J. Cvetanovic. Rates of reaction of ozone with chlorinated and conjugated olefins. JACS, 90:4248, 1968.

6. Pellizzari, E. D. Electron capture detection in gas chromatography. J. Chromat. 98:323-361, 1974.

7. Lillian, D., and H. B. Singh. Absolute determination of atmospheric halocarbons by gas phase coulometry. Anal. Chem. 46(8):1060-1063, 1974.

8. Cronn, D. R., R. A. Rasmussen, and E. Robinson. Phase I Report. Measurement of Tropospheric Halocarbons by Gas Chromatography-Mass Spectrometry. Washington State University, August 1976.

9. Rasmussen, R. A., D. E. Harsch, D. H. Sweany, J. P. Krasnec, and D. R. Cronn. Determination of atmospheric halocarbons by a temperature-programmed gas chromatographic freezeout concentration method. J. Air Pollut. Control Assoc. 27(6):529-581, 1977.

10. Russell, J. W., and L. A., Shadoff. The sampling and determination of halocarbons in ambient air using concentration on porous polymer. J. Chromat. 134:375-384, 1977.

11. Singh, H. B., L. Salas, D. Lillian, R. R. Arnts, and A. Appleby. Generation of accurate halocarbon primary standards with permeation tubes. Environ. Sci. Technol. 11:511-513, 1977.

12. Pellizzari, E. D. Measurement of carcinogenic vapors in ambient atmospheres. Final Report EPA 600/7-78-062, April 1978.

13. Singh, H. B., L. J. Salas, and L. A. Cavanagh. Distribution, sources and sinks of atmospheric halogenated compounds. J. Air Pollut. Control Assoc. 27:332-336, 1977.

14. National Institute for Occupational Safety and Health Manual of Analytical Methods. 2nd Edition, Part II. NIOSH Monitoring Methods. Vol. 3, April 1977.

15. Melcher, R. G., R. R. Langner, and R. O. Kagel. Criteria for the evaluation of methods for the collection of organic pollutants in air using solid sorbents. Am. Ind. Hyg. Assoc. 39(5):349-361, 1978.

16. Schnell, W., and G. Fischer. Carbon dioxide laser absorption coefficients of various air pollutants. Appl. Optics. 14(a):2058-2059, 1975.

17. National Academy of Science, Nonfluorinated halomethanes in the environment. Panel on low molecular weight halogenated hydrocarbons of the coordinating committee for scientific and technical assessments of environmental pollutants, 1978.

18. Pasquini, D. A. Evaluation of glass sampling tubes for industrial breath analysis. Am. Ind. Hyg. Assoc. 39(1):55-62, 1978.

19. Desbaumes, E., and C. Imhoff. Use of Saran bags for the determination of solvent concentration in the air of workshops. Staub-Reinhalt. Luft. 31(6):36-41, 1971.

20. Drasche, H., L. Funk, and R. Herbolsheimer. Storing of air samples for the analysis of contaminants especially of chlorinated hydrocarbons. Staub-Reinhalt Luft 32(9):20-25, 1972.

4. SOURCES AND EMISSIONS

Tetrachloroethylene, also called perchloroethylene (PERC), is principally used as a solvent for the dry cleaning of fabrics and, to a lesser extent, in the vapor degreasing of metals. Because of its volatility and its dispersive use pattern, much of the PERC produced worldwide is emitted into the atmosphere. These emissions from localized sources, subject to atmospheric transport and transformation factors (Chapter 5), may pose a hazard to human health (Chapter 9). Anthropogenic emissions are major, if not sole, sources of ambient levels of PERC. There are no known natural sources.

To gauge the effects present and future emissions of PERC may have on human health, this chapter presents profiles of PERC production, usage, and emissions.

4.1 PRODUCTION

Tetrachloroethylene may be produced by several processes:

1. Chlorination of trichloroethylene:

$$CHCl = CCl_2 + Cl_2 \xrightarrow[SbCl_3]{80°C} CHCl_2\,CCl_3$$

$$2CHCl_2CCl_3 + Ca(OH)_2 \xrightarrow{80°C} Cl_2C = CCl_2 + CaCl_2 + 2H_2O$$

2. Dehydrochlorination of S-tetrachloroethane:

$$CHCl_2\text{-}CHCl_2 + Cl_2 \longrightarrow CCl_2 = CCl_2 + 2HCl$$

3. Oxygenation of S-tetrachloroethane:

$$2CHCl_2CHCl_2 + O_2 \longrightarrow 2CCl_2 = CCl_2 + 2H_2O$$

4. Chlorination of acetylene

$$CCl_2 = CCl_2 + Cl_2 \xrightarrow{200°C} CCl_3\text{-}CCl_3$$

$$CH \equiv CH + 3\ CCl_3CCl_3 \xrightarrow[catalyst]{200\text{-}400°C} 4CCl_2 = CCl_2 + 2HCl$$

5. Chlorination of hydrocarbons:

$$C_3H_8 + 8\ Cl_2 \longrightarrow CCl_2 = CCl_2 + CCl_4 + 8HCl$$

(propane)

$$2CCl_4 \longrightarrow CCl_2 = CCl_2 + 2Cl_2$$

6. Oxychlorination of 1,2-dichloroethane:

$$2C_2H_4Cl_2 + 5Cl_2 \longrightarrow C_2H_2Cl_4 + C_2HCl_5 + 5HCl$$

$$C_2H_2Cl_4 + C_2HCl_5 \longrightarrow C_2HCl_3 + 2HCl + CCl_2 = CCl_2$$

$$7HCl + 1.75\ O_2 \longrightarrow 3.5\ H_2O + 3.5\ Cl_2$$

$$2C_2H_4Cl_2 + 1.5\ Cl_2 + 1.75\ O_2 \longrightarrow C_2HCl_3 + CCl_2 = CCl_2 + 3.5\ H_2O$$

The bulk of PERC production in the United States is derived from the oxychlorination of 1,2-dichloroethane or via pyrolysis of hydrocarbons.[1]

Recent information collected by the International Trade Commission places PERC production in the United States, in 1977, at 300,000 metric tons.[2] The total U.S. market in 1977 for PERC was reported to be 263,000 metric tons.[3] Imports of PERC may be sizeable although they are partially offset by exports. For example, during April and May 1978, 7,200 metric tons of PERC were imported.[3] During the same period, exports totalled 5,800 metric tons.[4,5] Stephenson[6] estimated 1975 U.S. production at 333,000 metric tons.

Snelson et al.[7] estimated worldwide production of PERC at 750,000 metric tons with use as a dry cleaning solvent accounting for 65 percent of the total production end use as of 1973. United States production for 1973 was estimated by Arthur D. Little, Inc. at 440,000 metric tons; use as a dry cleaning solvent and in textile processing accounted for 65 percent of production.[8] Of the worldwide production of 750,000 metric tons in 1973,

the United States was estimated to have produced 45 percent of the total.[7] Fishbein reported that 680,000 metric tons were produced worldwide in 1972.[9]

According to U.S. Tariff Commission statistics, the U.S. production figures for PERC have remained relatively constant during the decade 1967 to 1977.

In the period from 1960 to 1970, the annual production increase averaged 12 percent.[10] Blackford[10] estimated worldwide demand for PERC to reach 1.2 x 10^6 tons per year by 1980. For the period 1968-1973, the world production growth rate was 6 percent per year.[8] However, due to decreased usage as a chemical intermediate and because of competition from other dry cleaning solvents (petroleum-based), growth is likely to be in the range of 3 to 4 percent from 1978 to 1983.[5]

The major producers and production capacities are shown in Table 4-1. Locations of U.S. production facilities are shown in Figure 4-1.

4.2 USAGE

Tetrachloroethylene has the following uses:[9,11] (1) dry cleaning solvent; (2) textile scouring solvent; (3) dried vegetable fumigant; (4) rug and upholstery cleaner; (5) stain, spot, lipstick, and rust remover; (6) paint remover; (7) printing ink ingredient; (8) heat transfer media ingredient; (9) chemical intermediate in the production of other organic compounds; and (10) metal degreaser.

Use as a dry cleaning solvent in 1973 consumed approximately 65 percent of the total U.S. production.[8] About 90 percent of the dry cleaners in the United States use PERC, and this solvent constitutes approximately 80 percent of the dry cleaning market.[12]

TABLE 4-1. MAJOR PRODUCERS OF TETRACHLOROETHYLENE[5]

Organization	Yearly capacity, tons
Dow Chemical	150,000
PPG	120,000
Vulcan	95,000
Diamond Shamrock	82,500
Ethyl Corporation	50,000
Stauffer Chemical	35,000
E. I. du Pont de Nemours	not reported
Occidental Petroleum	not reported

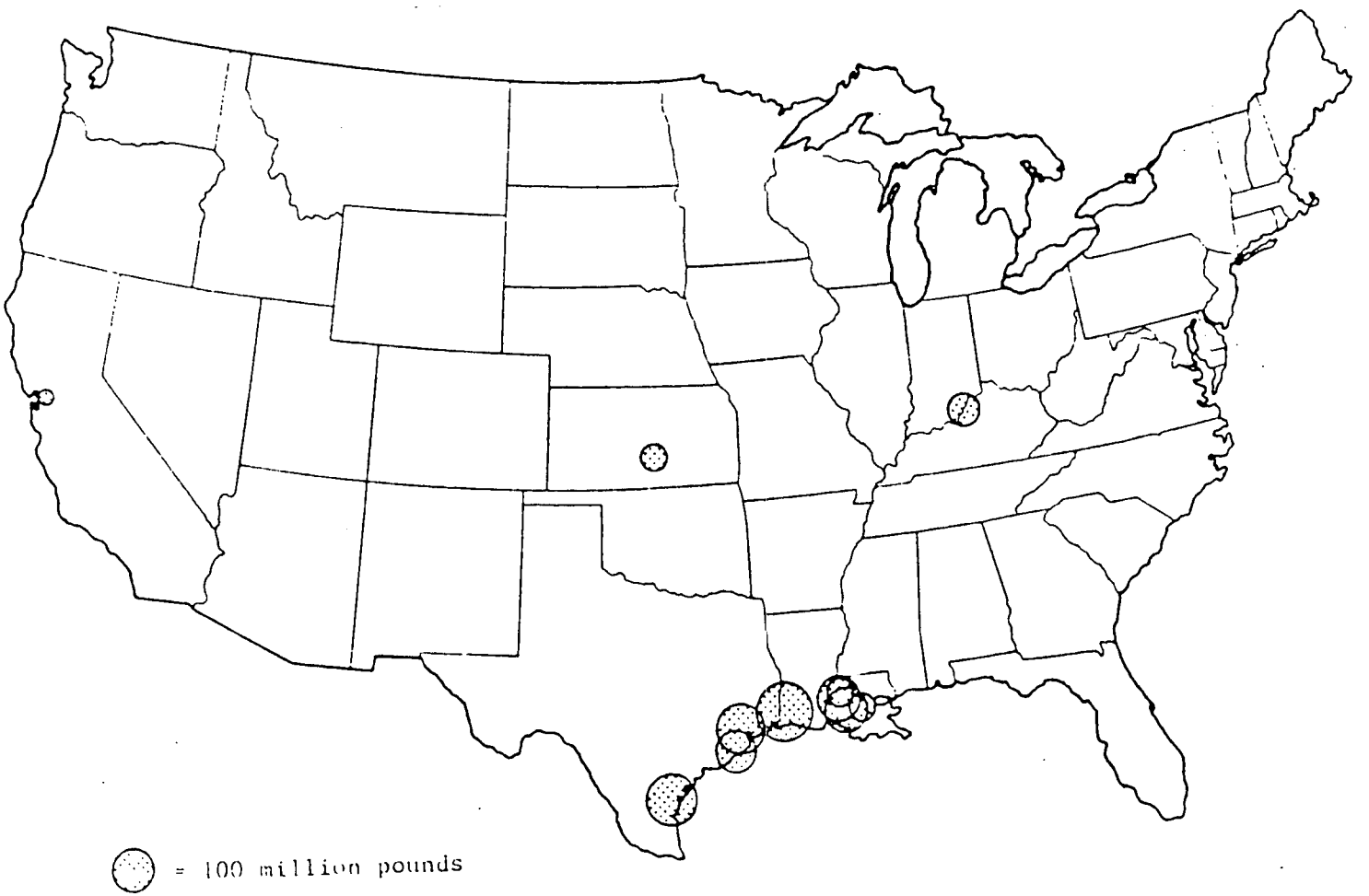


Figure 4-1. Locations of U.S. tetrachloroethylene production facilities producing more than 100 million pounds.[13]

According to Blackford,[10] increases in the number of coin-operated dry cleaning machines account for the relatively constant amounts of PERC used by the industry. These machines offset the decreased consumer usage of professional shops. These coin-operated establishments were reported to use more PERC per pound of clothing than do the professional shops and represent a major source of PERC emissions to the atmosphere.[13]

4.3 EMISSIONS

Emissions of tetrachloroethylene arise during its production, use as a chemical intermediate in industrial processes, from storage containers, during disposal, and use as a solvent.

Lillian et al.[14] estimated annual worldwide emissions of PERC into the troposphere at 450,000 metric tons. Singh,[15] taking into account historical use and production patterns, estimated that emissions to May 1976 were 11.7 million metric tons. Singh estimated that emissions are greater than 90 percent of the amount of PERC used in the United States.[16] Snelson et al.[7] estimated worldwide emissions in 1973 at 622,700 metric tons (83 percent of 1973 worldwide production). The authors estimated the U.S. contribution to worldwide emissions at 45 percent. Stephenson[6] estimated that 255,000 metric tons of PERC are released to the atmosphere annually in the United States. Shamel et al.[8] estimated that emissions of PERC in the United States in 1973 were 272,000 metric tons. Use as a dry cleaning and textile processing solvent were estimated to account for 77 percent of total estimated U.S. emissions.[8] The authors estimated the U.S. contribution to worldwide emissions (609,000 metric tons) at 45 percent. Using data obtained from the literature, government agencies, and industrial companies, Eimutis and Quill[17] estimated that annual emissions of PERC from degreasing operations were 77,885 metric tons.

4.4 SUMMARY

Of the approximately 300,000 metric tons of tetrachloroethylene (PERC) produced in the United States annually, 80 to 95 percent is emitted to the atmosphere. Due to the dispersive use pattern, emissions occur at many sites throughout the United States.

4.5 REFERENCES FOR CHAPTER 4

1. Lowenheim, F. A., and M. K. Moran. Perchloroethylene. In: Faith, Keyes, and Clark's Industrial Chemicals. Fourth edition, 1975. pp. 604-611.

2. Chemical and Engineering News, June 12, 1978. p. 49.

3. Chemical Marketing Reporter, August 7, 1978.

4. Chemical Marketing Reporter, July 10, 1978.

5. Chemical Marketing Reporter, August 14, 1978.

6. Stephenson, M. E. An approach to the identification of organic compounds hazardous to the environment and human health. Paper presented at the International Symposium of Chemical and Toxicological Aspects of Environmental Quality, Munich, Germany. September 9, 1975.

7. Snelson, A., R. Butler, and F. Jarke. Study of Removal Processes for Halogenated Air Pollutants. EPA-600/3-78-058. Environmental Sciences Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, N. C., 1978.

8. Shamel, R. E., J. K. O'Neill, and R. Williams. Preliminary economic impact assessment of possible regulatory action to control atmospheric emissions of selected halocarbons. EPA-450/3-75-073. U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, 1975.

9. Fishbein, L. Potential Industrial Carcinogens and Mutagens. EPA-560/5-77-005, Office of Toxic Substances, Environmental Protection Agency. May, 1977.

10. Blackford, J. L. Perchloroethylene. Chemical Economics Handbook, SRI International, Menlo Park, California, 1975.

11. Clinical Toxicology of Commercial Products, Gosselin et al., 4th Edition, 1976.

12. U.S. Environmental Agency statistics based on data supplied by industry sources, 1978.

13. Fuller, B. B. Air Pollution Assessment of Tetrachloroethylene, Mitre Corp., February, 1976.

14. Lillian, D., H. B. Singh, A. Appleby, L. Lobban, R. Armis, R. Gumpert, R. Hague, J. Toomey, J. Kazazis, M. Antell, D. Hansen, and B. Scott. Atmospheric fates of halogenated compounds. Environ. Sci. Technol. 9(12):1042-1048, 1975.

15. Singh, H. B. Atmosphere halocarbons: Evidence in favor of reduced average hydroxyl radical concentration in the troposphere. Geophy. Res. Lett. 4(3):101, 1977.

16. Singh, H. B. Personal Communication, October 1978.

17. Eimutis, E. C., and R. P. Quill. Source Assessment: Noncriteria Pollutant Emissions. EPA-600/2-77-107e. Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, 1977.

5. ATMOSPHERIC TRANSPORT, TRANSFORMATION, AND FATE

The potential for ambient air concentrations of tetrachloroethylene, also called perchloroethylene (PERC), to pose a hazard to human health is influenced by many processes which occur in the troposphere. Such factors include: transformation of PERC into other atmospheric components which may also pose a health hazard; diffusion into the stratosphere where PERC may participate in ozone (O_3) destruction reactions; meteorological factors to include urban transport; and the tropospheric chemical reactivity of PERC.

5.1 TROPOSPHERIC REACTIVITY

5.1.1 Residence Time

Concern that PERC may participate, to a significant degree, in stratospheric O_3 destruction reactions is allayed by recent investigations that indicate a tropospheric lifetime for PERC of 1 year or less.[1-3] These investigations, however, suggest that the tropospheric lifetime for PERC is longer than previously believed.[4-8] The estimates of a longer lifetime (16 weeks to 1 year) are indicated by recent estimations[2,3,9] of a hydroxyl free radical (·OH) concentration in the atmosphere, lower by a factor of five than concentrations commonly accepted in the past.

Reaction with ·OH is the principal process by which many organic compounds, including PERC, are scavenged from the troposphere. These radicals are produced upon irradiation of O_3 to produce singlet atomic oxygen [$O^1(D)$] which then reacts with water vapor. The tropospheric lifetime of a compound is related to the ·OH concentration according to the expression:

$$\tau_{\text{lifetime}} = \frac{1}{k\,[\cdot OH]}$$

where k is the rate constant of the reaction.

Singh,[2,3] using an atmospheric budget model, calculated an average ·OH concentration of 2×10^5 to 6×10^5 molecules cm^{-3}. A tropospheric lifetime for PERC of 21 ± 5 weeks was calculated. From the isopleth modelling approach of Crutzen and Fishman,[9] a similar average concentration of ·OH (2×10^5 to 4×10^5 molecules cm^{-3}) was derived.

Altshuller,[1] using an average ·OH concentration of 3×10^5 molecules cm^{-3} and the kinetic data of Chang and Kaufman,[10] calculated a tropospheric lifetime for PERC of 1 year. The rate constant expression ($9.44 \times 10^{-12} e^{-1199/T}_{(297\text{-}420°K)}$ cm^3 $molecule^{-1}$ $second^{-1}$) of Chang and Kaufman[10] was used.[1] Chang and Kaufman[10] had calculated a tropospheric lifetime for PERC of 19 weeks. This estimate was, in part, based on a surface ·OH concentration of 1×10^6 molecules per cm.[3]

As the tropospheric lifetime time for PERC would be expected to increase as the ·OH concentration decreased, hydroxyl radical mechanisms have a direct bearing on the amount of PERC that can diffuse into the stratosphere. If current estimates of ·OH abundance are correct, approximately 2 to 3 percent of the tropospheric PERC could diffuse into the stratosphere.[11]

Higher levels of ·OH have been reported for the southern hemisphere compared to those in the northern hemisphere; this gradient may be caused by atmospheric carbon monoxide (CO), an effective sink for ·OH.[11] Measure ments of PERC and some other reactive halocarbons indicate that concentrations are higher in the northern hemisphere (where the concentration of ·OH is low) and where most of the PERC is released.[12]

5.1.2 Chamber Studies

Lillian et al.[5] irradiated a mixture of PERC, nitrogen dioxide (NO_2), and reactive hydrocarbon (60% paraffin, 13% olefin, and 27% aromatic). The concentrations were: PERC, 700 ppb (4.7 mg/m^3); NO_2, 500 ppb (0.94 mg/m^3); hydrocarbon, 1000 ppb. During 13 hours of irradiation, the concentration of PERC decreased. While PERC decreased, an increase in phosgene ($COCl_2$) was observed.

The experiments of Gay et al.[13] evidenced a wide variety of transformation products when a mixture of PERC (5000 ppb; 33.9 mg/m^3) and NO_2 (1800 ppb; 3.4 mg/m^3) was irradiated with ultraviolet radiation. Hydroxyl free radicals were generated. Products observed were O_3, hydrogen chloride (HCl), CO, formic acid, $COCl_2$, and trichloroacetyl chloride. In these experiments, NO_2 was photolyzed, and O_3 and free radicals were formed. Tetrachloroethylene formed an epoxide intermediate which, upon rearrangement, formed trichloroacetyl chloride. Seven percent of the PERC reacted after 140 minutes irradiation; the amount of HCl produced was almost four times the amount of $COCl_2$. Compared to vinyl chloride, trichloroethylene, 1,2-dichloroethylene, ethylene, and 1,1-dichloroethylene, the reactivity of PERC was low. The slow rate of disappearance of PERC under these reaction conditions is indicative that free chlorine radicals did not participate to any significant degree. Carbon tetrachloride (CCl_4) was not reported as a transformation product.

Singh et al.[14] reported that trichloroacetyl chloride may undergo heterogenous reactions to form CCl_4. It was observed experimentally that CCl_4 was formed when PERC in air was irradiated; concentrations of CCl_4 continued to increase after all the PERC had reacted. At the same time, trichloroacetyl chloride continued to react, suggesting its role as the

CCl_4 precursor. Photodecomposition of PERC, over 7 days, led to the formation by weight of about 8 percent CCl_4 and 70 to 85 percent $COCl_2$. Singh and co-workers concluded that, under these simulated tropospheric conditions, PERC is photolyzed followed by chlorine-sensitized photo-oxidation.[14]

These reaction conditions and observations are not suggested as representative of "real world" tropospheric conditions; it was suggested that trichloroacetyl chloride may undergo surface reactions in the gas chromatograph to form CCl_4.[15]

Lillian and co-workers[4] observed a conversion of PERC, on a chlorine basis, to $COCl_2$ of 60 percent. A mixture of PERC (800 ppb; 5.4 mg/m^3) and NO_2 (500 ppb; 0.94 mg/m^3) was irradiated at a relative humidity of 50 percent. The maximum $COCl_2$ concentration observed was 0.95 ppm. The authors estimated on the basis of the observed results that an ambient concentration of 10 ppb (0.068 mg/m^3) PERC, such as observed in New York City (Chapter 6), could lead to the formation of 12 ppb $COCl_2$. However, the estimate of the tropospheric half-life by these investigators was less than 1 week; the more recent estimates,[1-3] which suggest a higher half-life for PERC, may indicate that ambient levels of $COCl_2$ resulting from PERC reaction mechanisms may be lower than previously believed.

In the absence of irradiation, PERC does not react or reacts slowly with O_3, NO, and NO_2.[5] A low rate of reaction between O_3 and PERC also has been observed by Williamson and Cvetanovic.[16]

Using rate data[17] pertaining to PERC reaction with O_3 and ·OH, Altshuller[1] calculated that PERC reacts 3×10^3 more rapidly with ·OH than with O_3. Assuming an average ·OH concentration of 3×10^5 molecules cm^{-3}, the rate

of reaction was 5×10^{-8}. In the PERC reaction with O_3, an average O_3 concentration of 10^{12} molecules cm^{-3} was used, resulting in a rate of 1.5×10^{-11}.

Mathias et al.[18] also observed a very slow rate of reaction of PERC with O_3 compared to the reaction with alkenes.[17]

Huybrechts[19] observed a yield of 85 ± 5 percent trichloroacetyl chloride and 15 ± 5 percent $COCl_2$ when PERC was irradiated in the presence of O_2. Trace quantities of carbon tetrachloride (CCl_4) and tetrachloroethylene epoxide also were observed. Mathias et al.[18] observed that $COCl_2$ was the major product when PERC was irradiated in an oxygen-enriched environment. Tetrachloroethylene epoxide, observed when PERC was irradiated in the presence of O_3 only, was not formed in the presence of O_2.

5.2 ENVIRONMENTAL SIGNIFICANCE OF TETRACHLOROETHYLENE TRANSFORMATION PRODUCTS

The environmental significance of the production of $COCl_2$ from PERC has been discussed by Singh and co-workers.[20,21] The amount of $COCl_2$ produced is directly related to the residence time and reactivity of PERC in ambient air. As PERC emissions are likely to be higher in urban areas, the reactivity of this halocarbon may result in high concentrations of $COCl_2$ during adverse meteorological conditions in and around urban centers.[21] A recent review[22] indicates that $COCl_2$ is a secondary anthropogenic pollutant of concern.

The formation of carbon tetrachloride (CCl_4), as well as methyl chloroform, from PERC in the troposphere has been reported to be negligible.[23] Phosgene appeared to be the major transformation product. While the studies of Gay et al.[13] have indicated that trichloroacetyl chloride may be formed through

chlorine atom migration in an epoxide intermediate, evaluation of ·OH and oxygen atom rate constants indicates that less than 1 percent of PERC in ambient air will react with atomic oxygen and, of the activated epoxides formed, only a small percentage will undergo rearrangement.[24]

5.3 REMOVAL OF TETRACHLOROETHYLENE FROM THE TROPOSPHERE

The reaction sequence by which PERC may be scavenged from the troposphere is as follows:[24]

$$C_2Cl_4 + HO\cdot \longrightarrow HOC(Cl)_2C(Cl)_2\cdot$$

$$HOC(Cl)_2C(Cl)_2\cdot + O_2 \longrightarrow HOC(Cl)_2C(Cl)_2O_2\cdot$$

$$HOC(Cl)_2C(Cl)_2O_2\cdot \xrightarrow[\text{abstraction}]{\text{oxygen}} HOC(Cl)_2C(Cl)_2O\cdot$$

$$HOC(Cl)_2C(Cl)_2O\cdot \longrightarrow HOC(Cl)_2\cdot + COCl_2$$

$$HOC(Cl)_2\cdot + O_2 \longrightarrow COCl_2 + HO_2\cdot$$

Howard[23] suggested that the reaction path for the atmospheric oxidation of PERC may follow the scheme below, leading to production of oxalochloride:

$$C_2Cl_4 + \cdot OH \longrightarrow C_2Cl_2OH\cdot$$

$$\longrightarrow CCl_2CClOH\cdot + Cl\cdot$$

$$CCl_2CCl_2OH\cdot + O_2 \longrightarrow O_2CCl_2CCl_2OH$$

$$O_2CCl_2CCl_2OH + NO \longrightarrow COClCCl_2OH\cdot + NO_2 + Cl\cdot$$

$$\cdot OH + COClCCl_2OH \longrightarrow COClCOCl + H_2O + Cl\cdot$$

Compared to other ethylene compounds studied, Howard reported that PERC exhibits unusually low reactivity toward hydroxyl radicals.[23]

Snelson et al.[8] suggested that trichloroacetyl chloride and $COCl_2$ would hydrolyze to the corresponding chloroacetic acids and hydrogen chloride

via homogeneous gas phase hydrolysis. The acids then would presumably be washed out of the atmosphere. The results of Singh et al.[21] indicate that because phosgene is very stable in the gas phase, negligible tropospheric loss via gas phase hydrolysis would be expected. The two important sinks of phosgene are heterogenous decomposition and slow liquid phase hydrolysis.[21] It was concluded by Singh[21] that phosgene is removed slowly from the atmosphere. After intermittent rainfall, a slight decline in $COCl_2$ was observed.[25]

The observed diurnal variations of PERC indicate that PERC is present in ambient air in higher concentrations in the morning and evening than at other times.[5,25]

The diurnal variation in New York City shown in Figure 5-1 exhibited peaks in PERC concentration at approximately 10 a.m. and 6 p.m.[5] Peaks in the PERC concentration at approximately 10 a.m. and 6 p.m. were observed by Ohta et al. in Tokyo,[26] who reported that concentrations tended to be highest on cloudy days and lowest on rainy days.

Singh et al.[25] suggested that the reduced solar flux in winter months would permit a much longer transport of PERC and other chloroethylenes because of reduced reactivity.

Based on estimates and measurements of ·OH concentration during summer and winter months and the rate of ·OH reaction with PERC, Altshuller[1] estimated that a 1 percent consumption of PERC by ·OH reaction would take 14 days during the month of January as opposed to 1 day in July. With respect to reaction of PERC with ·OH, appreciable concentrations of PERC from anthropogenic sources could be transported to rural continental sites during all seasons.

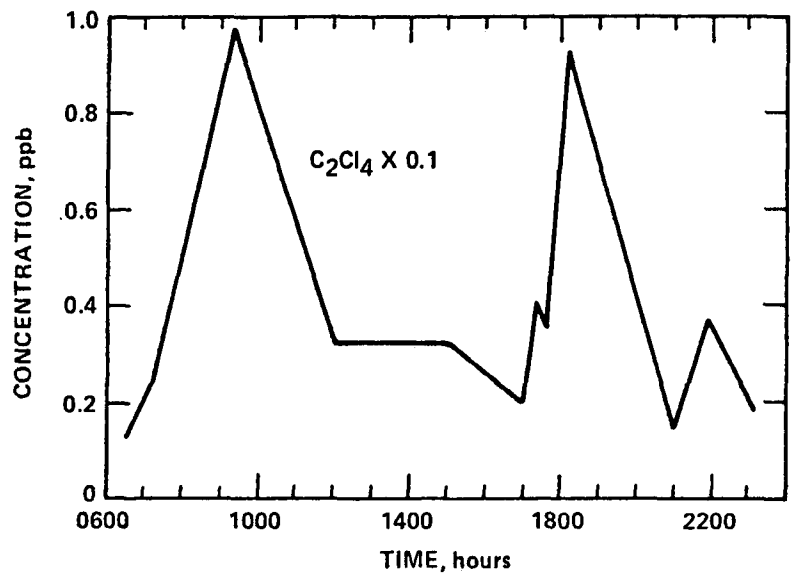


Figure 5-1. Diurnal variations in tetrachloroethylene concentrations in New York City.[5]

5.4 SUMMARY

Tetrachloroethylene is reactive in the troposphere to the extent that it has an estimated lifetime from 16 weeks to 1 year. Concentrations of PERC in ambient air are subject to diurnal variations and are expected to be higher in and around urban centers. Due to seasonal variations in solar intensity, tropospheric concentrations of PERC are expected to be higher in the winter season.

The principal scavenging mechanism for PERC in the troposphere is through a reaction pathway mediated by hydroxyl free radicals. The residence time of PERC is highly dependent on hydroxyl radical concentrations in ambient air.

The major transformation product as a result of tropospheric reactions involving PERC is phosgene. Minor products that may be formed are trichloroacetyl chloride and carbon tetrachloride.

5.5 REFERENCES FOR CHAPTER 5

1. Altshuller, A. P. Lifetimes of organic molecules in the troposphere and lower stratosphere. Environ. Sci. Technol., in press.

2. Singh, H. B., L. J. Salas, H. Swiegeishi, and A. H. Smith. Fate of halogenated compounds in the atmosphere. Interim Report 1977, EPA-600/3-78-017, 1978.

3. Singh, H. B. Atmospheric halocarbons. Evidence in favor of reduced average hydroxyl radical concentration in the troposphere. Geophy. Res. Lett. 4(3): 101-104, 1977.

4. Crutzen, P. J., I. S. A. Isaksen, and J. R. McAfee. The impact of the chlorocarbon industry on the ozone layer. J. Geophy. Rev. 83:345-363, 1978.

5. Lillian, D., H. B. Singh, A. Appleby, L. Lobban, R. Arnts, R. Gumpert, R. Hague, J. Toomey, J. Kazazis, M. Antell, D. Hansen, and B. Scott. Atmospheric fates of halogenated compounds. Environ. Sci. Technol. 9(12): 1042-1048, 1975.

6. Yung, Y. L., M. B. McElroy, and S. C. Wofsy. Atmospheric halocarbons: A discussion with emphasis on chloroform. Geophy. Res. Lett. 2(9): 397-399, 1975.

7. Pearson, C. R., and G. McConnell. Chlorinated C_1 and C_2 hydrocarbons in the marine environment. Proc. Roy. Soc. Lond. B. 189: 305-332, 1975.

8. Snelson, A., R. Butler, and F. Jarke. Study of removal processes for halogenated air pollutants. EPA-600/3-78-058. Environmental Sciences Research Laboratory, U. S. Environmental Protection Agency, Research Triangle Park, N.C., 1978.

9. Crutzen, P., and J. Fishman. Average concentrations of OH in the tropospheric and the budgets of CH_4, CO, H_2, and CH_3CCl_3. Geophy. Res. Lett. 4(8):321-324, 1977.

10. Chang, J. S., and F. Kaufman. Kinetics of the reactions of hydroxyl radicals with some halocarbons: $CHFCl_2$, CHF_2Cl, CH_3CCl_3, C_2HCl_3, and C_2Cl_4. J. Chem. Phys. 66(11):4989-4994, 1977.

11. Singh, H. B. Personal communication, 1978.

12. Singh, H. B., L. J. Salas, H. Shigeishi, and E. Scribner. Global distribution of selected halocarbons, SF_6, and N_2O. Phase II Interim Report, SRI International, Menlo Park, California, May 1978.

13. Gay, B. W., P. L. Hanst, J. J. Bufalini, and R. C. Noonan. Atmospheric oxidation of chlorinated ethylenes. Environ. Sci. Technol. 10(1): 58-67, 1976.

14. Singh, H. B., D. Lillian, A. Appleby, and L. Lobban. Atmospheric formation of carbon tetrachloride from tetrachloroethylene. Environ. Lett. 10(3): 253-256, 1975.

15. Singh, H. B. Personal communication, 1978.

16. Williamson, D. G. and R. J. Cvetanovic. Rates of reaction of ozone with chlorinated and conjugated olefins. J. Am. Chem. Soc. 90: 4248, 1968.

17. Atkinson, R., K. R. Darnell, A. C. Lloyd, A. M. Winer, and J. N. Pitts, Jr. Kinetics and mechanisms of the reactions of the hydroxyl radical with organic compounds in the gas phase. Advances in Photochemistry, Volume 11, 1978.

18. Mathias, E., E. Sanhueza, I. C. Hisatsune, and J. Heicklen. The chlorine atom sensitized oxidation and ozonolysis of C_2Cl_4. Can. J. Chem. 52: 3852-3862, 1974.

19. Huybrechts, G., J. Olgregts, and K. Thomas. Trans. Faraday Soc. 63: 1647, 1967.

20. Singh, H. B., D. Lillian, and A. Appleby. Anal. Chem. 47: 860-864, 1975.

21. Singh, H. B. Phosgene in the ambient air. Nature 264(5585): 428-429, 1976.

22. National Institute for Occupational Safety and Health. Criteria for a recommended standard....Occupational Exposure to Phosgene, 1976.

23. Howard, C. J. Rate constants for the gas-phase reactions of OH radicals with ethylene and halogenated ethylene compounds. J. Chem. Phy. 65(11):148-154, 1976.

24. Personal communication. T. E. Graedel, Bell Laboratories to H. B. Singh, SRI International, October 1978.

25. Singh, H. B., L. Salas, H. Shigeishi, and A. Crawford. Urban-nonurban relationships of halocarbons, SF_6, N_2O, and other atmospheric trace constituents. Atmos. Environ. 11: 819-828, 1977.

26. Ohta, T., M. Morita, I. Mizoguchi, and T. Tada. Washout effect and diurnal variation for chlorinated hydrocarbons in ambient air. Atmos. Environ. 11: 985-987, 1977.

6. AMBIENT CONCENTRATIONS

6.1 AMBIENT AIR

A wide variety of halogenated aliphatic hydrocarbons, including tetrachloroethylene (PERC), have been determined in ambient air. Ambient measurements of PERC have been conducted in both the United States and other areas of the world. These determinations provide a basis for assessing the levels to which human populations may be exposed.

Measured ambient air concentrations differ widely and undoubtedly reflect the influences of a variety of factors, e.g., meteorological conditions, tropospheric reactivity, diurnal variations, and source emissions.

Tables 6-1 and 6-2 provide summary information regarding background and urban concentrations of PERC, respectively.

Evidence for variability in ambient air concentrations is shown by the results of Lillian et al.[1] at eight U.S. locations. The lowest concentration was reported at Whiteface Mountain, New York (0.03 ppb; 2×10^{-4} mg/m^3). The maximum level recorded was in New York City (10 ppb; 0.067 mg/m^3). Typical levels are shown in Table 6-3. As shown in Figure 6-1, the range of concentrations at each site also was quite variable and was observed to vary by almost an order of magnitude. Figure 6-2 shows the diurnal variation at New York City. The Whiteface Mountain measurement average was at the limit of sensitivity of the gas chromatographic system utilized. The gas chromatograph (GC) was equipped with an electron capture detector and flame ionization detector. Permeation tubes were used for GC calibration. The overall error associated with the analysis was less than ± 15 percent. Tetrachloroethylene

TABLE 6-1. BACKGROUND MEASUREMENTS OF TETRACHLOROETHYLENE

Location	Type of site	Date of measurement/ analytical method	Concentration ppb	Concentration mg/m^3	Reference
White Face Mountains, N. Y.	Nonurban	Sept. 17, 1974 GC/EC	<0.02 to 0.19	$<1.35 \times 10^{-4}$ to 12.8×10^{-4}	Lillian et al., 1975[1]
Sandy Hook, N. J.	Ocean (3 miles offshore)	July 2, 1974 GC/EC	0.15 to 1.4	10.17×10^{-4} to 94.9×10^{-4}	Ibid.
San Bernadino Mountains, Calif.	1,800 meters	Fall, 1972 GC/EC	0.09	6.10×10^{-4}	Simmonds et al., 1974[4]
California Coast	Coastal (inward flowing maritime air)		0.01	0.67×10^{-4}	Ibid.
Badger Pass, Calif. (Yosemite National Park)	Mountain 2,360 meters elevation	May 12-16, 1976	0.0307 ± 0.0105	$2.08 \times 10^{-4} \pm 0.71 \times 10^{-4}$	Singh et al., 1977[7]
Point Arena, Calif.	Marine	1976	0.0334 ± 0.0046	2.26×10^{-4} 0.31×10^{-4}	Singh et al., 1977[6]
Stanford Hills, Calif.	Clean Air	Nov. 24-30, 1975	0.0383 ± 0.0111	$2.59 \times 10^{-4} \pm 0.75 \times 10^{-4}$	Singh et al., 1977[10]
Point Reyes, Calif.	Clean Air	Dec. 2-12, 1975	0.0431 ± 0.0178	$2.92 \times 10^{-4} \pm 1.2 \times 10^{-4}$	Ibid.
North Atlantic Ocean	Ocean	Oct., 1973	0.021 ± 0.003	$1.44 \times 10^{-4} \pm 0.22 \times 10^{-4}$	Lovelock, 1974[12]
Northeast Atlantic Ocean	Ocean		0.0007	4.7×10^{-6}	Murray and Riley, 1973[13]

TABLE 6-2. URBAN CONCENTRATIONS OF TETRACHLOROETHYLENE

Location	Date of Measurement	Concentration, ppb (mg/m^3) Max.	Min.	Average	References
California					
Los Angeles	Apr. 29-May 4, 1976	2.267 (0.015)	0.0608 (0.0004)	0.674 ± 0.498 (0.0045 ± 0.0033)	Singh et al., 1977[7]
Los Angeles Basin	Fall, 1972	3.84 (0.0260)	0.37 (0.0025)	1.25 (0.00847)	Simmonds et al., 1974[4]
Palm Springs	May 5-11, 1976	1.153 (0.0075)	0.0177 (0.00012)	0.278 ± 0.232 (0.00188 ± 0.00157)	Singh et al., 1977[7]
Pasadena	Fall, 1972	4.2 (0.028	0.19 (0.0012	2.2 (0.015)	Simmonds et al., 1974[4]
Riverside	April 25-May 3, 1977	2.325 (0.01577)	0.096 (0.00065)	0.983 ± 0.454 (0.00667 ± 0.00307)	Singh et al., 1978[6]
Delaware					
Delaware City	July 8-10, 1974	0.51 (0.0034)	<0.02 (<0.0001)	0.24 (0.0016)	Lillian et al., 1975[1]
Maryland					
Baltimore	July 11-12, 1974	0.29 (0.0019	<0.02 (<0.0001)	0.18 (0.0012)	Ibid.
New Jersey					
Bayonne	March, 1973-Dec., 1973	8.2 (0.0055)	0.30 (0.0020)	1.63 (0.0110)	Ibid.
New Brunswick	-	-	0.5 (0.003)	-	Lillian et al., 1976[2]
New Brunswick	-	-	0.12 (0.0081)	-	Lillian et al., 1974[3]
Seagirt	June 18-19, 1974	0.88 (0.059)	0.10 (0.067)	0.32 (0.0022)	Lillian et al., 1975[1]

TABLE 6-2 (continued). URBAN CONCENTRATIONS OF TETRACHLOROETHYLENE

Location	Date of Measurement	Concentration, ppb (mg/m^3) Max.	Min.	Average	References
New York					
New York City	June 27-28, 1974	9.75 (0.0661)	1.0 (0.006)	4.5 (0.030)	Lillian et al., 1975[1]
Texas*					
Deer Park	-	-	0.002 (0.018×10^{-3})	-	Pellizzari, 1978[5]
	-	-	0.29 (0.002)	-	
Freeport	-	-	0.013 (0.094×10^{-3})	-	Ibid
	-	-	0.23 (1.585×10^{-3})	-	
Houston	-	-	0.004 (0.029×10^{-3})	-	Ibid
Laporte	-	-	trace	-	
	-	-	0.012 (0.083×10^{-3})	-	Ibid
Pasadena	-	-	0.003 (0.029×10^{-3})	-	Ibid
England					
Liverpool	March 25, 1972	-	0.01 (0.08×10^{-3})	-	Murray and Riley, 1973[13]
Japan					
Tokyo	-	-	1.2 (8.1×10^{-3})	-	Ohta et al., 1976[17]

*2-hr average measurements; GC/MS measurements made near sources of emissions

Date	Time	Location	Type of Site	ppb
6/27/74	11 p.m.	New York City	Urban	1.2
9/17/74	Noon	Whiteface Mountain, NY	Nonurban	0.09
7/2/74	2 p.m.	Sandy Hook, NJ	3 miles offshore	0.73
7/19/74	1 p.m.	Seagirt, NJ	National Guard Base	0.25
7/17/74	12:28 p.m.	Wilmington, OH	5,000 feet elevation above inversion	<0.02
7/17/74	12:03 p.m.	Wilmington, OH	1,500 feet elevation in an inversion layer	0.73

*Quantification was made by GC/EC

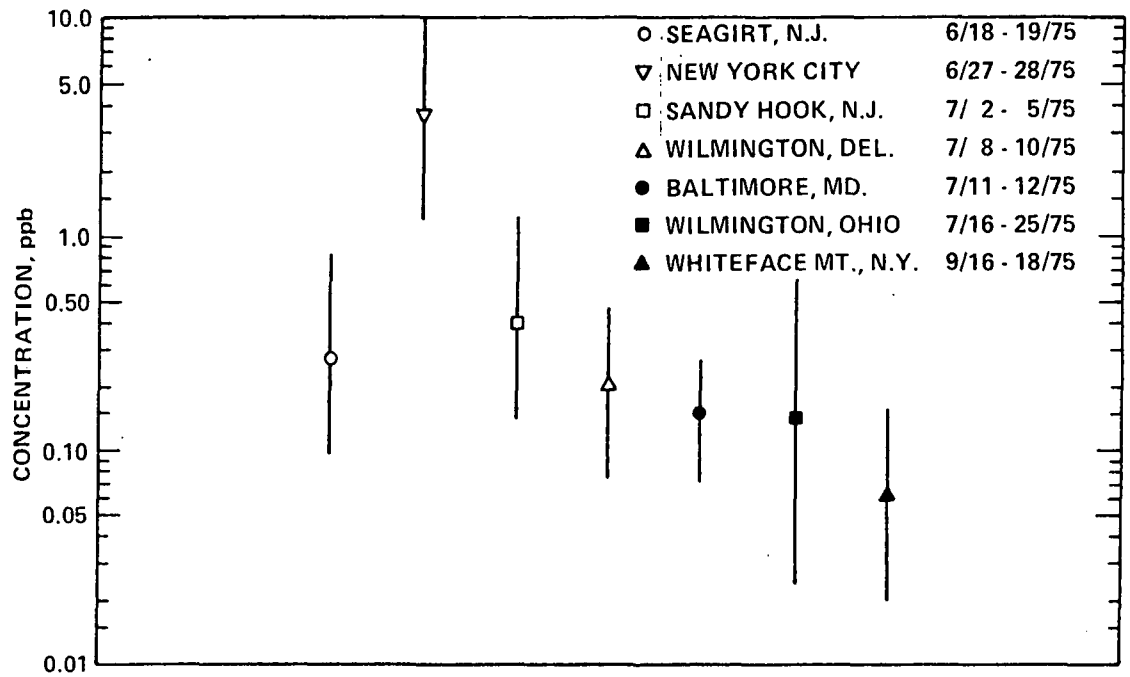


Figure 6-1. Tetrachloroethylene values at various locations.[1]

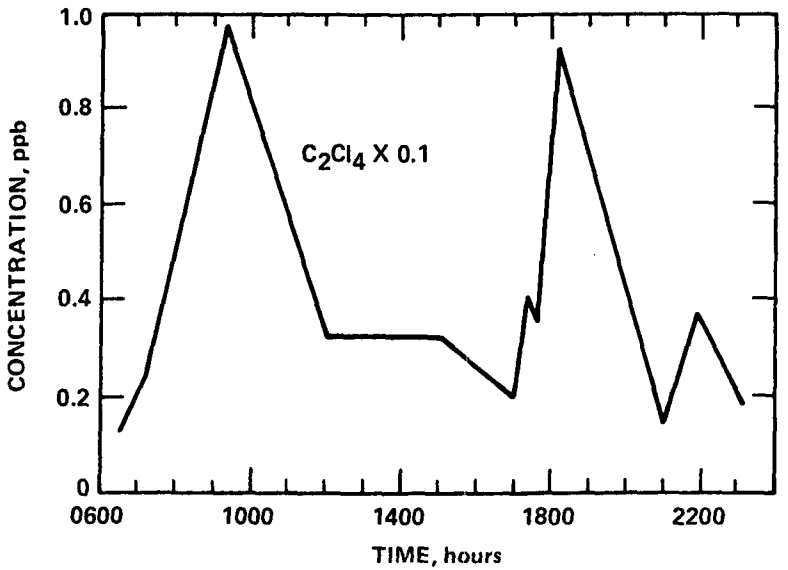


Figure 6-2. Diurnal variations in tetrachloroethylene concentrations in New York City.[1]

could be measured at least 50 percent of the time at all locations at concentrations exceeding 0.06 ppb (4×10^{-4} mg/m^3), and the distribution of the halocarbon was attributed to its tropospheric reactivity. The authors suggested that since sources of PERC are located primarily in urban areas, urban transport plays an important role in its distribution.

The urban air at a site in New Brunswick, New Jersey was found to contain 0.5 ppb (33.9×10^{-4} mg/m^3) by Lillian and co-workers.[2] A coulometrically operated gas chromatographic system using two electron capture detectors was used. An earlier study by Lillian and Singh,[3] using a different analytical technique, evidenced a concentration of 0.12 ppb (8.1×10^{-4} mg/m^3) in New Brunswick.

A study concerning the ambient air levels of several halogenated hydrocarbons was conducted by Simmonds and co-workers[4] in the Los Angeles Basin during the fall of 1972. Ambient concentrations were determined over a three-day sampling period at 42 sites. Analyses were made with a gas chromatograph equipped with an electron capture detector used coulometrically. Ambient concentrations were confirmed by comparison with a known solution prepared by multiple dilution. Precision and accuracy of the experimental procedure were not reported. Efforts were reported to have been made to avoid sampling in those areas in close proximity to known users of halocarbons.

The highest concentration of PERC was found in the Pasadena area (4.2 ppb; 0.028 mg/m^3) on a day of visible smog and stable inversion conditions. The lowest concentration was recorded in maritime air flowing inland (less than 0.01 ppb; 0.67×10^{-4} mg/m^3). Wind speed was recorded at 10 knots. High concentrations of PERC, judged by the authors to be due to local emissions, were found in the central Los Angeles business district.

Background levels taken at an altitude of 1,800 meters gave a 24-hour average concentration of 0.09 ppb (6.1×10^{-4} mg/m^3). Measurements were made in the San Bernadino Mountains during a 48-hour period.

At one coastal site, higher than expected concentrations of PERC were found (2.1 ppb; 0.014 mg/m^3). The investigators conjectured that either meteorological conditions caused an air mass to accumulate in the area or that the average was a result of local emissions.

Vertical profile measurements indicated that the concentration of PERC decreased with altitude. This decrease also was observed above a significant inversion layer at 1,700 meters. Diurnal measurements suggested that PERC was subject to fluctuations over a 24-hour period. Diurnal measurements were conducted in the West San Gabriel Valley.

Overall, a progressive decrease in the concentration of PERC, as well as three other halogenated compounds, was seen upon moving from the inland valleys to the coast.

A series of studies on the distribution and content of halogenated hydrocarbons in ambient air has been conducted by Pellizzari.[5] PERC was detected in the ambient air at measurement sites in New Jersey, California, Louisiana and Texas.

High concentrations were found in the air near a chemical waste disposal site and chemical manufacturing facility in Edison, New Jersey. Four locations, constituting upwind, downwind and crosswind directions, were selected for monitoring. Meteorological conditions at the time of measurement were recorded. Samples of ambient air (twice daily) were taken over a period of three days. Each sampling period was about 2 hours in duration and a volume of 100 to 150 liters was collected. A bed of Tenax GC in a glass cartridge was used to

concentrate PERC and other ambient air pollutants. Quantification was made by GC/MS. Tetrachloroethylene was one of six halogenated compounds detected in the ambient air in practically all the samples taken near the disposal site. Downwind sites evidenced higher PERC concentrations than upwind sites. Values reported ranged from trace amounts to a maximum concentration of 58 ppb (0.394 mg/m^3). The maximum concentration was recorded in the ambient air at the waste disposal site.

In Texas, PERC was detected in the ambient air at 15 of 18 locations. The site locations were selected on the basis of their proximity to areas of chemical manufacture and storage and transport facilities. The highest recorded concentrations were 0.29 ppb (1.9×10^{-3} mg/m^3) and 0.23 ppb (1.5×10^{-3} mg/m^3) at two sites. Concentrations measured at other sites were less than 0.012 ppb (0.81×10^{-4} mg/m^3). Site locations included several in the Houston area, Pasadena, Deer Park, Freeport, and La Porte. Levels of PERC are presented in Table 6-2.

Tetrachloroethylene also was detected in the ambient air at 4 of 5 sites in Geisman, Louisiana, an area of chemical industry and production of PERC. While detected at the upwind and crosswind measuring sites, it was not detected at the downwind site. The estimated highest concentration of PERC was 0.014 ppb (0.95×10^{-4} mg/m^3).

Analysis (1975) of ground level air for PERC at a location (Midland County, Michigan) 200 miles downwind from Chicago gave PERC concentrations of 30 to 50 ppt (0.2×10^{-3} to 0.3×10^{-3} mg/m^3). Analysis was performed by pre-concentrating air samples prior to temperature-programmed GC-EC determinations. Identity and quantification were confirmed by GC-MS.[6]

Measurements of PERC concentrations in urban, rural, and marine environments have been made by Singh et al.[7-11] using a GC/EC method.

Ambient air samples from Menlo Park, California (urban), evidenced 0.11 ppb (0.74×10^{-3} mg/m^3) PERC.[7] Measurements in Badger Pass, California (clean air), at an elevation of 2,360 meters, gave an average concentration of 0.0307 ± 0.0105 ppb ($2.08 \times 10^{-4} \pm 0.71 \times 10^{-4}$ mg/m^3).[8] The coefficient of variation was 34 percent. Singh et al.[7] used the Badger Pass measurements as representative of the northern hemisphere background concentrations in the lower troposphere. Point Arena,[6], a clean air site in the marine environment, gave an average concentration of 0.0334 ± 0.0046 ppb ($2.26 \times 10^{-4} \pm 0.31 \times 10^{-4}$ mg/m^3) when measured in May 1977. These data were reported by Singh et al.[7] to be representative of the average background concentration in the marine environment of the northern hemisphere. The coefficient of variation was 14 percent. Both sites were representative for background concentrations. At Reese River, Nevada (elevation 1,982 meters), an average PERC concentration of 0.0318 ± 0.0031 ppb ($2.1 \times 10^{-4} \pm 0.21 \times 10^{-4}$ mg/m^3) was reported.[6] The coefficient of variation was 10 percent. Quantification was made by GC/EC operated coulometrically.

Mill Valley, California, a site that may be affected by urban transport, recorded an average PERC concentration of 0.0652 ± 0.0489 ppb ($2.57 \times 10^{-3} \pm 0.33 \times 10^{-3}$ mg/m^3). The coefficient of variation was 75 percent. Riverside, California, an urban location, recorded an average concentration of 0.9832 ± 0.4541 ppb ($6.6 \times 10^{-3} \pm 3.0 \times 10^{-3}$ mg/m^3). The coefficient of variation was 46 percent.[7]

Subsequent measurements of ground-level samples by Singh et al.[9] in both the northern and southern hemispheres gave average background concentrations of 0.040 ± 0.012 ppb ($2.7 \times 10^{-4} \pm 0.08 \times 10^{-4}$ mg/m^3) and 0.012 ± 0.003 ppb

($0.081 \times 10^{-3} \pm 0.02 \times 10^{-3}$ mg/m^3), respectively. Globally, the average background concentration of PERC was 0.026 ± 0.007 ppb ($1.7 \times 10^{-4} \pm 0.47 \times 10^{-4}$ mg/m^3); the coefficient of variation was 27 percent.

Tetrachloroethylene was judged by Singh and co-workers to be ubiquitous as it was measured 100 percent of the time.[7] In the studies by Singh, the average urban level of PERC was 30 times the background concentration.

Phosgene, an expected photooxidation product of chloroethylenes, was found to have a background concentration of 0.016 ppb (1.08×10^{-4} mg/m^3).[10] Urban levels of phosgene were a factor of three higher than background.

The two major products of the photochemical oxidation of chloroethylenes are likely to be phosgene and chloroacetyl chlorides.[7] Methods for accurately measuring low levels of chloroacetyl chlorides are not currently available.

Singh et al.,[11] in two ground-level field studies conducted in California (Stanford Hills and Point Reyes), found an average background level of 0.0407 ± 0.0144 ppb ($2.76 \times 10^{-4} \pm 0.97 \times 10^{-4}$ mg/m^3) PERC. The coefficient of variation was 35 percent. Tetrachloroethylene was identified using retention time and ionization efficiency. Calibrations were performed using standard multiple dilution procedures starting with pure material. The sample size was 5.8 ml. Monitoring was established at each site on a 24 hour per day basis. The lower detection limit was reported as 0.005 ppb (0.3×10^{-4} mg/m^3). The overall accuracy of measurements was reported as ± 10 percent. The authors indicated that the slightly higher concentration measured at one of the sites was caused by a nearby emissions source. When winds were blowing from the source, a maximum concentration of 3.7 ppb (0.025 mg/m^3) was recorded. The maximum concentration recorded at the other site was 2.49 ppb (0.016 mg/m^3).

An average tropospheric background concentration of 0.0156 ± 0.0046 ppb ($0.105 \times 10^{-3} \pm 0.031 \times 10^{-3}$ mg/m^3 PERC was obtained over the Pacific northwest (48°N), in March 1976, by Cronn et al.[12] The coefficient of variation was 30 percent. Quantification was made by GC/EC of 37 samples (500 ml each) of air after component separation by a freeze-out method. Instrument calibrations were performed by static dilution of standards. Tetrachloroethylene was barely detectable 15,000 to 20,000 feet above the tropopause. In April 1977, collection and analysis of 26 air samples obtained at 37°N resulted in an average tropospheric background concentration of 0.0099 ± 0.0047 ppb ($0.67 \times 10^{-4} \pm 0.32 \times 10^{-4}$ mg/m^3) PERC.[13] The coefficient of variation was 48 percent.

The detection of ambient air levels of PERC also has been reported from Western Ireland, Tokyo, Great Britain, Germany, France, Belgium, Italy, and the Atlantic Ocean. Measurements made by Lovelock[14] over Western Ireland during June and July of 1974 indicated an average concentration of 0.028 ± 0.009 ppb ($1.89 \times 10^{-4} \pm 0.61 \times 10^{-4}$ mg/m^3). The coefficient of variation was 32 percent. Similar concentrations were obtained by Lovelock in the tropospheric air over the north Atlantic Ocean during October 1973. The concentration was 0.021 ± 0.003 ppb ($1.44 \times 10^{-4} \pm 0.22 \times 10^{-4}$ mg/m^3). The analytical procedure used was GC/EC. Tetrachloroethylene was characterized by retention time only.

Measurements taken in the ambient air over the northeast Atlantic Ocean by Murray and Riley[15] yielded an average concentration of 0.7×10^{-3} ppb (4.7×10^{-6} mg/m^3). The concentration reported was 5 mg/m^3. The range of measurements during this study varied between 0.1×10^{-3} to 0.9×10^{-3} ppb (0.67×10^{-6} to 6.1×10^{-6} mg/m^3). Measurements were made at 11 sites. In contrast, higher levels were found in the ambient air over rural and developed areas of Britain. The average concentration of PERC in the air over four sites was

found to be 0.0028 ppb (19×10^{-6} mg/m^3). A gas chromatograph equipped with an electron capture detector was used. The estimated coefficient of variation of the method was reported as less than 15 percent.

Ground-level measurements made by Cox et al.[16] in the northern hemisphere (Cork, Ireland) in 1974 resulted in an average PERC concentration of 0.0276 ± 0.0093 ppb ($0.187 \times 10^{-3} \pm 0.063 \times 10^{-3}$ mg/m^3). Analyses were performed by GC/EC. The coefficient of variation was 34 percent.

Measurements made on rural air samples obtained in southeastern Washington indicated a PERC concentration of 0.020 ± 0.010 ppb ($0.13 \times 10^{-3} \pm 0.07 \times 10^{-3}$ mg/m^3).[17] Analysis was made in a temperature-programmed GC-MS system. Precision defficulties experienced in the PERC measurements were attributed to trace impurities in the carrier gas.

McConnell[18] has stated that PERC is universally present in ambient air at concentrations normally in the range of 0.001 to 0.014 ppb.

Pearson and McConnell[19] found 15 to 40 ppb (0110 to 0.27 mg/m^3) in the ambient air in the vicinity of an organochlorine manufacturing site in Great Britain.

In Tokyo, Ohta et al.[20] concluded from their measurement data that PERC is evenly distributed in the ambient air. Measurements made at 26 geographically selected sites from May 1974 to April 1975 indicated that the annual average concentration was 1.2 ppb (8.1×10^{-3} mg/m^3). Measurements were made on a gas chromatograph equipped with an electron capture detector. The investigators reported that the analytical error was below 10 percent.

Correia et al.[21] detected PERC in the ambient air at 29 sites in six countries (Great Britain, The Netherlands, Germany, Belgium, France, and

Italy). Concentrations ranged from less than 0.01 to 4.72 ppb ($<0.678 \times 10^3$ mg/m^3 to 0.032 mg/m^3). It was judged that quantities found were almost independent of the site of measurement and that PERC is ubiquitous.

6.2 OTHER MEDIA

6.2.1 Water

Various studies have shown that PERC is found in both natural and municipal waters. A recent review by Deinzer et al.[22] has summarized many of the findings.

6.2.2.1 Natural Waters--Surface waters, such as rivers and lakes, are the most important sources of drinking water in the United States. Attempts have been made to show an epidemiological link between the presence of halogenated organic compounds in drinking water and cancer.[23]

Stephenson[24] ranked PERC fourteenth in a list of 67 halocarbons in regard to its potential as a human health hazard. Rankings were based on various criteria: (a) production and industrial waste, (b) use pattern, (c) persistence, (d) dispersion tendency, (e) conversion potential, and (f) biological consequences.

Dowty et al.[25] detected PERC by GC-MS techniques in untreated Mississippi River water as well as in treated water. An approximate six-fold reduction in concentration occurred after sedimentation and chlorination. The relative concentration was approximately three times less than trichloroethylene after identical treatment. Tetrachloroethylene in water from a commercial deionizing charcoal filtering unit showed a marked increase over the amount found in finished water from treatment facilities or commercial sources of bottled water. It had the highest relative concentration of 18 compounds identified and was approximately 13-fold higher in concentration than

trichloroethylene. The value of charcoal filtering to remove organics from water requires further study.

Suffet et al.[26] reported detection of PERC in river waters supplying drinking water to Philadelphia, Pennsylvania. The Belmont Water Treatment Plant, with an average capacity of 78 million gallons per day obtains influent from the Schuykill River.

Pearson and McConnell[19] found an average PERC concentration of 0.12 ppb in Liverpool Bay sea water; the maximum concentration found was 2.6 ppb. Sediments from Liverpool Bay were found to contain 4.8 ppb (w/w). No direct correlation was found between PERC concentration in sediments and in the waters above.

Rainwater collected near an organochlorine manufacturing site was found to contain 0.15 ppb (w/w) PERC;[19] it was not detected in well waters.[19]

Upland waters of two rivers in Wales were found to contain approximately 0.15 ppb PERC; similar levels of trichloroethylene were found.[19]

Löchner[27] found that levels of PERC in Bavarian lake waters ranged between 0.015 to 3 ppb (0.015×10^{-3} to 2.7×10^{-3} mg/l). European surface waters were reported to have uniform PERC concentrations ranging from 0.2×10^{-3} to 0.002 mg/l.[27]

Analyses of river, canal water, and sea water containing effluent from production and user sites in four countries revealed PERC concentrations ranging from 0.01 to 46 ppb (0.01 to 46 µg/liter).[21]

6.2.2.2 Municipal Waters--Bellar[28] measured the concentration of PERC in water obtained from sewage treatment plants in several cities. Before treatment, the average concentration was 6.2 µg PERC per liter. The treated water before chlorination contained 3.9 µg PERC per liter. After chlorination, the effluent contained 4.2 µg PERC per liter.

Tetrachloroethylene has been detected in the drinking water of a number of U.S. cities. These include: Evansville, Indiana;[29] Kirkwood, Missouri;[29] New Orleans, Louisiana;[30] Jefferson Parish, Louisiana;[28] Cincinnati; Ohio;[29] Miami, Florida;[29] Grand Forks, North Dakota;[29] Lawrence, Kansas;[29] New York City;[29] and Tucson, Arizona.[29]

Concentrations recorded for the above cities were less than 1 µg per liter. An exception was Jefferson Parish, which had a measured concentration of 5 ppb (5 µg/liter). Keith et al.[29] did not detect PERC in the drinking water of Philadelphia. Tetrachloroethylene was found in Evansville tap water from July 1971 to December 1972. The Ohio River Basin, a heavily industralized area, is upstream from Evansville and serves as a major source of drinking water for that community.

Dowty et al.[30] determined levels of PERC in the drinking water for New Orleans. Considerable variation in the relative concentrations of the various halogenated compounds was observed from day to day.

In municipal waters supplying the cities of Liverpool, Chester, and Manchester, England, 0.38 ppm (w/w) PERC was found.[19]

Munich (Germany) drinking water was analyzed by Löchner.[27] Samples taken at various sampling points and times gave a range of 1.1×10^{-3} to 2.4×10^{-3} mg/liter. Raw sewage at Munich contained 0.088 mg/liter PERC. Upon mechanical clarification the 24-hour average concentration of PERC was 0.0068 mg/liter.

6.3 SUMMARY

Tetrachloroethylene, also called perchloroethylene (PERC), has been detected both in ambient air and in natural and municipal waters in many geographical regions of the United States and elsewhere.

Ground-level measurements of the average background tropospheric concentrations of PERC indicate that, in the northern hemisphere, concentrations are approximately 0.03 to 0.05 ppb (0.20×10^{-3} to 0.34×10^{-3} mg/m^3). Background concentrations in the southern hemisphere are considerably less. Measurements made in the upper troposphere indicate that the concentration of PERC diminishes with increased altitude; concentrations have been measured in the range of 0.0099 to 0.0156 ppb (0.67×10^{-4} to 0.105×10^{-3} mg/m^3).

Concentrations in ambient air reflect source emissions, urban transport, diurnal variations, seasonal variations, and tropospheric reactivity. In the United States, average concentrations at or near urban centers ranged from 0.18 to 4.5 ppb (0.0012 to 0.03 mg/m^3). Maximum peak concentrations have been reported as high as 10 ppb (0.07 mg/m^3). While waste disposal sites may evidence maximum ambient air concentrations exceeding 50 ppb (0.34 mg/m^3), concentrations in the ambient air at or near industrial locations are generally similar to those concentrations found at urban centers.

Tetrachloroethylene has been detected in river waters supplying urban centers with drinking water and in the drinking water of many U.S. cities. Concentrations are approximately 1 µg per liter in the drinking waters of the cities evaluated. Variation in the amount of PERC in drinking water may occur on a day-to-day basis.

6.4 REFERENCES FOR CHAPTER 6

1. Lillian, D., H. B. Singh, A. Appleby, L. Lobban, R. Arnts, R. Gumpert, R. Hague, J. Toomey, J. Kazazis, M. Antell, D. Hansen, and B. Scott. Atmospheric fates of halogenated compounds. Environ. Sci. Technol. 9(12):1042-1048, 1975.

2. Lillian, D., H. B. Singh, and A. Appleby. Gas chromatographic analysis of ambient halogenated compounds. J. Air Pollut. Control Assoc. 26(2):141-143, 1976.

3. Lillian, D., and H. B. Singh. Anal. Chem. 46:1060, 1975.

4. Simmonds, P. G., S. L. Kerrin, J. E. Lovelock, and F. H. Shair. Distribution of atmospheric halocarbons in the air over the Los Angeles basin, Atmos. Environ. 8:209-216, 1974.

5. Pellizzari, E. D. Measurement of carcinogenic vapors in ambient atmospheres. EPA-600/7-78-062, April 1978.

6. Russell, J. W., and L. A. Shadoff. The sampling and determination of halocarbons in ambient air using concentration on porous polymer. J Chromat. 134:375-384, 1977.

7. Singh, H. B., L. J. Salas, H. Shiegeishi, and A. H. Smith. Fate of halogenated compounds in the atmosphere. Interim report--1977. EPA 600-3-78-017, January 1978.

8. Singh, H. B., L. Salas, H. Shiegeishi, and A. Crawford. Urban-nonurban relationships of halocarbons, SF_6, N_2O, and other atmospheric trace constituents. Atmos. Environ. 11:819-828, 1977.

9. Singh, H. B., L. J. Salas, H. Shigeishi, and E. Scribner. Global Distribution of Selected Halocarbons, Hydrocarbons, SF_6, and N_2O. Phase II Interim Report. SRI International, Memlo Park, California, May 1978.

10. Singh, H. B. Phosgene in the ambient air. Nature. 264:428-429, 1976.

11. Singh, H. B., L. J. Salas, and L. A. Cavanagh. Distribution, sources and sinks of atmospheric halogenated compounds. J. Air Pollut. Control Assoc. 27(4):332-336, 1977.

12. Cronn, D. R., R. A. Rasmussen, E. Robinson, and D. E. Harsch. Halogenated compound identification and measurement in the troposphere and lower stratosphere. J. Geophy. Res. 82(37):5935-5944, 1977.

13. Cronn, D. R. R. A. Rasmussen, and E. Robinson. Report for Phase II. Measurement of Tropospheric Halocarbons by Gas Chromatography-Mass Sepctrometry. Washington State University, October 1977.

14. Lovelock, J. E. Atmospheric halocarbons and stratospheric ozone. Nature. 252:292-294, 1974.

15. Murray, A. J. and J. P. Riley. The determination of chlorinated aliphatic hydrocarbons in air, natural waters, marine organisms, and sediments. Anal. Chim. Acta 65:261-270, 1973.

16. Cox, R. A., R. G. Derwent, and A. E. J. Eggleton. Photochemical oxidation of halacarbons in the troposphere. Atmos. Environ. 10:305-308, 1976.

17. Grimsrud, E. P., and R. A. Rasmussen. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos. Environ. 9:1014-1017, 1975.

18. McConnell, G., D. M. Ferguson, and C. R. Pearson. Chlorinated hydrocarbons and the environment. Endeavor 34(121):13-18, 1975.

19. Pearson,C. R., and G. McConnell. Chlorinated C, and C_2 hydrocarbons in the marine environment. Proc. Roy. Sci London B 189:305-332, 1975.

20. Ohta, T., M. Morita, and I. Mizoguchi. Local distribution of chlorinated hydrocarbons in the ambient air in Tokyo, Atmos. Environ. 10:557-560, 1976.

21. Correia, Y., G. J. Martens, F. H. Van Mensch, and B. P. Whim. The occurrence of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in Western Europe in Air and Water. Atmos. Environ. 11:1113-1116, 1977.

22. Deinzer, M., F. Schaumburg, and E. Klein. Environmental Health Sciences Center Task Force Review on halogenated organics in drinking water. Environ. Health Persp. 24:209-239, 1978.

23. Harris, R.H., and S. S. Epstein. Drinking water and cancer mortality in Louisiana. Science. 193:55, 1976.

24. Stephenson, M. E. An approach to the identification of organic compounds hazardous to the environment and human health. Paper presented at International Symposium of Chemical and Toxicological Aspects of Environmental Quality, Munich, Germany. September 9, 1975.

25. Dowty, B. J., D. R. Carlisle, and J. L. Laseter. New Orleans drinking water sources tested by gas chromatography - mass spectrometry. Environ. Sci. Technol. 9:762-765, 1975.

26. Suffet, I. H., L. Brenner, and J. V. Radziul. GC/MS Identification of Trace Organic Compounds in Philadelphia Waters. Chap. 23. In: Identification and Analysis of Organic Pollutants in Water, L. H. Keith, (ed.). Ann Arbor Science, 1977.

27. Löchner, F. Perchloroethylene: Taking Stock. Umwelt 6:434-436, 1976. (English translation).

28. Bellar, T. A., J. J. Lichtenberg, and R. C. Kroner. The occurrence of organohalides in chlorinated drinking waters. J. Am. Waterworks Assoc. 66:703-706, 1974.

29. Keith, L. H., A. W. Garrison, F. R. Allen, H. H. Carter, T. L. Floyd, J. D. Pope, and A. D. Thruston, Jr. Identification of Organic Compounds in Drinking water from Thirteen U.S. Cities: Chap. 22. In: Identification and Analysis of Organic Pollutants in Water. L. H. Keith, ed. Ann Arbor Science, 1977.

30. Dowty, B. J., D. R. Carlisle, J. L. Laseter, and J. Storer. Halogenated hydrocarbons in New Orleans drinking water and blood plasma. Science. 187:75-77, 1975.

7. ECOLOGICAL EFFECTS

7.1 EFFECTS ON AQUATIC ORGANISMS

Limited information on the effects of tetrachloroethylene (PERC) on aquatic organisms is available. The toxicity of PERC to fish and other aquatic organisms has been gauged by flow-through and static testing methods.[1] The flow-through method, applicable in investigations involving volatile compounds, exposes the organism(s) continuously to a constant concentration of PERC; oxygen is continuously replenished while waste products are removed. A static test, on the other hand, exposes the organism(s) to the added initial concentration only.

Alexander et al.[2] used flow-through and static methods to investigate the toxicity of several chlorinated solvents, including PERC, to adult fathead minnows (Pimephales promelas Rafinesque).

The static and flow-through results for the 96-hour experiments indicated that PERC was the most toxic of the solvents tested. The lethal concentration (LC50) necessary to kill 50 percent of the minnows in the flow-through test was 18.4 mg/liter; the 95 percent confidence limits were 14.8 to 21.3 mg/liter. In comparison, the results of the static-type experiments gave an LC50 of 21.4 mg/liter; the 95 percent confidence limits were 16.5 to 26.4 mg/liter.

The fish also were observed for the following effects: loss of equilibrium, melanization, narcosis, and swollen hemorrhaging gills. Only fish severely affected by high concentrations of the solvents did not recover. Short exposures to the solvents at the sublethal level seemed to

produce only reversible effects. The effective concentration (EC50) of PERC producing one or more of these effects was 14.4 mg/liter.

In these experiments, fish were held in raw dechlorinated lake water prior to testing. In the static test experiments, dissolved oxygen was monitored daily and at no time was it below 5 mg/liter.

Pearson and McConnell[3] investigated the toxicity of tetrachloroethylene (PERC) on the dab (Limanda limanda) barnacle larvae (Barnacle nauplii), and on unicellular algae (Phaeodactylum tricornutum). Tetrachloroethylene was metered into influent seawater in an all-glass apparatus in the fish toxicity test. The oxygen available was that dissolved in the seawater. The LC50 was 5 mg per liter.

To assess the toxicity of PERC to barnacle larvae, 20 larvae were enclosed in a glass-stoppered bottle containing PERC in seawater. After 48 hours, mortality was observed. The LC50 for PERC was 3.5 mg per liter.

Toxicity to the unicellular algae was assessed by measuring alterations in the uptake of carbon from atmospheric carbon dioxide during photosynthesis. Uptake of carbon dioxide was measured by the use of sodium-^{14}C-carbonate. The EC50 was 10.5 mg per liter in the case of PERC.

7.2 BIOACCUMULATION

7.2.1 Levels of Tetrachloroethylene in Tissues and Foodstuffs

Pearson and McConnell[3] suggested that chronic and sublethal effects of PERC may result from exposure to low concentrations of PERC if the halocarbon can be bioaccumulated. As a first step in addressing the question of bioaccumulation, these investigators determined levels of PERC in a variety of invertebrate and vertebrate species (Tables 7-1 and 7-2).

Among marine invertebrates, wet tissue concentrations of PERC were found to range from 1 to 9 ppb. The highest concentration (8 to 9 ppb) found was in the crab (Cancer pagurus). Higher levels were found in marine algae (13 to 22 ppb). In tissues of fish, a range of 0.3 to 41 ppb was found. Concentrations in the liver of three species of fish were found to greatly exceed those found in the flesh. Tissue levels from all species are shown in Table 7-1.

The average concentration of PERC in seawater taken from Liverpool Bay, an area where many species of organisms were collected, was 0.12 ppb. A comparison of this value with those presented in Table 7-1 suggests that up to a 50-fold uptake of PERC can occur. However, there is little indication that bioaccumulation occurs in the food chain.

Dickson and Riley[4] detected PERC in three species of mollusks and in five species of fish near Port Erin, Isle of Man. Samples were sealed in glass jars and cooled to -78°C. Analysis was made within 3 days of collection. Levels of PERC in various tissues are shown in Table 7-3. Relative to the seawater levels, these compounds were only slightly enriched in the tissues (<25 times). Tetrachloroethylene had one of the lowest mean concentration factors. In contrast, the analog trichloroethylene had the highest mean concentration factor.

McConnell et al.[5] in a review of the incidence of PERC in the food chain, reported that PERC was detected in a variety of foodstuffs (Table 7-4). The three highest concentrations reported were in English butter, margarine, and Spanish olive oil.

TABLE 7-1. LEVELS OF TETRACHLOROETHYLENE IN TISSUES OF MARINE ORGANISMS, BIRDS AND MAMMALS[3]

Species	Source	Tissue	Trichloro-ethylene* ppb	PERC ppb
Invertebrates				
Plankton	Liverpool Bay	-	0.05 - 0.4	0.05 - 0.5
Plankton	Torbay	-	0.9	2.3
Ragworm (Nereis diversicolor)	Mersey Estuary	-	Not detected	2.9
Mussel (Mytilus edulis)	Liverpool Bay	-	4 - 11.9	1.3 - 6.4
	Firth of Forth	-	9	9
	Thames Estuary	-	8	1
Cockle (Cerastoderma edule)	Liverpool Bay	-	6 - 11	2 - 3
Oyster (Ostrea edulis)	Thames Estuary	-	2	0.5
Whelk (Buccinum undatum)	Thames Estuary	-	Not detected	1
Slipper limpet (Crepidula formicata)	Thames Estuary	-	9	2
Crab (Cancer pagurus)	Tees Bay	-	2.6	2.3
	Liverpoool Bay	-	10 - 12	8 - 9
	Firth of Forth	-	15	7
Shorecrab (Carcinus maenus)	Firth of Forth	-	12	6
Hermit crab (Eupagurus bernhardus)	Firth of Forth	-	15	15
	Thames Estuary	-	5	2
Shrimp (Crangon crangon)	Firth of Forth	-	16	3

(continued)

TABLE 7-1 (continued).

Species	Source	Tissue	Trichloro-ethylene* ppb	PERC ppb
Starfish (Asterias rubens)	Thames Estuary	-	5	1
Sunstar (Solaster sp.)	Thames Estuary	-	2	2
Sea Urchin (Echinus esculentus)	Thames Estuary	-	1	1
Marine Algae				
Enteromorpha compressa	Mersey Estuary	-	19 - 20	14 - 14.5
Ulva lactuca	Mersey Estuary	-	23	22
Fucus vesiculosus	Mersey Estuary	-	17 - 18	13 - 20
Fuscus spiralis	Mersey Estuary	-	16	13
Fish				
Ray (Raja clavata)	Liverpool Bay	flesh liver	0.8 - 5 5 - 56	0.3 - 8 14 - 41
Plaice (Pleuronectas platessa)	Liverpool Bay	flesh liver	0.8 - 8 16 - 20	4 - 8 11 - 28
Flounder (Platyethys flesus)	Liverpool Bay	flesh liver	3 2	2 1
Dab (Limanda limanda)	Liverpool Bay	flesh liver	3 - 5 12 - 21	1.5 - 11 15 - 30
Mackerel (Scomber scombrus)	Liverpool Bay	flesh liver	5 8	1 not detected

(continued)

TABLE 7-1 (continued).

Species	Source	Tissue	Trichloro-ethylene* ppb	PERC ppb
Dab (Limanda limanda)	Redcar, Yorks	flesh	4.6	5.1
	Thames Estuary	flesh	2	3
Plaice (Pleuronectus platessa)	Thames Estuary	flesh	3	3
Sole (Solea solea)	Thames Estuary	flesh	2	4
		suts	11	1
Redgurnard (Aspitnigla cuculus)	Thames Estuary	flesh	11	1
		suts	6	2
Scad (Trachurus trachurus)	Thames Estuary	flesh	2	4
Pout (Trisopterus luscus)	Thames Estuary	flesh	2	2
Spurdog (Squalus acanthias)	Thames Estuary	flesh	3	1
Mackerel (Scomber scombrus)	Torbay, Devon	flesh	2.1	Not detected
Clupea sprattus	Torbay, Devon	flesh	3.4	1.6
Cod (Gadus morrhua)	Torbay, Devon	flesh	0.8	<0.1
		Air bladder	<0.1	3.6
Sea and Freshwater Birds				
Gannet (Sula bassana)	Irish Sea	liver	4.5 - 6	1.5 - 3.2
		eggs	9 - 17	4.5 - 26
Shag (Phalacrocerax aristotelis)	Irish Sea	eggs	2.4	1.4
Razorbill (Aka torda)	Irish Sea	eggs	28 - 29	32 - 39

(continued)

TABLE 7-1 (continued).

Species	Source	Tissue	Trichloro-ethylene* ppb	PERC ppb
Kittiwake (Rissa tridactyla)	North Sea	eggs	33	25
Swan (Cygnus olor)	Frodsham Marsh	liver	2.1	1.9
		kidney	14	6.4
Moorhen (Gallinula chloropus)	Merseyside	liver	6	3.1
		muscle	2.5	0.7
		eggs	6.2 - 7.8	1.3 - 2.5
Mallard (Anas platyrhymcos)	Merseyside	eggs	9.8 - 16	1.9 - 4.5
Mammals				
Grey Seal (Halichoerus Grypus	Farne Island	blubber	2.5 - 7.2	0.6 - 19
		liver	3 - 6.2	0 - 3.2
Common Shrew (Sorex araneus)	Frodsham Marsh	-	2.6 - 7.8	1

*Levels for trichloroethylene included for comparative purposes

TABLE 7-2. ACCUMULATION OF TETRACHLOROETHYLENE BY DABS[1]

Tissue	Period of Exposure (days)	Mean Exposure Concentration (ppb)	Mean Concentration in Tissue (ppb)	Accumulation Factor
flesh	3 - 35	300	2,800†. (13)	x 9
liver	3 - 35	300	113,000 (14)	x 400
flesh	3 - 35	30	160 (9)	x 5
liver	3 - 35	30	7,400# (9)	x 200
flesh	10	200	1,300 (7)	x 6
liver	10	200	69,000 (7)	x 350

Numbers in parentheses are number of specimens analyzed

†one fish had a flesh concentration of 29,700 ppb and was omitted from calculations

#one fish had flesh concentration of 50,300 ppb and was omitted from calculations

TABLE 7-3. CONCENTRATION OF PERC AND TRICHLOROETHYLENE IN MOLLUSKS AND FISH NEAR THE ISLE OF MAN[4]

Species	ng/g dry weight tissue PERC	TRICHLOROETHYLENE
Eel (Conger conger)		
brain	6	62
gill	2	29
gut	3	29
liver	43	43
muscle	1	70
Cod (Gadus morhua)		
brain	3	56
gill	-	21
heart	3	11
liver	8	66
muscle	2	8
skeletal tissue	-	-
stomach	6	7
Coalfish (Pollachius birens)		
alimentary canal	-	306
brain	-	71
gill	4	-
heart	-	-
liver	6	70
muscle	2	8
Dogfish (Scylliorhinus canicula)		
brain	12	40
gill	13	176
gut	-	41
heart	-	274
liver	9	479
muscle	-	41
spleen	-	307

(continued)

TABLE 7-3 (continued)

Species	ng/g dry weight tissue PERC	TRICHLOROETHYLENE
Bib (*Trisopterus luscus*)		
brain	-	-
gill	27	40
gut	4	-
liver	0.3	143
muscle	-	187
skeletal tissue	-	185
Baccinum undatum		
digestive gland	33	2
muscle	39	-
Modiolus modiolus		
digestive tissue	-	56
mantle	63	250
muscle	16	33
Pecten maximus		
gill	88	detected
mantle	40	-
muscle	24	-
ovary	-	-
testis	176	-

TABLE 7-4. CONCENTRATION OF TETRACHLOROETHYLENE IN FOODSTUFFS[5]

Foodstuff	Perchloroethylene µg/kg
Dairy Produce	
Fresh milk	0.3
Cheshire cheese	2
English butter	13
Hens' eggs	ND
Meat	
English beef (steak)	0.9
English beef (fat)	1.0
Pigs' liver	5
Oils and Fats	
Margarine	7
Olive oil (Spanish)	7
Cod liver oil	2
Vegetable cooking oil	0.01
Castor oil	3
Beverages	
Canned fruit drink	2
Light ale	ND
Canned orange juice	ND
Instant coffee	3
Tea (packet)	3
Wine (Yugoslav)	ND
Fruits and Vegetables	
Potatoes (S. Wales)	ND
Potatoes (N. W. England)	0.7
Apples	2
Pears	2
Tomatoes[c]	1.2
Black grapes (imported)	ND
Fresh Bread	1

7.2.2 Laboratory Studies

As shown in Table 7-2, dabs (Limanda limanda) exposed to 300 ppb for 3 to 35 days were found to have an accumulation factor (liver) for PERC of 400. When the dabs were returned to clean seawater, the accumulation factor was reduced to 100. Analysis of the levels of PERC in flesh after dabs were returned to clean seawater indicated an accumulation factor of less than 10. The ratio between liver and flesh concentrations is approximately 100 to 1.

After dabs were returned to clean seawater, the level of PERC dropped to 1/100 of the original level in 4 days and to 1/1000 of the initial level after 11 days (Figure 7-1). The relationship between flesh and liver concentrations in the dab is shown in Figure 7-2.

Pearson and McConnell[3] estimated that the chemical half-life of PERC in water is 6 years. If correct, then pollution of natural waters could lead to an increase of PERC in the tissues of many aquatic species. Evaporative losses to the atmosphere would be expected to reduce the amounts bioaccumulated.

Löchner[6] stated, without supporting data, that levels of PERC between 1×10^5 and 1×10^7 ppb have been found in animal feeds but increased PERC levels could not be detected in the meat of food animals fed these feeds.

Neely et al.,[7] in experiments with trout (Salmo gardineri), found that PERC was concentrated in muscle; the bioconcentration correlated with the n-octanol/water partition coefficient of PERC.

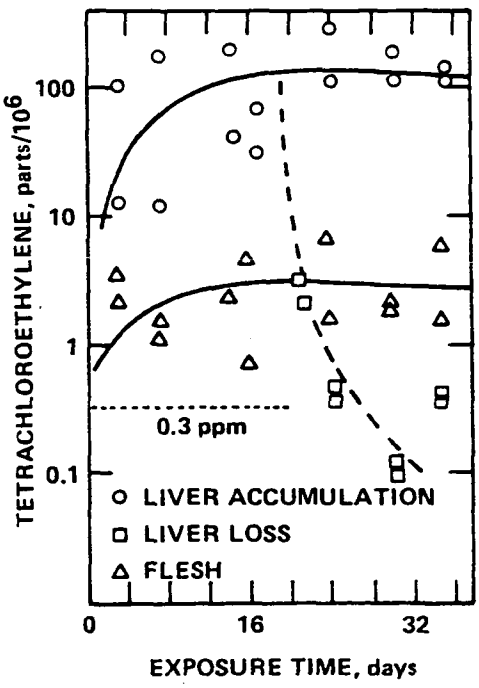


Figure 7-1. Accumulation and loss of tetrachloroethylene by dabs.[3]

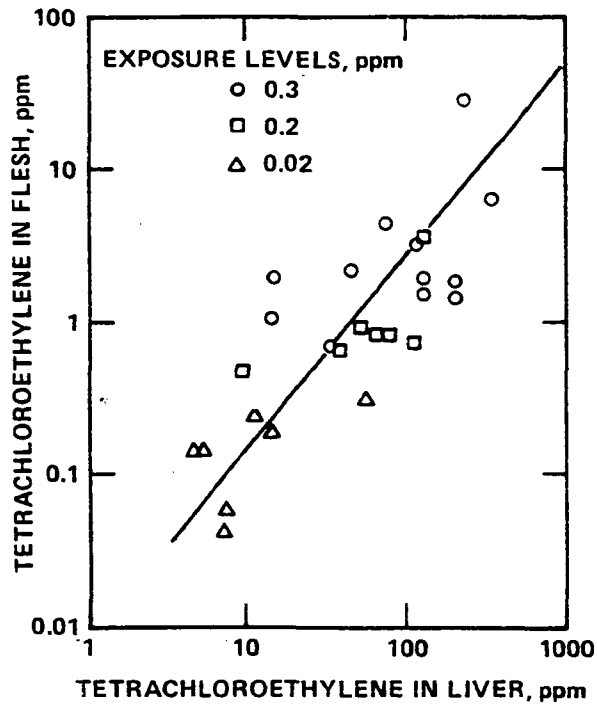


Figure 7-2. Relation between flesh and liver concentrations of tetrachloroethylene in dabs.[3]

7.3 SUMMARY

Available evidence indicates that tetrachloroethylene may be toxic to vertebrate and invertebrate marine organisms. There also is evidence which suggests that PERC may reduce the photosynthetic capabilities of certain marine algae.

While there is no direct evidence that PERC bioaccumulates up the food chain, laboratory studies indicate that PERC may accumulate in tissues of various species of fish, birds, mollusks, and mammals. When fish are continuously exposed to sea water containing PERC, the halocarbon accumulates in tissues, but levels rapidly decline when fish are returned to clean sea water.

Tetrachloroethylene has been detected in µg/kg amounts in dairy products, meat, oils and fats, beverages, fruits and vegetables, and bread from the United Kingdom. Analysis for PERC in foods produced in the United States has not been reported.

7.4 REFERENCES FOR CHAPTER 7

1. Committee on Methods for Toxicity Tests with Aquatic Organisms: Methods for acute toxicity tests with fish, macroinvertebrates, and Amphibians. Ecol. Res. Series, EPA 660/3-75-009, 1975.

2. Alexander, H. C., W. M. McCarty, and E. A. Bartlett. Toxicity of perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, and methylene chloride to fathead minnows. Bull. Environ. Contam. Toxicol. 20:344-352, 1978.

3. Pearson, C. R., and G. McConnell. Chlorinated C_1 and C_2 hydrocarbons in the marine environment. PROC. Roy. Soc. Lond. B. 189:305332, 1975.

4. Dickson, A. G., and J. P. Riley. The distribution of short-cham halogenated aliphatic hydrocarbons in some marine organisms. Marine Pollut. Bull. 7(9):167-169, 1976.

5. McConnell, G., D. M. Ferguson, and C. R. Pearson. Chlorinated hydrocarbons and the environment. Endeavor 34(121):13-18, 1975.

6. Löchner, F. Perchloroethylene: taking stock. Umwelt 6:434-436, 1976 (English translation).

7. Neeley, W. B., D. R. Branson, and G. E. Blan. Partition coefficient to measure bioconcentration potential or organic chemicals in fish. Environ. Sci. Technol. 8:1113, 1974.

8. TOXIC EFFECTS OBSERVED IN ANIMALS

Documented toxic effects associated with tetrachloroethylene (PERC) exposure in laboratory animals include effects on the central nervous system (CNS), cardiovascular system, skin, liver, kidney, and the immune system.

A number of recent reviews[1-7] support the assessment of the toxic effects of tetrachloroethylene in animals as presented below. Summaries of these toxic effects and of toxic dose data also appear in Tables 8-1 and 8-2.

8.1 EFFECTS ON THE NERVOUS SYSTEM

Acute effects of PERC are very much dominated by CNS depression. Abnormal weakness, handling intolerance, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsciousness are among the symptoms, considered to be manifestations of effects on the CNS, which have been observed in exposed animals.

Symptoms of acute CNS depression have been seen in experimental animals[1-7] and in dogs treated with therapeutic (antihelmintic) doses[8-10] of PERC.

Rowe et al.[11] reported that behavioral changes were not observed in rats, guinea pigs, rabbits, or monkeys exposed repeatedly for 7 hours a day at vapor concentrations of PERC up to 401 ppm (2,720 mg/m^3).

A single 4-hour exposure to 2,270 ppm (15,400 mg/m^3) PERC caused rats to suffer an 80 percent loss of both avoidance and escape responses.[12] Savolainen et al.[13] demonstrated behavioral impairment in rats exposed

TABLE 8-1. SUMMARY OF THE EFFECTS OF TETRACHLOROETHYLENE ON ANIMALS

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rabbits (female)			single application (skin) single installation (eye)	primary eye and skin irritant	Duprat et al., 1976[32]
Rabbit	13 m mole/ kg	oral	single dose	marked increase in serum enzymes i.e., alkaline phosphatase, SGOT, and SGPT within 24 hours	Fujii et al., 1975[29]
Mice	200 ppm	inhalation	4 hours single exposure	moderate fatty infiltration of the liver 1 day after exposure but not 3 days after	Kylin et al., 1963[22]
Mice	200 ppm	inhalation	4 hours/day 6 days/week 1-8 weeks	fatty degeneration of the liver	Kylin et al., 1965[23]
Guinea pigs	100 ppm	inhalation	7 hours/day 5 days/week 132 exposures	increased liver weights in females	Rowe et al., 1952[11]
Guinea pigs	200 ppm	inhalation	7 hours/day 5 days/week	increased liver weights with some fatty degeneration in both males and females - slight increase in lipid content, and several small fat vacuoles in liver	Rowe et al., 1952[11]

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Guinea pigs	400 ppm	inhalation	7 hours/day 5 days/week 169 exposures	more pronounced liver changes than at 200 ppm slight cirrhosis was observed - increased liver weight, increase in neutral fat and esterified cholesterol in the liver, moderate central fatty degeneration, cirrhosis	Rowe et al., 1952[11]
Guinea pigs	2,500 ppm	inhalation	18 7-hour exposures	loss of equilibrium, coordination and strength increase in weights of liver and kidney, fatty degeneration of the liver, cloudy swelling of tubular epithelium of the kidney	Ibid.
Rabbits Rats Monkeys	100-400 ppm	inhalation	7 hours/day 5 days/week 6 months	no abnormal growth, organ function or histopathologic findings	Ibid.
Rabbits	2,500 ppm	inhalation	28 7-hour exposures	central nervous system (CNS) depression without unconsciousness	Ibid.
Rat	2,500 ppm	inhalation	1-13 7-hour exposures	loss of consciousness and death	Ibid.
Rat	1,600 ppm	inhalation	18 7-hour exposures	drowsiness, stupor, increased salivation, extreme restlessness, disturbance of equilibrium and coordination, biting and scratching reflex	Ibid.

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rat	3,000-6,000	inhalation	single exposure up to 8 hours	increase in liver weight, increase in total lipid content of liver accompanied by a few diffusely distributed fat globules	Ibid.
Rabbit	15 ppm	inhalation	3-4 hours/day 7-11 months	depressed agglutinin formation	Mazza 1972[24]
Rabbit	2,212 ppm (15 mg/l)	inhalation	45 days 4 hrs/day 5 days/week	liver damage indicated by elevated SGPT, SGOT, SGLDH: marked reduction of Schmidt index	Ibid.
Rats	70 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	no pathological findings	Carpenter 1937[19]
Rats	230 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	similar, but less severe pathological findings as with 470 ppm - congestion and light granular swelling of kidneys	Carpenter 1937[19]
Rats	470 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	congested livers with cloudy swelling, no evidence of fatty degeneration or necrosis: evidence of kidney injury - increased secretion, cloudy swelling and desquamation of kidneys: congestion of spleen	Ibid.
Rats	2,750-9,000 ppm	inhalation	single exposure	no deaths	Ibid.

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rats	19,000 ppm	inhalation	30-60 minutes	congested livers with granular swelling, some deaths	Ibid.
Rabbits	15 ppm	inhalation	3-4 hours/day 7-11 months	moderately increased urinary urobilinogen, pathomorphological changes in the parenchyma of liver and kidneys	Navrotskii et al., 1971[42]
Rabbit	2,211 ppm (15 mg/l)	inhalation	45 days	significant reduction of glomerular filtration rate and the renal plasma flow; decrease of highest excretory tubular capacity (kidney damage)	Brancaccio et al., 1971[26]
Mice (Swiss) Male 10 Animals	2.5 ml/kg	i. p.		100 mg percent or more protein found in 1 of 6 mice - proximal convoluted tubules were swollen in all animals and necrotic in one	Plaa & Larson, 1965[28]
10 Animals	5.0 ml/kg	i.p.		2 of 4 mice had 100 mg percent or more protein in urine	
		(urine samples were collected 24-hours post-injection)			

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rabbit	2,211 ppm (15 mg/l)	inhalation	45 days	increased plasma and urine levels of adrenal cortical and adrenal medullar hormones; increased excretion of principal catecholamine metabolite (not statistically significant)	Mazza & Brancaccio, 1971[25]
Mouse		i. p.		liver dysfunction	Klassen & Plaa, 1966[20]
Mouse		i. p.		LD_{50}	Ibid.
Dog		i. p.		caused significant liver dysfunction indicated by elevated SGPT	Klaasen & Plaa, 1967[21]
Dog	i. p.			caused PSP (phenolsulfonephtalein) retention indicating kidney dysfunction	Klassen & Plaa, 1967[21]
Dog	i. p.			LD_{50} in dog	Ibid.
Rats	300 ppm	inhalation	7 hours/day days 6-15 of gestation	decreased maternal weight gains, increased fetal reabsorptions	Schwetz, et al., 1975[43]
Mice	300 ppm	inhalation	7 hours/day days 6-15 of gestation	maternal liver weights increased relative to body weight; increased incidences of fetal subcutaneous edema, delayed ossification of skull bones, and split sternebrae	Ibid.

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rat	44.2 ppm	inhalation	entire gestation period	decreased levels of DNA and total nucleic acids in the liver, brain, ovaries, and placenta	Aninina 1972[44]
Mouse	15-74 ppm	inhalation	5 hours/day 3 months	decreased electroconductance of muscle and "amplitude" of muscular contraction	Dmitrieva, 1968[18]
Rats	15 ppm	inhalation	4 hours/day 5 months	EEG changes and protoplasmal swelling of cerebral cortical cells, some vacuolated cells and signs of karyolysis	Dmitrieva, 1966[14]
Rats	73 and 147 ppm	inhalation	4 hours/day 4 weeks	EEG and electromyogram changes; decreased acetylchlolinesterase activity	Dmitrieva, 1966[14]
Dogs (male beagles)	0.5-1.0% v/v 5,000 & 10,000 ppm	inhalation	7 min house air followed by 10 minutes tetrachloroethylene 8 µg/kg Epinephrine given I.V. (1) a control dose after 2 min of breathing air (2) challenge dose after 5 min of breathing test compound	cardiac sensitization (development of serious arrhythmia or cardiac arrest) was not induced at the concentrations tested (other similar compounds gave positive results at same concentration)	Reinhardt et al., 1973[3(
Cats	3,000 ppm	inhalation	4 hours	no anesthesia	Lehmann, 1911[45]
Cats	14,600 ppm	inhalation	1-2 hours	anesthesia	Lehmann and Schmidt-Kehl, 1936[46]

(continued)

TABLE 8-1 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Mouse	40 mg/l 5,900 ppm	inhalation		minimal fatal concentration	Lamson et al.,1929[47]
Mouse	4-5 ml/kg	oral		death in 2-9 hours from CNS depression	Ibid.
Rabbit	5 ml/kg	oral in oil		death in 17-24 hours	Ibid.
Cat	4 mg/kg	oral in oil		death within hours	Ibid.
Dog	9,000 ppm	inhalation		narcosis, marked salivation, "narrow margin of safety"	Ibid.
Dog	4-25 ml/kg	oral in oil		death in 5-48 hours	Ibid.

TABLE 8-2. TOXIC DOSE DATA

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
LD_{50}	male mouse	oral	8100 mg/kg	death	36 hr.	Wenzel & Gibson[48]
LD_{50}	mouse	i.p.	2.9 ml/kg 28 mM/kg 4700 mg/kg	death	24 hr.	Klaasen & Plaa, 1966[20]
ED_{50}	mouse	i.p.	2.9 ml/kg 28-32 mM/kg	liver dysfunction		
LD_{50}	mouse	i.p.	34 mM/kg	death	24 hr.	Gehring 1968[49]
ED_{50}	mouse	i.p.	24 mM/kg	liver toxicity		
LD_{50}	dog	i.p.	2.1 ml/kg 21 mM/kg 3400 mg/kg	death	24 hr.	Klaasen & Plaa, 1967[21]
ED_{50}	dog	i.p.	0.74 ml/kg 7.2 mM/kg	liver damage	24 hr.	Ibid.
ED_{50}	dog	i.p.	1.4 ml/kg	kidney dysfunction	24 hr.	Ibid.
LD_{50}	mouse	subcutaneous	390 mM/kg	death	10 da.	Plaa et al., 1958[50]
ED_{50}	mouse	subcutaneous	27 mM/kg	liver toxicity		Ibid.

(continued)

TABLE 8-2 (continued).

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
LD_{50}	mouse	oral (undiluted)	0.109 ml	death		Dybing and Dybing, 1946[51]
LD_{50}	mouse	oral (in oil)	0.134 ml	death		Ibid.
LD_{50}	mouse	oral	8850 mg/kg	death		Handbook of Toxicology, W. B. Saunders, 1959[53]
* LCLo	mouse	inhalation	23000 mg/m^3	death	2 hr.	
LD_{50}	rat			death		Withey & Hall, 1975[52]
* LCL_o	rat	inhalation	4000 ppm	death	4 hr.	Handbook of toxicology, 1959[53]
* LCL_o	rat	inhalation	4000 ppm	death	4 hr.	
** LDL_o	dog	oral	4000 mg/kg	death		Archivfuer Hyg. Bakteriol. 116:131, 1936[54]
** LDL_o	dog	i.v.	85 mg/kg	death		Carpenter et al., 1949[55]

(continued)

TABLE 8-2 (continued).

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
**LDL_o	cat	oral	4000 mg/kg	death		Clayton, 1962[56]
**LDL_o	rabbit	oral	5000 mg/kg	death		Lamson et al., 1929[57]
**LDL_o	rabbit	subcutaneous	2200 mg/kg	death		Barsoum and Saad, 1934[58]

*LCL_o - lethal concentration low the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in humans or animals.

**LDL_o - lethal dose low the lowest dose of a substance other than an LD_{50} introduced by any route other than inhalation over any given period of time and reported to have caused death in humans or animals introduced in one or more divided portions.

to 200 ppm (1,357 mg/m^3) PERC vapor 6 hours a day for 4 days. Marked increases in the frequency of ambulation in the open field were most significant 1 hour after exposure when compared to controls. High tissue concentrations of PERC were reached in fat and brain from a relatively short exposure. A significant decrease in the ribonucleic acid (RNA) content of the brain was measured as well as an increase in nonspecific cholinesterase activity.

Encephalography was utilized to study the action of PERC on rats.[14-18] Alterations in EEG patterns were associated with increased electrical impedence of the cerebral cortex at exposures as low as 15 ppm (102 mg/m^3), 4 hours/day for 15 to 30 days. Histologic examination revealed sporadic swollen and vacuolized protoplasm in some cerebral cortical cells. These interacting changes in the bioelectrical activity and electric conductivity of the brain in rats exposed to PERC are indications of long-term effects on the CNS.

8.2 EFFECTS ON THE LIVER AND KIDNEY

Tetrachloroethylene is generally regarded as being both hepatotoxic and nephrotoxic.

In 1937, Carpenter[19] exposed three groups of albino rats to PERC vapor concentrations averaging 70, 230, or 470 ppm (475, 1,560, or 3,188 mg/m^3) for 8 hours/day, 5 days/week, for up to 7 months. A group of 18 unexposed animals served as controls.

The rats exposed to 470 ppm (3,188 mg/m^3) for 150 days, followed by a 46-day rest period, developed cloudy and congested livers with swelling; there was no evidence of fatty degeneration or necrosis. These rats

also had increased renal secretion with cloudy swelling and desquamation of kidneys, as well as congested spleens with increased pigment. The pathologic changes were similar but less severe in the rats exposed to 230 ppm (1,560 mg/m^3). In some instances, there was congestion and light granular swelling of the kidneys after 21 exposures. After 150 exposures and a 20-day rest, congestion was found in the kidneys and spleens. The livers showed reduced glycogen storage. Carpenter did not find microscopic evidence of damage to liver, kidney, or spleen in rats exposed at 70 ppm (475 mg/m^3) for 150 exposures totaling 1,200 hours. In addition, microscopic examination of heart, brain, eye, or nerve tissue did not reveal any damaging effects in any of the chronically exposed rats. Functional parameters, including icteric index, Van den Bergh test for bilirubin, and blood and urine analysis, were normal after the exposures. Fertility of female rats, as measured by a fertility index (actual number of litters/possible number of litters), was increased slightly after repeated exposures to 230 or 470 ppm (1,560 or 3,188 mg/m^3) PERC.

Carpenter also tried to determine the highest concentration of PERC vapor that would not anesthetize rats exposed for 8 hours. Exposure to 31,000 ppm (210,273 mg/m^3) was lethal within a few minutes. Rats exposed to 19,000 ppm (128,871 mg/m^3) died after 30 to 60 minutes. Animals exposed to 19,000 ppm (128,877 mg/m^3) but removed from the inhalation chamber just prior to unconsciousness, developed congestion and granular swelling of the liver. Similar liver effects were seen after exposure at 9,000 ppm (61,047 mg/m^3). There was also marked

granular swelling of the kidneys. A single exposure at 9,000, 4,500, or 2,750 ppm (61,047, 30,523, or 15,261 mg/m^3) did not cause death to any of the rats in this study; however, post-mortem examinations of the rats exposed to those concentrations revealed a slight increase in the prominence of liver and kidney markings.

Rowe et al.[11] exposed rabbits, monkeys, rats, and guinea pigs to PERC vapor for 7 hours, 5 days/week for up to 6 months. Exposure concentrations ranged from 100 to 2,500 ppm (678 to 16,957 mg/m^3). Three of the four species tested -- rabbits, monkeys, and rats -- showed no effects of repeated exposures to concentrations up to 400 ppm (2,713 mg/m^3). There were no adverse effects on growth, liver weight or lipid content, gross or on microscopic anatomy observed in any animal. In contrast, guinea pigs showed marked susceptibility to PERC in this study. The liver weights of female guinea pigs increased significantly after 132 seven-hour exposures at 100 ppm (678 mg/m^3). At 200 ppm (1,356 mg/m^3), there was a slight depression of growth in female guinea pigs and increased liver weights in both males and females. Slight to moderate fatty degeneration of the liver also was observed. These effects were more pronounced in guinea pigs that received 169 7-hour exposures at 400 ppm (2,713 mg/m^3). At this concentration, there also were increased amounts of neutral fat and esterified cholesterol in livers. Gross and microscopic examination of the tissues revealed slight to moderate fatty degeneration in the liver with slight cirrhosis. Rowe et al. stated that at 395 ppm (2,680 mg/m^3) increased kidney weights also were observed in guinea pigs but not in other species.

Klaasen and Plaa[20,21] showed that short-term PERC exposures at higher concentrations, and longer exposures at lower concentrations, can produce damage to kidney and liver. They estimated the ED50 (effective dose in 50 percent of the animals tested) for liver and kidney damage in dogs[10] and in mice,[9] as well as the LD50 value (lethal dose in 50 percent of the animals treated). The ED50 values were measured by sulfobromophthalein (BSP), serum glutamic-pyruvic transaminase (SGPT), glucose, protein, and phenolsulfonephthalein (PSP) indicators of liver or kidney dysfunction. Klaasen and Plaa also determined the potency ratio, which they defined as the ratio of the LD50 to the ED50. All effects were observed after single intraperitoneal (i.p.) doses. After administration, effects on the liver and kidneys were determined by microscopic examination and by determination of SGPT elevation for the liver and PSP excretion for the kidneys.

Kylin et al.[22] noted moderate fatty degeneration of the liver with a single 4-hour exposure to 200 ppm (1,356 mg/m^3) tetrachloroethylene. They studied the hepatotoxic effect of a single inhalation exposure to PERC in female albino mice. The mice were exposed to PERC concentrations of 200, 400, 800, or 1600 ppm (1,356, 2,713, 5,426, or 10,852 mg/m^3) for 4 hours, then sacrificed 1 or 3 days after exposure. Tissues were studied microscopically to assess the extent of necrosis and the degree of fat infiltration of the liver. Mice exposed at 200 ppm (1,356 mg/m^3) for 4 hours and killed 1 day later showed moderate infiltration of fat in the liver, but there was no evident increase in the mice killed 3 days after the same exposure. Moderate to massive infiltration was observed

in mice killed 1 or 3 days after exposure at 400 ppm (2,713 mg/m^3) or more, but no cell necrosis was observed even after 4 hours exposure up to 1600 ppm (10,852 mg/m^3) PERC.

Exposure to 200 ppm (1,356 mg/m^3) for 4 hours daily, 6 days a week, for up to 8 weeks was found to increase the severity of the lesions caused by PERC.

Kylin et al.[23] exposed four groups of 20 albino mice to 200 ppm (1,356 mg/m^3) PERC. Each group was exposed for 4 hours per day, 6 days/week, for 1, 2, 4, or 8 weeks. Microscopic examinations were performed on livers and kidneys of the exposed mice and controls. Fatty degeneration was particularly marked and tended to be more severe with longer exposure to PERC.

Chemical determination of the liver fat content was performed in addition to the histologic examination. Correlation between the histologically evaluated degree of fatty degeneration and the concentration of extracted fat was +0.74. Liver fat content of the exposed animals was between 4 and 5 mg/g body weight as compared to 2 to 2.5 mg/g for the control animals. The actual fat content of the livers did not increase with duration of exposure as did the extent of the fatty infiltration. No liver cell necrosis was observed. No effect on the kidneys was reported.

Mazza[24] exposed 15 male rabbits, 4 hours per day, 5 days a week, for 45 days to 2,790 ppm (18,924 mg/m^3) PERC. He looked at the effect of PERC on serum enzyme levels in an attempt to determine the specific location of initial liver injury as well as the severity of the damage

to the liver. The Schmidt Index, which is the sum of serum glutamic-oxaloacetic transaminase (SGOT) and the SGPT divided by the serum glutamate dehydrogenase (GDH), was used as an indication of hepatic disorders. Enzymatic determinations were made before exposure and 15, 30, and 45 days after exposure to PERC. All three of the enzymes showed an increase in activity, but the GDH increased the most, reducing the Schmidt Index from 6.70 to 1.79. Mazza concluded that this reduction indicates the prevalence of mitochondrial injury over cytoplasmic injury in the liver.

Mazza and Brancaccio[25] exposed 10 rabbits for 4 hours per day, 5 days a week, for 45 days to 2,790 ppm (18,924 mg/m^3) PERC. These investigators found a moderate, but not statistically significant, increase in levels of adrenal cortical and medullar hormones--plasma and urinary corticosteroids and catecholamines--including increased excretion of 3-methoxy-1-hydroxymandelic acid, the principal catecholamine metabolite.

Brancaccio et al.[26] exposed 12 male rabbits for 4 hours per day, 6 days per week, for 45 days to 2,280 ppm (15,465 mg/m^3) PERC to look at effects on kidney function. They noted a reduction in glomerular filtration and renal plasma flow, and a highly significant decrease in the maximum tubular excretion. They concluded that PERC causes kidney damage, primarily in the renal tubule. These findings were in agreement with earlier histological findings of Pennarola and Brancaccio[27] in which kidney injury, following exposure to PERC, appeared to be primarily in the renal tubule.

Plaa and Larson[28] dosed mice with PERC by i.p. injection. Ten mice received 2.5 mg/kg and 10 others received 5.0 mg/kg. Urine samples were

collected from surviving mice 24 hours after the injection of PERC. Protein was measured in the urine in 1 of 6 surviving mice injected with the lower dose and in 2 of 4 survivors of the higher dose at levels of 100 or more mg percent.

However, none of the survivors had greater than 150 mg percent glucose in the urine. The kidneys of the mice given the lower dose were examined microscopically. The proximal convoluted tubules were swollen in all animals and necrotic in one.

Fujii[29] observed an increase in serum enzyme activities (i.e., alkaline phosphatase, SGOT, and SGPT) within 24 hours after a single dose of 13 mmole/kg given orally to rabbits. These changes in serum enzyme activities, indicative of liver damage, were mild and transient but followed a pattern similar to that seen with carbon tetrachloride. Increases in serum lipoprotein concentrations were still evident two weeks after treatment.

8.3 EFFECTS ON THE HEART

The possible cardiovascular effects of PERC have not been systematically investigated. Reinhardt et al.[30] noted that PERC does not appear to sensitize the myocardium to epinephrine. In this study of dogs, a response considered indicative of cardiac sensitization was the development of a seriously life-threatening arrhythmia or cardiac arrest following a challenge dose of epinephrine. Tetrachloroethylene inhalation exposure for 10 minutes at concentrations of 5,000 or 10,000 ppm (33,915 or 67,830 mg/m^3) did not result in a positive response in any of the 17 dogs.

In the same study, sensitization did occur with the PERC analog, trichloroethylene, as well as with 1,1,1-trichloroethane, and trichlorotrifluroethane. The investigators noted the possibility that PERC has the potential for cardiac sensitization, but to a lesser degree than the other chlorinated hydrocarbons studied.

Christensen and Lynch[10] observed depression of the heart and respiration in five dogs, each given a single oral dose ranging from 4 to 5.3 ml/kg PERC. Autopsy showed fatty infiltration of both heart and liver tissue. The small intestine was extremely shriveled and showed marked inflammation.

Barsoum and Saad[31] determined that the greatest dilutions of PERC that would have a depressant effect on an isolated toad's or rabbit's heart were 1:3,000 and 1:4,000, respectively.

8.4 SKIN AND EYE

Duprat et al.[32] have shown PERC to be a primary eye and skin irritant in rabbits. Instillation of the chemical into the eye produced conjunctivitis with epithelial abrasion. However, healing of the ocular mucosa was complete within 2 weeks. Tetrachloroethylene had a severe irritant effect when a single application was made to the skin of the rabbit.

8.5 OTHER EFFECTS REPORTED IN ANIMALS

Other effects which have been associated with exposure to PERC include changes in the immune system. Long-term inhalation exposure to PERC has been shown to cause distinct changes in immunological response in rabbits.[33]

Tarasova[34] described the action of PERC on mast cells. Morphology of cells from treated animals was more varied. Cells appeared swollen.

Vacuolization of the cytoplasm and conglomeration of granules was noted as well as increased degranulation.

Bonashevskaya and his co-workers[35-38] have reported effects associated with acute, subacute, and chronic inhalation of low doses (2 to 20 mg/m^3) of tetrachloroethylene. Adverse effects on the CNS, serum enzyme activity, and liver were observed as well as effects on the lung, adrenal glands, and mast cell system.

Rats fed a high protein diet appeared to be more resistant to the effects of subcutaneous injection of tetrachloroethylene than rats fed a protein deficient diet.[39]

Treatment of rats with a single i.p. dose of 1.3 ml/kg PERC alters the excretory function of the common bile duct and pancreas.[40] Hamada and Peterson[41] demonstrated that the mechanism by which PERC increases "bile duct pancreatic fluid" flow does not appear to involve secretin or cholinergic stimulation.

Therapeutic doses of PERC in dogs have been shown to have effects on the heart, liver, and small intestine.[10]

8.6 SUMMARY

Tetrachloroethylene causes central nervous system depression in animals. Signs of functional disturbances in animals which are viewed as expression of CNS depression include abnormal weakness, handling intolerance, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsciousness. Tetrachloroethylene is irritating to the eyes and skin; solvent action on natural oils causes defatting of the skin. Damage to the liver and/or kidney has been shown to occur in various animal species

following exposure to PERC by various routes of administration including inhalation. Long-term inhalation exposure to PERC has been shown to cause changes in immunological response.

8.7 REFERENCES FOR CHAPTER 8

1. Criteria for a recommended standard...Occupational Exposure to Tetrachloroethylene (Perchloroethylene). HEW Publication No. (NIOSH) 76-185. U.S. Department of HEW, PHS, CDC, NIOSH. July, 1976.

2. Fuller, B. B. Air Pollution "Assessment of Tetrachloroethylene." Mitre Technical Report - 7143. February, 1976. 88 pp.

3. Bull, Richard J. "Human Health Effects: Tetrachloroethylene." Revised draft. U.S. EPA. August, 1978.

4. Walter, P., A. Craigmill, J. Villaume, S. Sweeney, and G. L. Miller. "Chlorinated Hydrocarbon Toxicity (1,1,1-Trichloroethane, Trichloroethylene and Tetrachloroethylene)" - A Monograph. Nat. Tech. Infor. Serv. Springfield, Va. PB-257 185/9, May 1976.

5. Parker, J. C., L. J. Bahlman, N. A. Feidel, H. P. Stein, A. W. Thomas, B. S. Woolf, and E. J. Baier. Tetrachloroethylene (Perchloroethylene). Current NIOSH Intelligence Bulletin #20. Am. Ind. Hyg. Assoc. J. 39:3, 1978.

6. Fishbein, L. Industrial mutagens and potential mutagens. I. Halogenated aliphatic derivatives. Mutal. Res. 32:267-308, 1976.

7. Environmental Protection Agency. An Assessment of The Need for Limitations on Trichloroethylene, Methyl Chloraform, and Perchloroethylene. Draft Final Report, Volumes I, II, III. Office of Toxic Substances. EPA Contract No. 68-01-4121, September 1977.

8. Miller, T. A. Anthelmintic activity of tetrachloroethylene against various stages of Ancylostoma canium in young dogs. Am. J. Vet. Res. 27(119):1037-1040, 1966.

9. Snow, D. H. The effects of pyrantel pamoate and tetrachloroethylene on several blood enzyme levels in the greyhound. Aust. Vet. J. 49:269-272, 1973.

10. Christensen, B. V., and H. J. Lynch. The effect of anthelmintics on the host. I. Tetrachloroethylene. II. Hexylresorcinol. J. Pharmacol. Expt. Therap. 48:311-316, 1933.

11. Rowe, V. K., D. D. McCollister, H. C. Spencer, E. M. Adams, and D. D. Irish. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. Arch. Ind. Hyg. Occup. Med. 5:566-579, 1952.

12. Goldberg, M. E., H. E. Johnson, U. C. Pozzani, and H. F. Smyth, Jr. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvent vapors on pole-climb performance in rats. Am. Ind. Hyg. Assoc. J. 25:369-375, 1964.

13. Savolainen, H., P. Pfäffli, M. Tegén, and H. Vainio. Biochemical and behavioral effects of inhalation exposure to tetrachloroethylene and dichloromethane. J. Neuropathol. and Exp. Neurol. 36:941-949, 1977.

14. Dmitrieva, N. V. Maximum permissible concentration of tetrachloroethylene in factory air. Hyg. Sanit. 31:387-393, 1966. (English translation.)

15. Dmitrieva, N. V., and E. V. Kuleshov. Changes in the bioelectric ativity and electric conductivity of the brain in rats chronically poisoned with certain chlorinated hydrocarbons. Hyg. Sanit. 36:23-29, 1971. (English translation.)

16. Dmitrieva, N. V., E. V. Kuleshov, and E. K. Orjonikidze. Changes in the impedance and bioelectrical activity of the cerebral cortex of rats under the action of anesthetic drugs. Zhur. vysshei Nervnoi Deyatel 'nosti 18(3):463-468, 1968. (English translation.)

17. Dmitrieva, N. V. Changes in the bioelectrical activity in the cerebral cortex of rats with the narcotic effect of substances with different polarization properties. Experimental' naya Khirurgiya i Anestezidogiya 6:72-75, 1973. (English translation.)

18. Dmitrieva, N. V. Bioelectric activity and electric conducting properties of muscles exposed to chlorinated hydrocarbons. Farmakologiya i Toksikologiya 31(2):228-230, 1968. (English translation.)

19. Carpenter, C. P. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 9:323-336, 1937.

20. Klaassen, C. D., and G. L. Plaa. Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. Toxicol. Appl. Pharmacol. 9:139-151, 1966.

21. Klaasen, C. D., and G. L. Plaa. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol. Appl. Pharmacol. 10:119-131, 1967.

22. Kylin, B., H. Reichard, I. Sümegi, and S. Yllner. Hepatotoxicity of inhaled trichloroethylene, tetrachloroethylene and chloroform. Single exposure. Acta Pharmacol. Toxicol. 20:16-26, 1963.

23. Kylin, B. I. Sümegi, and S. Yllner. Hepatotoxicity of inhaled trichloroethylene and tetrachloroethylene - long-term exposure. Acta Pharmacol. Toxicol. (Kbh). 22:379-385, 1965.

24. Mazza, V. Enzyme changes in experimental tetrachloroethylene intoxication. Folia Med. 55(9-10):373-381, 1972. (English translation.)

25. Mazza, V., and A. Brancaccio. Adrenal cortical and medullar hormones in experimental tetrachloroethylene poisoning. Folia Med. 54:204-207, 1971. (English translation.)

26. Brancaccio, A., V. Mazza, and R. DiPaola. Renal function in experimental tetrachloroethylene poisoning. Folia Med. 54:233-237, 1971. (English translation).

27. Pennarola, B., and A. Brancaccio. Histopathological findings in experimental perchloroethylene poisoning. Folia Med. 51:1146, 1968.

28. Plaa, G. L., and R. E. Larson. Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. Toxicol. Appl. Pharmacol. 7:37-44, 1965.

29. Fujii, T. The variation in the liver function of rabbits after administration of chlorinated hydrocarbons. Jap. J. Ind. Health 17:81-88, 1975. (English translation).

30. Reinhardt, C. F., L. S. Mullin, and M. B. Maxfield. Epinephrine-induced cardiac arrhythmia potential of some common industrial solvents. J. Occup. Med. 15:953-955, 1973.

31. Barsoum, G. S., and K. Saad. Relative toxicity of certain chlorine derivatives of the aliphatic series. Q. J. Pharmacol. 7:205-214, 1934.

32. Duprat, P., L. Delsaut, and D. Gradiski. Irritant potency of the principal aliphatic chloride solvents on the skin and ocular mucous membranes of rabbits. Europ. J. Toxicol. 3:171-177, 1976.

33. Shmuter, L. M. The effect of chronic exposure to small concentrations of chlorinated hydrocarbons on the production of various classes of immunoglobulins. Gig. i Sanit. 37:36-40, 1972. (English translation).

34. Tarasova. Morphological-functional changes in mast cells during action of 1,2,3-trichloropropane and tetrachloroethylene. Gig. i Sanit. 11:106-109, 1975. (English translation).

35. Bonashevskaya, T. I. Morphological characteristics of adaptation processes of liver to effect of certain chemical substances. Gig. i Sanit. (4):45-50, 1977. (English translation).

36. Bonashevskaya, T. I. Certain results of a morphological and functional investigation of the lungs in a hygienic assessment of atmospheric pollution. Gig. i Sanit. (2):15-20, 1977. (English translation).

37. Tsulaya, V. R., and T. I. Bonashevskaya. Toxicological characteristics of certain chlorine derivatives of hydrocarbons. Gig. i Sanit. (8):50-53, 1977. (English translation).

38. Bonashevskaya, T. I., N. N. Belyayeva, et al. Polyploidization as a compensation mechanism for the effect of chemical factors in the environment. Gig. i Sanit. (12):81-83, 1977. (English translation).

39. Dumitrache et al. Role of proteins in organism resistance to tetrachloroethylene. Rev. Ig. Bacteriol, Virusol, Parazitol, Epidemiol., Pneumoftiziol, Ig. 24(3):147-151, 1975.

40. Harms, M. S., R. E. Peterson, J. M. Fujimoto, C. P. Erwin. Increased "Bile Duct-Pancreatic Fluid" flow in chlorinated hydrocarbon-treated rats. Toxicol. Appl. Pharmacol. 35:41-49, 1976.

41. Hamada, N., and R. E. Peterson. Effect of chlorinated aliphatic hydrocarbons on excretion of protein and electrolytes by rat pancreas. Toxicol. Appl. Pharmacol. 39:185-194, 1977.

42. Navrotskii, V. K., L. M. Kaskin, I. L. Kulinskaya, L. F. Mikhailovskaya, L. M. Shmuter, Z. I. Burlaka-Vovk, B. V. Zqdorozhnyi. Comparative evaluation of the toxicity of a series of industrial poisons during their long-term inhalation action in low concentrations. Tr. Sezda. Gig. Ukr. SSR, 8th, 224-226, 1971. (English translation).

43. Schwetz, B. A., B. K. Leong, and P. J. Gehring. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32:84-96, 1975.

44. Aninina, T. Effect of aliphatic hydrocarbons and fluorinated and chlorinated derivatives on the content of nucleic acids in animal tissues during embryogenesis. Tr. Permsk. Cas. Med. Inst. 110:69-71, 1972.

45. Lehmann, K. B. Experimental studies on the influence of technically and hygienically important gases and vapors on the organism. Arch. Hyg. 74:1-60, 1911. (In German).

46. Lehmann, K. B., and L. Schmidt-Kehl. The 13 most important chlorinated hydrocarbons of the aliphatic series from the standpoing of occupational hygiene. Arch. Hyg. 116:131-268, 1936. (In German).

47. Lamson, P. D., B. H. Robbins, and C. B. Ward. The pharmacology and toxicology of tetrachloroethylene. Amer. J. Hyg. 9:430-444, 1929.

48. Wenzel, D. G., and R. D. Gibson. Toxicity and anthelminitic activity of n-butylidine chloride. J. Pharm. Pharmacol. 3:169-176, 1951.

49. Gehring, P. Hepatotoxicity of various chlorinated hydrocarbon vapors relative to their narcotic and lethal properties in mice. Toxicol. Appl. Pharm. 13:287-298, 1968.

50. Plaa, G. L., E. A. Evans, and C. H. Hine. Relative hepatotoxicity of seven halogenated hydrocarbons. J. Pharmacol. Expt. Ther. Vol. 123:224-229, 1958.

51. Dybing, F., and O. Dybing, The toxic effect of tetrachloroethane and tetrachloroethylene in oily solution. Acta Pharmacol. 2:223-226, 1946.

52. Withey, R. J., and J. W. Hall. The joint action of perchloroethylene with benzene or toluene in rats. Toxicol. 4:5-15, 1975.

53. Handbook of Toxicology, Volumes II-V, W. B. Saunders Co., Philadelphia, 1959. Volume V., p. 76.

54. Archiv fuer Hyg. Bakteriol. (Munchen) 116:131, 1936.

55. Carpenter, C. P., H. F. Smyth, Jr., and V. C. Pozzani. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31:434, 1949.

56. Clayton, J. W. The toxicity of fluorocarbons with special reference to chemical constitution. J. Occup. Med. 4:262-273, 1962.

57. Lamson, P. D., B. H. Robbins, and C. B. Ward. The pharmacology and toxicology of tetrachlorethylene. Am. J. Hyg. 9:430-444, 1929.

58. Barsoum, G. S., and K. Saad. Relative toxicity of certain chlorine derivatives of the aliphatic series. Qu. J. Pharm. Pharmacol. 7:205-214, 1934.

9. EFFECTS ON HUMANS

The known effects of tetrachloroethylene (PERC) on humans have been established primarily from clinical studies of individuals accidentally or occupationally exposed to high, and in some cases, unknown, concentrations of PERC.

Exposure to PERC causes a wide variety of toxicological effects in humans. Effects on the liver and kidney are the most striking.

In order to relate health effects of PERC to exposure levels of PERC that one might reasonably expect in ambient situations, it is the intent of this section to focus on those effects associated with the lowest levels of PERC. Both acute and chronic effects are delineated; acute effects have been arbitrarily designated as those observed as a result of exposures of approximately 3 hours or less.

9.1 EFFECTS ON THE LIVER

9.1.1 Acute

Mild hepatitis was diagnosed by Stewart[1] in a worker occupationally exposed to high, unknown concentrations of PERC for less than 30 minutes. Infrared analysis of the patient's exhaled breath 1.5 hours after exposure showed 105 ppm (712 mg/m^3) PERC. Urinary urobilinogen levels were elevated on the 9th day of the post-exposure period. The serum glutamic-oxaloacetic transaminase (SGOT) level showed a slight increase on the 3rd and 4th days. Stewart concluded this patient had experienced marked depression of the central nervous system (CNS) followed by transient, minimal liver injury. The diagnosis of CNS depression was based on the abnormal findings of the Romberg Test (9.4.1). The increase in urinary urobilinogen was suggested as one indicator of hepatic

injury due to PERC. Elevations in the levels of urobilinogen and other indicators of liver damage have been reported in other case studies involving acute exposures.[2,3] The effects on the CNS are described in Section 9.4.

Stewart et al.[2] reported an accidental overexposure of an individual to PERC during a 3.5 hour period. The individual also had been simultaneously exposed to an estimated 230 ppm of Stoddard Solvent, a petroleum-based dry cleaning solvent which contains aliphatic and aromatic hydrocarbons. However, Stoddard Solvent was not found in the postexposure exhaled air. Simulated exposure conditions suggested that the average concentration of PERC in the work environment during the exposure period was 393 ppm (2,666 mg/m^3). Total serum bilirubin and urinary urobilinogen were above normal on the 9th day following exposure. The level of serum glutamic-pyruvic transaminase (SGPT) was slightly elevated on the 18th post-exposure day. Stewart and co-workers suggested that an acute exposure, such as that experienced, may, in fact, represent a continuing insult to the liver in view of the observations that the excretion rate of PERC from some body tissues is slow. Since impaired liver function parameters became evident 9 days following exposure, this may indicate that the liver damage is due to chronic exposure to PERC excreted only slowly from the body after exposure. However, it is not to be construed that exposures of individuals to low-level ambient air concentrations of PERC result in liver damage due to the slow release of PERC from body tissues. There is no data relating to such situations.

Elevated SGOT values and an enlarged liver were reported by Saland.[3] Nine individuals were exposed to unknown concentrations of PERC for 3 minutes. All signs of dysfunction returned to normal.

Nursing infants may represent a special group highly sensitive to the effects of PERC. An enlarged liver and obstructive jaundice were diagnosed by Bagnell and Ellenberger[4] in a 6-week-old, breast-fed infant. The infant was never directly exposed to PERC vapors. The child's father worked in a dry cleaning establishment where PERC vapors were present. During regular lunchtime visits to the exposure site, the mother had been exposed to the same vapors. These visits lasted between 30 and 60 minutes. The concentration of PERC in the work place was unknown. In the infant, bilirubin, SGOT, and serum alkaline phosphatase were elevated; other blood and urinary parameters of liver function were normal. Normal liver function was found in both parents although the child's father had experienced repeated episodes of dizziness and confusion. Analysis of the mother's blood 2 hours after one of her lunchtime visits indicated a PERC level of 0.3 mg per 100 ml. Her breast milk, 1 hour after a visit, contained 1.0 mg per 100 ml. After 24 hours, the concentration of PERC in the breast milk decreased to 0.3 mg per 100 ml. Chlorinated hydrocarbons were not found in the mother's urine. One week after breast feeding was discontinued, serum bilirubin and serum alkaline phosphatase levels in the infant returned to a normal range. The findings suggest that PERC may be selectively concentrated in breast milk and that the neonatal liver may be sensitive to toxicological effects of PERC.

Sparrow[5] reported liver dysfunction and an increase in urinary hydroxyproline in a 19-year-old male exposed to PERC for a few minutes once a week for 4 years. Because of predisposing factors in the individual's medical history, no conclusions can be drawn regarding the effects of PERC in this case. These factors included a history of partial baldness and an absence of immunoglobulin A, which may be associated with autoimmune disease.

9.1.2 Chronic

Hepatotoxic effects as a result of inhaling PERC have been documented by a number of investigators.[6-13] In most studies, the concentration of PERC was greater than 100 ppm (678 mg/m^3). The observed effects are presented in Table 9-1.

Liver function parameters observed to be altered as a result of PERC exposure include sulfobromophtlalein retention time, thymol turbidity, serum bilirubin, serum protein patterns, cephalin-cholesterol flocculation, serum alkaline phosphatase, SGOT, and serum lactic acid dehydrogenase (LDH).

Effects observed included cirrhosis of the liver,[6] toxic hepatitis,[8,10] liver cell necrosis,[9,10] and enlarged liver,[3,10]

In some cases, liver dysfunction parameters returned to normal following cessation of exposure.[8] In one case, the liver was enlarged 6 months after cessation of exposure.[10] Renal insufficiency, in addition to liver dysfunction, was evidenced in one individual.[11]

In the study by Larsen et al.,[11] SGOT values increased 4 to 5 times normal 1 day after initial symptoms of abdominal pains and blood-tinged vomiting. Two days later, SGOT returned to a normal range. Serum bilirubin was normal throughout the diagnosis. Variations in the levels of SGOT and other liver function parameters during the post-exposure period indicate that repeated testing during this interval is required for complete diagnosis.

Larsen et al.[11] also reported that PERC exposure may have led to coma and a grand mal seizure in one individual. However, this cause-effect relationship is unproven.

Details of the above mentioned studies are described in Table 9-1.

TABLE 9-1. EFFECTS OF TETRACHLOROETHYLENE ON LIVER ASSOCIATED WITH CHRONIC EXPOSURES OF HUMANS

PERC Concentration ppm	PERC Concentration mg/m^3	Duration of Exposure	Number of Individuals Exposed	Effects	Reference
230 to 385	1,560 to 2,611	2 days/wk up to 6 yrs	4	Liver dysfunction evidenced by dulfobromophthalein retention time, serum protein patterns. One individual had cirrhosis of liver and 3+ reaction to cephalin-cholesterol flocculation test.	Coler and Rossmiller, 1953[6]
75% of measurements less than 100 ppm (678 mg/m^3)		unknown	113	Thymol turbidity and bilirubin determinations altered.	Franke and Eggeling, 1969[7]
unknown		12-16 hr/day often 7 day/wk 11 wk	1	Toxic hepatitis; liver function tests unspecified.	Hughes, 1954[8]
unknown		> 1 yr	1	Individual had died of cardiovasculer failure; toxic liver cell necrosis observed upon autopsy. Chlorinated hydrocarbons not found in liver.	Trense and Zimmerman, 1969[9]
unknown		2.5 mo	1	Hepatitis, enlarged liver, acholic stools, nausea, vomiting, jaundice of the white of the eye, and generalized itching were found. Alkaline phosphatase, SGOT, and bilirubin measurements consistent with liver disease. Liver biopsy performed 2 wk post-exposure showed degeneration of parenchymal cells, exaggeration of sinosoids and focal collections of mononuclear cells - liver still enlarged after 6 wk post-exposure.	Meckler and Phelps, 1966[10]
unknown		unknown	1	Women had worn clothing which had been dry-cleaned. Admitted to hospital in comatose state with grand mal seizure. Bilirubin, SGOT and LDH elevated. Renal insufficiency also evident. SGOT and LDH returned to normal during hospitalization.	Larson et al., 1977[11]

TABLE 9-1 (continued).

PERC Concentration ppm	PERC Concentration mg/m^3	Duration of Exposure	Number of Individuals Exposed	Effects	Reference
unknown		unknown	1	Male had worn clothing which had been dry-cleaned. Initial symptoms were abdominal pain and blood-tinged vomiting. SGOT increased 4 to 5 times normal 1 day after initial symptoms. Jaundice of eye and enlarged liver were not detected. SGOT returned to normal. Serum bilirubin normal throughout diagnosis.	Ibid.
unknown		6 yr	1	Liver dysfunction; returned to normal 20 days after cessation of exposure.	Moeschlin, 1965[12]
unknown		unknown	1	Enlarged liver; patient had history of alcoholism.	Dumortier et al., 1964[13]
59 to 442	400 to 3,000	unknown	25	Increases in serum aminotransferases; decreased activity of cholinesterase presumably as a result of damage to liver cells.	Chmielewski et al., 1976[14]

In a study of 25 workers who had been occupationally exposed to PERC, Chmielewski et al.[14] found that the activities of alanine and asparagine aminotransferase were significantly elevated ($t_{0.05} = 2.032$) in a group of 16 workers compared to non-exposed controls. This group of 16 workers had been exposed to PERC vapors in the range of 59 to 442 ppm (400 to 3,000 mg/m^3). Aminotransferase activity in a group of 9 workers exposed to levels of PERC at or below 29 ppm (200 mg/m^3) was normal. These enzyme imbalances were indicative, to the investigators, of liver cell damage by PERC. Such alterations in aminotransferase activity are suggestive of an imbalance in the glycolytic-gluconeogenic pathway.

Low excretion of 17-ketosteroids (11/25 cases) and abnormal EEG tracings (4/16 cases) also were observed by the investigators.

9.2 EFFECTS ON KIDNEY

Diminished urine excretion, (5 to 10 ml urine per hour), uremia, and elevated serum creatinine was observed in a woman who had worn clothing cleaned at a dry cleaning establishment.[11] Upon treatment, diuresis and serum creatinine returned to normal. Renal biopsy suggested toxic nephropathy. Liver dysfunction also was evidenced by increased SGOT and bilirubin levels.

In another situation in which an individual had worn clothing permeated with PERC vapors, elevated serum creatinine and blood uremia was observed.[11] Mild proteinuria and leukocytes and erythrocytes in the urine were observed. Serum creatinine decreased with peritoneal dialysis. Renal biopsy evidenced necrosis in the renal tubules.

Advanced membranous nephropathy was diagnosed by Ehrenreich et al.[15] in an individual who had been exposed to PERC and other solvent vapors for more than 15 years. [Membranous nephropathy is a chronic renal disease involving

glomeruli and occurs principally in adults.[16]] Upon improvement after steroid treatment, a mild proteinuria (1 to 2 g/day) and a slightly elevated blood pressure persisted.

A co-worker of the above individual, exposed to various solvents for 11 years developed kidney, heart, and respiratory difficulties. He became ill, lapsed into a coma, and died of severe acidosis. Upon autopsy, indications of membranous nephropathy were found. However, a causal relationship with solvent exposure was not established.

9.3 EFFECTS ON OTHER ORGANS/TISSUES

9.3.1 Effects on the Pulmonary System

A 7-hour occupational exposure of a male to an unknown concentration of PERC produced findings consistent with acute pulmonary edema.[17] Bubbling rales were heard over the entire lung field. Complete recovery was made 4 days after hospital admission. Liver and kidney function tests in this patient were normal.

Hemorrhagic pneumonia and edema of the lungs were found in a male dry cleaning plant worker upon autopsy. The individual had been exposed occupationally to PERC for 4 months. The primary cause of death was cardiac arrest; no causal relationship was suggested between this cause of death and PERC.[9]

9.3.2 Hematological Effects

Alkaline phosphatase in leukocytes is a defense mechanism against bacterial infection and plays an active part in phagocytosis.

In an investigation of the effects of PERC on alkaline phosphatase activity in human neutrophilic leukocytes, Friborska[18] found that activity was within the normal range. In this study of occupational exposure, seven

workers were exposed to PERC and four had been exposed to both PERC and trichloroethylene. For controls, 20 unexposed individuals were used. Trichloroethylene exposure, as opposed to PERC, raised the activity of the alkaline phosphatase above the control level. For those individuals exposed to both compounds, no synergistic or additive effect was observed.

A slight depression in the total white blood cell count of 3 of 9 firemen exposed for 3 minutes to unknown concentrations of PERC was observed by Saland.[3] These observations were made 12 days after exposure.

9.3.3 Effects On The Skin

Contact of PERC with the skin may cause dryness, irritation, blistering, and burns.

Stewart and Dodd[19] reported that individuals experienced a mild burning sensation on their thumbs after immersion in a solution of PERC for 5 to 10 minutes. After the thumbs were withdrawn, burning persisted without a decrease in intensity for 10 minutes before gradually subsiding after 1 hour. A marked erythema was present in all cases and subsided between 1 and 2 hours post-exposure.

Ling and Lindsay[20] reported severe burns when an individual, upon losing consciousness, fell into a pool of PERC on the floor. The burns gradually healed within 3 weeks following exposure.

9.4 BEHAVIORAL AND NEUROLOGICAL EFFECTS

In nearly all the occupational situations involving short-term exposures to PERC, an initial characteristic response is commonly depression of the central nervous system (CNS). Subacute exposures produce characteristics of a neurasthenic syndrome; the most frequently reported subjective complaints are dizziness, headache, nausea, fatigue, and irritation of the eyes, nose, and

throat; individuals may vary greatly in sensitivity. Long-term exposures have been reported to result in exacerabated symptoms or more serious behavior and neurological findings.

9.4.1 Effects of Short-Term Exposures

Stewart[1] reported normal neurological findings, except for the Romberg test, in an individual who had been exposed to approximately 105 ppm (712 mg/m^3) for less than 30 minutes. The Romberg test is designed to detect swaying motions when the subject stands with eyes closed. Upon return to work, the individual reported being very fatigued after 4 hours of light work. It was suggested that abnormal results of the Romberg test are the earliest indications of signs of intoxication due to PERC. In another study, Stewart[21] reported that lightheadedness was experienced when individuals were exposed to 101 ppm for 83 minutes.

Rowe et al.[22] reported that individuals exposed to an average PERC concentration of 106 ppm (range = 83 to 130) did not evidence central nervous system effects. At an average PERC concentration of 216 ppm, (1,465 mg/m^3) four of four individuals exposed for 45 minutes to 2 hours experienced slight eye irritation, developing 20 to 30 minutes into the exposure period. Minimal, transient eye irritation was noted which led the authors to suggest that the vapor concentration causing this effect in unacclimatized individuals lies between 100 and 200 ppm (678 and 1,356 mg/m^3). Dizziness and sleepiness also were noted. Recovery from all symptoms was complete within an hour after exposure. An exposure to an average concentration of 280 ppm (1,899 mg/m^3) for up to 2 hours resulted in complaints of lightheadedness, burning sensation in the eyes, congestion of frontal sinuses, and tightness about the mouth. Transient nausea was reported by one individual. The subjects felt that motor

coordination was impaired and mental effort was required for coordination. An average exposure concentration of 1,060 ppm (7,190 mg/m^3) for 1 minute was intolerable to three of four individuals. None experienced functional disturbances. Recovery was rapid. Motor coordination was accomplished only with mental effort when two individuals were exposed to an average PERC concentration of 600 ppm (4,070 mg/m^3). Recovery was complete within an hour after exposure.

No behavioral or neurological effects were reported by Carpenter[23] when four individuals were exposed to 500 ppm PERC for 70 minutes. Short-term exposures to higher concentrations resulted in reports by subjects of mental fogginess, lassitude, inebriation, loss of inhibition, and vertigo. At an exposure level of 1,500 ppm (10,174 mg/m^3), shortness of breath, nausea, mental sluggishness, and difficulties in maintaining balance were reported during the post-exposure period. Tinnitus, ringing of the ears, was reported upon exposure to 2,000 ppm (13,565 mg/m^3) for 7.5 minutes.

Weichardt and Lindner[24] recorded subjective responses of headaches, giddiness, numbness, alcohol intolerance, intolerance of fats and fried foods as a result of exposures to between 11 to 45 ppm (75 to 305 mg/m^3) for approximately 3 hours.

In a case study involving a nursing mother exposed daily for 30 to 60 minutes to unknown PERC concentrations, Bagnell and Ellenberger[4] recorded subjective complaints of dizziness. Transmitted effects of PERC, through breast milk, on the nursing infant are discussed in Section 9.1.1.

9.4.2 Long-Term Effects

In a comprehensive 3-month chamber study of 6 males and 6 females designed to elicit interactions between ethanol and diazepam (Valium®) and

PERC, Stewart et al.[25] found that exposure to 25 and 100 ppm (170 and 678 mg/m^3) PERC alone had no effect on the electroencephalogram (EEG) tracings. A slight but statistically significant detrimental effect upon the Flanagan coordination test was repeatedly found at an exposure level of 100 ppm (678 mg/m^3). This test requires subjects to follow a spiral pathway with a pencil, touching the sides of the pathway as few times as possible.

Each subject was exposed 5.5 hours daily. The total number of exposure days was 55. No other unusual behavioral or neurological finding were noted upon exposures to PERC alone. Subjective complaints were noted, however; one subject accounted for one-third the incidence of headache and two-thirds the incidence of nausea reported by the nine subjects who completed the study. The absence of EEG abnormalities, such as were found in an earlier study by Stewart and co-workers[26] suggest that EEG observations may not be reliable indicators of early signs of PERC narcosis. In their earlier study, impairment of coordination was occasionally noted during exposures to 150 ppm for 7.5 hours.

Stewart[27] noted subjective complaints of headaches (25 percent), eye, nose, or throat irritation (60 percent), sleepiness (40 percent), and lightheadedness in individuals exposed to 101 ppm for 7 hours. One-quarter of the individuals had difficulty in speaking. Upon repeated exposures to this level, mild eye and throat irritation were consistently reported by two of five test subjects. Abnormal Romberg test findings in three individuals were recorded within the first 3 hours of exposure. During the post-exposure period, repeat tests were normal. All other neurological test results were normal.

Similar subjective complaints, as well as neurological effects, of PERC also were recorded in other studies.[28-31]

9.4.3 Effects of Complex Mixtures

Additive or synergistic effects associated with exposure of complex mixtures containing PERC have not been found.

Administration of diazepam (Valium®) or ethanol in the form of vodka to 12 volunteers failed to elicit correlation with exposure to 25 or 100 ppm (170 or 678 mg/m^3) PERC.[25] A significant but inconsistent increase in the beta activity of the EEG during combined PERC exposure and diazepam dosing was noted. This effect was attributed to diazepam alone. Exposure to PERC did not exacerbate the behavioral and/or neurological effects noted with either alcohol or diazepam alone.

Diagnostic tests administered included the Michigan eye-hand coordination test, Rotary Pursuit, Flanagan coordination test, Romberg test, Saccade eye velocity test, dual-attention tasks, and a mood evaluation test.

Stewart[2] reported no neurological abnormalities during or 6 weeks after an accidental exposure to 393 ppm (2,666 mg/m^3) PERC and another dry cleaning solvent (Stoddard solvent) for 3.5 hours. Eye irritation and a feeling of unsteadiness were the only symptoms reported. The solvent to which the individual was exposed consisted of 50 percent PERC and 50 percent Stoddard solvent.

Clinical exposure of five individuals to a solvent mixture containing 1,1,1-trichloroethane (74 percent) and PERC (22 percent) did not reveal any deleterious neurological findings beyond which would be found upon exposure to each alone.[22] The exposure level of PERC was calculated at 100 ppm (678 mg/m^3). A complete examination was given at the end of the sixth hour of the

7 hour exposure period. Individuals were exposed for one, four, and five, 7-hour periods.

9.5 EPIDEMIOLOGICAL FINDINGS

Most of the epidemiological studies pertaining to PERC have been conducted in countries other than the United States. These occupational investigations have provided valuable information relating to the effects of PERC, but often workplace concentrations of PERC were either unknown or only roughly approximated.

Efforts to delineate health effects as a result of occupational exposures to PERC currently are being conducted by the National Institute of Occupational Safety and Health.[32] This organization is conducting an epidemiologic and industrial hygiene study of dry cleaning workers exposed to PERC.

In Germany, an epidemiological study involving 113 male and female workers from 46 dry cleaning plants revealed numerous subjective and clinical effects.[7] Serum glutamic-oxaloacetate transaminase and SGPT levels were considered as significantly different from those values obtained with a control population. However, since the controls (43 unexposed individuals) also included an indeterminant number of "patients" being treated for dust exposure, the observed liver function test values should be viewed with caution.

Excessive sweating and tremors were diagnosed in 40 percent of the workers, while irritation of the mucous membranes occurred in 33 percent. The concentrations of PERC associated with these effects were not reported although subsequent measurements indicated that 75 percent of the measurements made in the work place were less than 100 ppm (678 mg/m^3).

Excessive sweating and tremors of the fingers and eyelids were found in 22 of 200 dry cleaning plant employees.[33] Males (12) and females (10) were

affected. These individuals and 18 others who did not have the above clinical picture evidenced greater than 40 mg TCA per liter of urine. Laboratory determinations of erythrocyte sedimentation rate, SGOT, SGPT, and thymol turbidity were normal.

9.6 SUMMARY

Inhalation of tetrachloroethylene, also called perchloroethylene (PERC) can cause damage to the liver and kidney as well as affect central nervous system function.

Liver damage, as evidenced by elevations in some liver dysfunction parameters well into the post-exposure period, may be delayed. Cirrhosis, toxic hepatitis, liver cell necrosis, and enlarged livers have been associated with exposures to PERC.

Nursing infants may represent a population sensitive to the hepatotoxic effects of PERC. Transmittance of PERC, through breast milk, from a mother exposed to short-term (<3 hours) concentrations of PERC has been reported.

While recovery from the acute effects of PERC on the liver and kidney may be possible during the post-exposure period, such recovery may not be evidenced when the exposure is long term.

An initial response to acute exposures of approximately 100 ppm (678 mg/m^3) PERC can be depression of the central nervous system. Dizziness, headaches, and fatigue are common features. Exposure to higher concentrations may result in a decrease in motor coordination and tremors of fingers and eyelids. No lasting effects on the central nervous system have been reported.

9.7 REFERENCES FOR CHAPTER 9

1. Stewart, R. D. Acute tetrachloroethylene intoxication. J. Amer. Med. Assoc. 208(8):1490-1492, 1969.

2. Stewart, R. D., D. S. Erley, A. W. Schaffer, and H. H. Gay. Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene. Ind. Med. Surg. 30:327-330, 1961.

3. Saland, G. Accidental exposure to perchloroethylene. N. Y. State J. Med. 67:2359-2361, 1967.

4. Bagnell, P. C. and H. C. Ellenberger. Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. J. Can. Med. Assoc. 117: 1047-1048, 1977.

5. Sparrow, G. P. A connective tissue disorder similar to vinyl chloride disease in a patient exposed to perchloroethylene. Clin. Exp. Dermat. 2:17-22, 1977.

6. Coler, H. R. and H. R. Rossmiller. Tetrachloroethylene exposure in a small industry. Ind. Hyg. Occup. Med. 8:227, 1953.

7. Franke, W. and F. Eggeling. Clinical and statistical studies on employees of chemical cleaning plants exposed to perchloroethylene. Med. Welt 9:453-460, 1969 (English translation).

8. Hughes, J. P. Hazardous exposure to a so-called safe solvent. J. Amer. Med. Assoc. 156:234-237, 1954.

9. Trense, E. and H. Zimmerman. Fatal inhalation poisoning with chronically-acting tetrachloroethylene vapors. Zbl. Arbeitsmed. 19: 131-137, 1969 (English translation).

10. Meckler, L. C. and D. K. Phelps. Liver disease secondary to tetrachloroethylene exposure. J. Amer. Med. Assoc. 197(8):144-145, 1966.

11. Larson, N. A., B. Nielsen, and A. Ravin-Nielsen. Perchcloroethylene intoxication. A hazard in the use of coin laundries. Ugeskr. Laeg. 39(5):270-275, 1977 (English translation).

12. Moeschlin, S. Poisoning--diagnosis and treatment, First English edition, Grure and Stratton, 1965. pp. 320-321.

13. Dumortier, L., G. Nicolas, and F. Nicolas. A case of hepato-nephritis syndrome due to perchloroethylene. Arch. Mal. Prof. 25:519-522, 1964 (English translation).

14. Chmielewski, J., R. Tomaszewski, P. Glombiowski, W. Kowalewski, S. R. Viwiatkowski, W. Szozekocki and A. Winnicka. Clinical observations of the occupational exposure to tetrachloroethylene. Bull. Inst. Marit. Trop. Med. Gdynia 27(2):197-205, 1976.

15. Ehrenreich, T., S. L. Yunis, and J. Churg. Membranous nephropathy following exposure to volatile hydrocarbons. Environ. Res. 14: 35-45, 1977.

16. Ehrenreich, T. and J. Churg. Membranous nephropathy. In: Pathology Annual, S. C. Sommers, Ed. Appleton-Century-Crofts, New York, 1968.

17. Patel, R., N. Janakiraman, and W. D. Towne. Pulmonary edema due to tetrachloroethylene. Environ. Health Persp. 21:247-249, 1977.

18. Friborska, A. The phosphatases of peripheral white blood cells in workers exposed to trichloroethylene and perchloroethylene. Brit. J. Ind. Med. 26:159-161, 1969.

19. Stewart, R. D. and H. C. Dodd. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. Am. Ind. Hyg. Assoc. 25:439-446, 1964.

20. Ling, S. and W. A. Lindsay. Perchloroethylene Burns. Brit. Med. J. 3(5766):115, 1971.

21. Stewart, R. D., H. H. Gay, D. S. Erley, C. L. Hake, and A. W. Schaffer. Human exposure to tetrachloroethylene vapor. Arch. Env. Health. 2:40-46, 1961.

22. Rowe, V. K., D. D. McCollister, H. C. Spencer, E. M. Adams, and D. D. Irish. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. Arch. Ind. Hyg. Occup. Med. 5(6):566-579, 1952.

23. Carpenter, C. P. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 19:323-336, 1937.

24. Weichardt, H. and J. Lindner. Health hazards caused by perchloroethylene in dry cleaning plants from the point of view of occupational medicine and toxicology. Staub-Reinhalt Luft 35(11):416-420, 1975 (English translation).

25. Stewart, R. D., C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marloro, and M. V. Salama. Effects of perchloroethylene/drug interaction on behavior and neurological function. Final Report, National Institute for Occupational Safety and Health, April 1977.

26. Stewart, R. D., C. L. Hake, H. V. Forster, A. J. Lebrum, J. E. Peterson, and A. Wu. Tetrachloroethylene: Development of a biological standard for the industrial worker by breath analysis. Report No. NIOSH-MCOW-ENVM-PCE-74-6. National Institute of Occupational Safety and Health, 1974.

27. Stewart, R. D., E. D. Baretta, H. C. Dodd, and T. R. Torkelson. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health 20:224-229, 1970.

28. Method, H. C. Toxicity of tetrachloroethylene. J. Amer. Med. Assoc. 131:1468, 1946.

29. Lob, M. Dangers of Perchloroethylene. Arch. Gewerbepath. Gewerbehyg. 16:45-52, 1957 (English translation).

30. Eberhardt, H. and K. J. Freundt. Tetrachloroethylene poisoning. Arch. Toxikol (Berlin) 21:338-351, 1966 (English translation).

31. Gold, J. H. Chronic perchloroethylene poisoning. Can. Psychiatric Assoc. J. 14:627-630, 1969.

32. Memorandum. David P. Brown, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health. August 24, 1978.

33. Muenzer, M. and K. Heder. Results of an industrial hygiene survey and medical examinations of drycleaning firms. Zbl. Arbeitsmed. 22:133-138, 1972 (English translation).

10. PHARMACOKINETICS

10.1 HUMAN STUDIES

10.1.1 Absorption and Elimination

10.1.1.1 Pulmonary--Pulmonary absorption is the principal route by which tetrachloroethylene (PERC) enters the body; in certain occupations, e.g., metal degreasing, PERC may penetrate via dermal absorption.

During inhalation, PERC is absorbed by the blood via alveolar air. During exhalation, the concentration of PERC in expired air is a function of a number of factors: (1) duration of exposure and the concentration in inhaled air, (2) rate of respiration, (3) time elapsed following exposure, and (4) total body lipid and other tissue repositories.

An approach which has been used to measure the amount and kinetics of absorption and elimination of PERC via the lungs is serial breath analysis of alveolar air.

From controlled exposure studies, Stewart and co-workers[1-7] concluded that PERC is rapidly excreted via the lungs and is principally excreted unchanged; PERC may accumulate in the body to some extent. These findings have been confirmed recently in the controlled exposure studies of Monster,[8] who found, using serial breath analysis, that between 80 and 100 percent of PERC is excreted unchanged via the lungs.

In a recent abstract,[2] Stewart and co-workers reported that a small portion of PERC accumulated in the body and was slowly excreted. Breath samples were collected 8 to 24 hours following exposure of males and females to 25, 50, 100, and 150 ppm (170, 339, 678, and 1,017 mg/m^3) PERC. Exposure

periods were 1.3, 5.5, and 7.5 hours per day. Serial determinations of PERC in alveolar breath and blood, during and following exposure, indicated to the investigators that the halocarbon was rapidly absorbed and excreted via the lungs. The amount absorbed at a given vapor concentration (for exposures of 8 hours or less) was reported to be directly related to the respiratory minute volume. The minute volume may be defined as the product of tidal volume and the respiratory frequency over a one-minute period.

Tetrachloroethylene is excreted via the lungs in a complex exponential manner (Figure 10-1).[3] Tetrachloroethylene is believed to be stored in body tissues having high lipid content.[1] This storage site probably accounts for the prolonged retention of PERC. The concentration in alveolar air in the most immediate post-exposure period (up to 2 hours) is a reflection of the PERC concentration to which the individual was most recently exposed.[3,5] The breath decay curves shown in Figure 10-1 were obtained from five males experimentally exposed to an average PERC concentration of 101 ppm (685 mg/m^3) for 7 hours per day on five consecutive days. The curves show that a high percentage of absorbed PERC was excreted during each 17-hour period following exposure. A single 7-hour exposure of 15 volunteers to an average PERC concentration of 101 ppm (685 mg/m^3) resulted in a similar alveolar desaturation curve.[3] The range of concentrations from which the average was obtained was 62 to 137 ppm (420 to 929 mg/m^3). The increase of initial alveolar air concentrations after repeated exposure (Figure 10-1) and (Figure 10-2) was suggested to be a result of the accumulation of PERC in the bodies of the volunteers exposed repeatedly. The "hump" in the curve (Figure 10-2) is unexplained but was not considered to be artifactual. Breath samples, collected in glass pipettes and Saran bags, were analyzed by infrared spectroscopy.

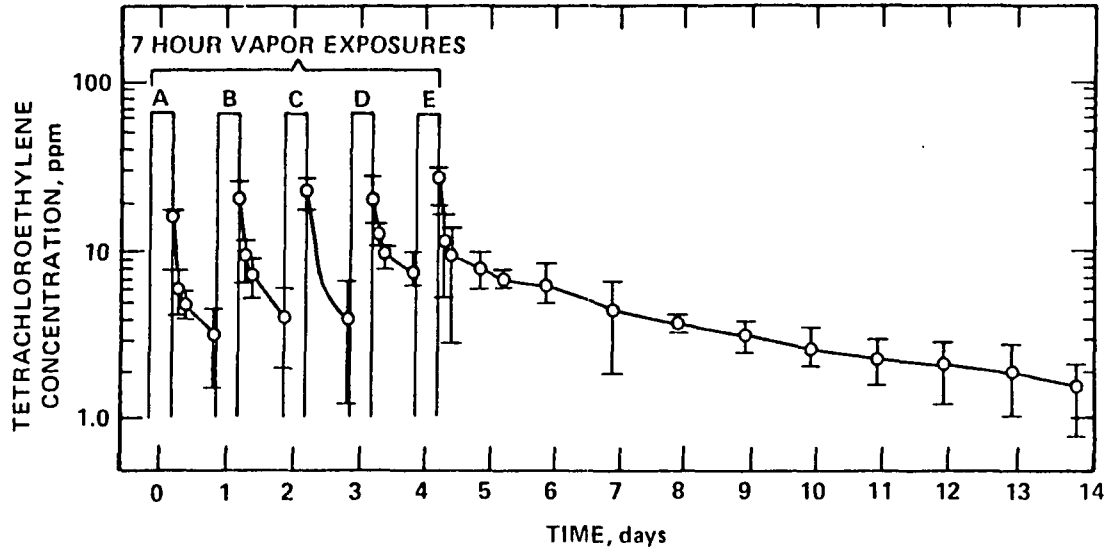


Figure 10-1. Mean and range breath concentrations of of five individuals during postexposure after five separate exposures to 96, 109, 104, 98, and 99 ppm.[3]

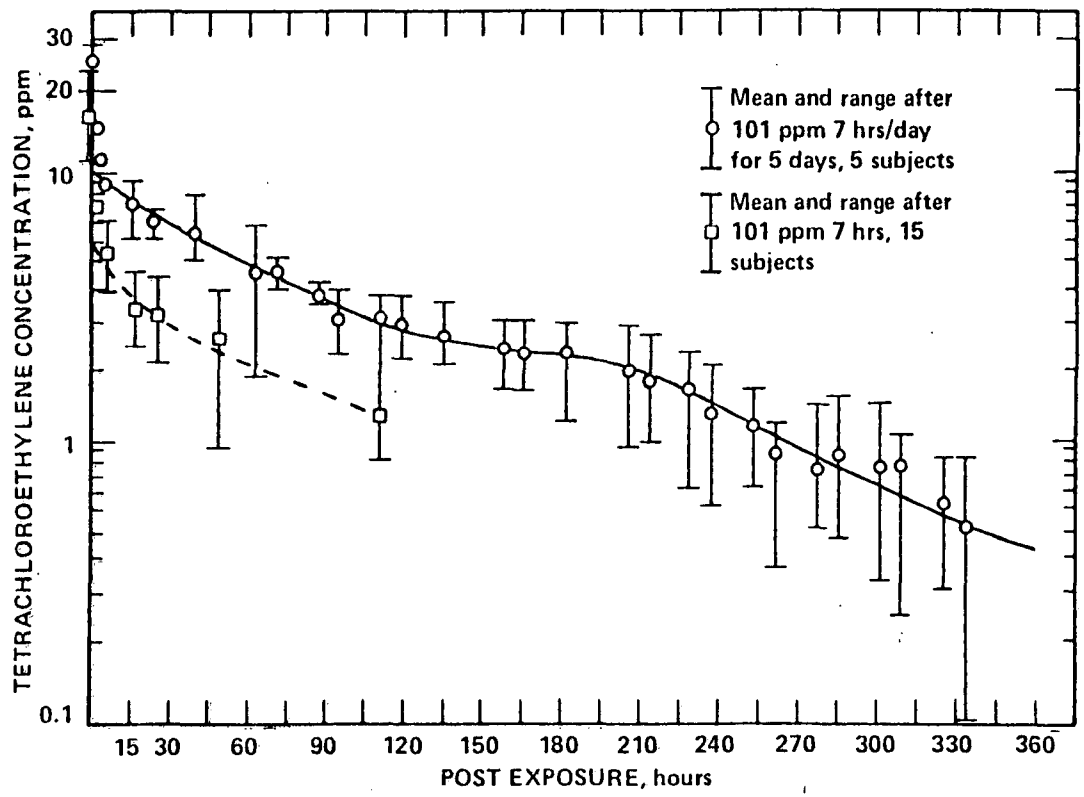


Figure 10-2. Mean and range of breath concentrations of tetrachloroethylene after exposure of individuals to a single or repeated exposures.[3]

After an exposure[4] of six volunteers to approximately 100 and 200 (678 and 1,356 mg/m^3) PERC, analyses of the breath decay curves indicated that (1) exposures of similar duration yielded decay curves with similar elimination rate constants, (2) the average concentration in the expired air was reflective of the vapor concentration for exposures of similar duration, and (3) the length of time PERC can be measured in expired air was proportional to both the vapor concentration and the duration of exposure.

The concentration of PERC in the blood of those individuals exposed to 194 ppm (1,316 mg/m^3) for 83 and 187 minutes approached an equilibrium near the end of the third hour of exposure. After exposure PERC was rapidly cleared from the blood and was undetectable 30 minutes later.

Evidence for a high rate of pulmonary retention of PERC was reported by Bolanowska and Golacka.[9] Five individuals were exposed to 51 ppm (390 mg/m^3) PERC for 6 hours; only 25 percent of the absorbed dose was reported to have been eliminated via the lungs. However, evaluation of the kinetic data indicated that the amount excreted had been greatly underestimated.

Monster,[8] in agreement with the general findings of Stewart and coworkers,[1-7] found that 80 to 100 percent of the PERC absorbed was excreted unchanged; metabolism to urinary trichloroacetic acid (TCA) accounted for less than 2 percent. Physical exercise increased concentrations of PERC in expired air and blood; similar observations were made by Stewart et al.[7]

Monster[8] exposed six male volunteers in a chamber for 4 hours to 72 ± 2 ppm (488 ± 13 mg/m^3) and to 144 ± 7 ppm (977 ± 47 mg/m^3) while at rest. The effects of a workload (bicycle ergometer) were determined in a separate exposure of the volunteers to 142 ± 6 ppm (963 ± 41 mg/m^3) PERC; individuals exercised for two 30-minute periods during the 4-hour exposure period. A

two-week interval occurred between each exposure mode. During the exercise mode, the individuals inhaled PERC vapors through a gas mask; exhalations were made into a Tedlar® bag. Aliquots of breath samples were analyzed with a gas chromatograph equipped with an electron capture detector.

The uptake of PERC by the lungs, as well as lung clearance, decreased with exposure ($p<0.05$); approximately 25 percent less was absorbed in the fourth hour as compared with the first hour of exposure. The total uptake (Table 10-1) was dependent on both lean body weight (coefficient of variation = 11 percent) and adipose tissue; the inter-individual coefficient of variation of body burden predicted from measurements of PERC in exhaled air or in blood was about 25 percent. The individual uptake at 144 ppm (977 mg/m^3) was 2.1 times higher than at 72 ppm (488 mg/m^3) when individuals were at rest.

TABLE 10-1. ESTIMATED UPTAKE OF SIX INDIVIDUALS EXPOSED TO TETRACHLOROETHYLENE WHILE AT REST AND AFTER REST/EXERCISE[8]

	Uptake in mg					
Subject	72 ppm at rest	144 ppm at rest	142 ppm Rest and exercise	body mass kg	Lean body mass kg	Minute vol at rest l/min
A	370	670	1,060	70	62	7.6
B	490	940	1,500	82	71	11.6
C	530	1,000	1,400	82	71	10.0
D	500	1,210	1,510	86	74	11.3
E	390	880	1,320	67	61	12.3
F	450	970	1,120	77	61	8.8

During exercise, total uptake increased about 40 percent; recovery of PERC in exhaled air was 78 percent, as compared to 92 percent when the individuals were at rest. Exercise had no effect on the half-life of PERC elimination or the rate constant of elimination. Minute volume and lung clearance were three-fold higher than the values obtained when the individuals were at rest.

The concentrations of PERC in blood and in exhaled air during the post-exposure period are shown in Figure 10-3. Contrary to the finding of Stewart et al. that blood concentrations of PERC were undetectable 30 minutes after exposure, Monster found that the decrease of PERC in the blood paralleled the decay in expired air. The slopes of the curves in Figure 10-3 suggest that the half-lives of PERC in exhaled air and blood for three body compartments are 12 to 16, 30 to 40, and 55 hours. The respective compartments are (1) tissues with high blood flow, (2) lean tissue, and (3) adipose tissue.

The concentration of TCA (from metabolism) in the blood increased for 20 hours postexposure before declining. Levels of TCA in blood and urine are discussed in Section 10.1.2.

The time course of the PERC concentrations in blood and expired air indicates that a long (>275 hours) period is necessary to eliminate PERC from the body completely. An accumulation of PERC in the body will result during repeated exposures.[3,8] After exposure, the blood concentration of PERC paralleled exhaled air concentration (Figure 10-3) and was 23 times higher than PERC in exhaled air.

In a similar study, Monster[10] found that trichloroethylene uptake is similar to that of PERC. One major difference between the two compounds

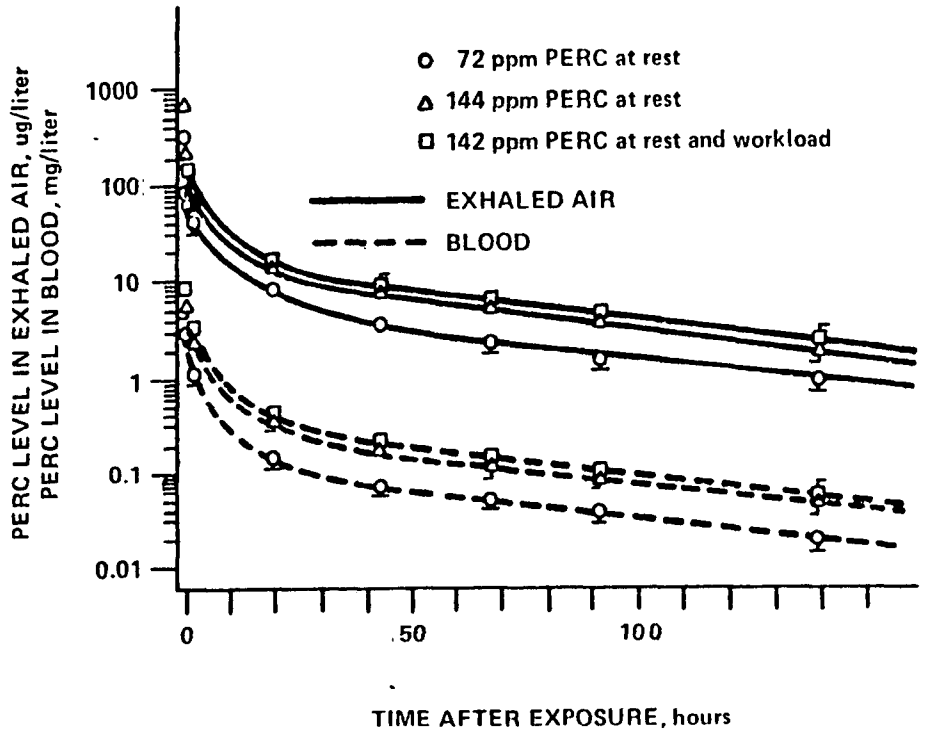


Figure 10-3. Tetrachloroethylene in blood and exhaled air following exposure to PERC for 4 hours. Each point represents geometric mean ± standard deviation of six individuals.[8]

is that only a small amount of the trichloroethylene absorbed is excreted by the lungs after exposure. Values for partition coefficients and lung clearance measurements between blood/vapor after exposure of 4 to 6 individuals to 70 to 140 ppm (475 and 950 mg/m^3) PERC for 4 hours indicated that (1) alveolar air concentration of PERC in the first few hours after exposure will be proportional to exposure concentration and to concentration in blood and other rapidly exchangeable tissues, and (2) during that later phase of elimination the alveolar air concentration will be proportional to the concentration in adipose tissue. The partition coefficient (37°C) for PERC between venous blood/alveolar air was found to be 16; the value of the partition coefficient between fat/blood was calculated at 90. It was estimated that 25 hours would be necessary for PERC to saturate adipose tissue to 50 percent of its equilibrium concentration with plasma; for trichloroethylene, 15 hours was estimated.

Metabolic considerations investigated in this study are discussed in Section 10.2.

Evidence that blood levels of PERC may be useful in determining individual uptake was obtained in a single exposure to 70 and 140 ppm (475 and 950 mg/m^3) for 4 hours.[11] Concentrations of PERC in blood, urine, and exhaled air were determined at 2 and 20 hours after exposure. An excellent correlation was obtained between exhaled air concentration and blood concentration. However, linear and multiple linear regression analysis showed an inter-person coefficient of variation of 20 to 25 percent for blood measurements at 2 and 20 hours and in exhaled air at 2 hours. Measurement of TCA in the urine was less reliable.

In repeated exposures where fluctuating, rather than constant, concentrations of PERC would be evident, the coefficients of variation may be even larger.

Guberan and Fernandez,[12] using a mathematical model to predict uptake and distribution of PERC in the body, reported that fatty tissues would show the slowest rate of PERC depletion because of the high solubility of PERC in fatty tissues. Serial breath concentration decay data obtained from 25 volunteers exposed to between 50 and 150 ppm (339 and 1,017 mg/m^3) for up to 8 hours were used in developing the model. As shown in Figure 10-4, theoretical curves of concentration in alveolar air (C_{alv}) divided by the concentration in inspired air (C_{ins}) versus exposure time for various post-exposure times can be used to estimate unknown concentrations to which an individual may be exposed.

Fernandez et al.[13] found that 2 weeks were necessary to eliminate PERC completely from the body after exposure to 100 ppm (678 mg/m^3) for 8 hours. These findings are in agreement with those of Monster et al.[8] In these chamber studies, 24 volunteers were exposed for 1 to 8 hours to vapor containing 100, 150, and 200 ppm (678, 1,017, and 1,356 mg/m^3) PERC. When exposure time increased, the PERC concentration in alveolar air increased. However, there was no direct proportionality between the period of exposure and the PERC concentration in the alveolar air samples.

10.1.1.2 Percutaneous--Absorption and elimination of PERC through the skin have been found to be a minor consideration or a minor consequence.[9,14,15] Absorption of PERC was reported by Stewart and Dodd.[14] Each of five individuals immersed one thumb in a beaker of PERC located in a ventilated hood. At intervals of 10 minutes, the concentration of PERC in exhaled air was measured. Before and periodically during each skin exposure, samples of breathing zone air were analyzed to preclude solvent vapor contamination. The mean peak breath concentration after a 40-minute immersion was 0.31

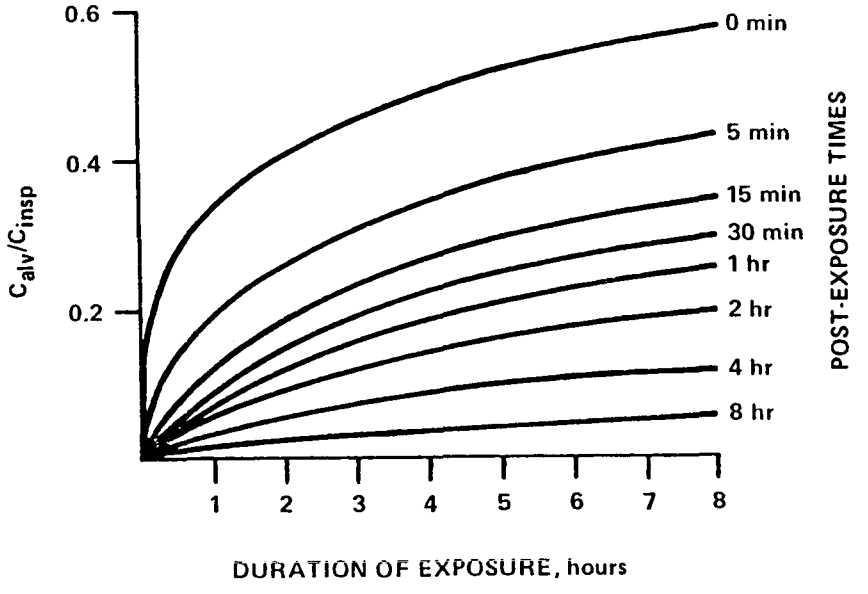


Figure 10-4. Predicted postexposure alveloar air concentrations of PERC at various times against duration of exposure.[12]

ppm (2.1 mg/m^3); 2 hours after exposure the mean breath concentration was 0.23 ppm (1.6 mg/m^3). Five hours after exposure, PERC was still detectable (0.16 to 0.26 ppm; 1.1 to 1.8 mg/m^3).

It was concluded that there is little likelihood that toxic amounts of PERC will be absorbed through the skin during normal use or exposure to the compound.

The elimination of PERC through the skin was found by Bolanowska and Golacka[9] to be approximately 0.02 percent per hour of the dose inhaled. One hand of a vapor-exposed individual was placed in an aluminum foil bag covered with polyethylene and sealed. After 1 hour the bag was removed and the PERC concentration in the air it contained was measured. In calculating the elimination through the skin, the authors assumed that the surface of one upper extremity is about 9 percent of the surface of the entire body.

The percutaneous absorption of PERC was recently investigated by Riihimäki and Pfäffli.[15] It was concluded that PERC concentrations found in ambient air were not likely to result in significant absorption. Three individuals, wearing full facepiece respirators to prevent pulmonary absorption and dressed in thin cotton pajamas and socks, were exposed to 600 ppm (4,069 mg/m^3) PERC for 3.5 hours. During each midhour for a period of 10 minutes they exercised on an ergometer. Tidal air and alveolar air, mixed, were collected in polyester-lined, polyethylene bags. Blood and exhaled air concentrations of PERC were determined up to 20 and 50 hours, respectively. Assuming that 98 percent of PERC is exhaled, the concentration of PERC calculated as being absorbed was 7 ppm (47.6 mg/m^3).

10.1.2 Urinary Excretion of PERC Metabolites

In both controlled and occupational exposures of humans to PERC, the principal urinary excretion product is trichloroacetic acid (TCA).

Trichloroethanol (TCE) has been reported as a metabolite, but it was indirectly measured by chromate oxidation of urine to TCA.

Hake and Stewart[16] found only traces of TCA in 24-hour urine specimens from individuals exposed to 150 ppm (1,017 mg/m^3) PERC and below. No TCE was detected.

Ogata et al.[17] found TCA amounting to 1.8 percent of the total dose of PERC in the urine of four individuals exposed to 87 ppm (590 mg/m^3) PERC for 3 hours. Trichloroethanol could not be detected, but the urine did contain 1 percent of an unidentified chlorine-containing compound. Urine was collected for 67 hours into the post-exposure period.

In the studies of Monster and co-workers discussed previously,[8,11] urinary TCA was found to represent less than 1 percent of the absorbed dose of PERC. In blood, TCA continued to increase until 20 hours post-exposure. From about 60 hours after exposure, the concentration decreased exponentially. A base level of 0.6 mg TCA per day was found in the urine of subjects prior to exposure. Results of blood and urine concentrations are shown in Figures 10-5 and 10-6. The ratio of TCA_{urine} and TCA_{blood} was three-fold higher in the period 0 to 22 hours after start of the exposure. The relatively high concentration in urine possibly was due to an unknown compound measured by the non-specific Fujiwara reaction; TCA in blood was measured by gas chromatography. The unknown compound was not PERC or TCE.

Exposure combined with exercise resulted in 20 percent higher levels of TCA excreted, while uptake of PERC increased 40 percent. The TCA concentration at 20 hours after exposure was 1.6 times the concentration at the end of exposure. Inferences drawn from these results regarding metabolism of PERC

are discussed in Section 10.2. It was concluded that TCA is not a reliable indicator of exposure to PERC.[11]

10.1.2.2 Occupational Studies--In a study involving six dry cleaning plant workers exposed to PERC, an increase in urinary TCA was observed over the 50-hour sampling period.[18] A control group not exposed to significant quantities, also evidenced a similar increase. The average length of exposure for these individuals was 17 months. The worker evidencing the highest level of TCA in the urine had been exposed to an 8-hour time-weighted average of 168 to 171 ppm (1,139 to 1,160 mg/m^3) PERC.

Trichloracetic acid and TCE were found in the urine of 40 workers exposed to PERC concentrations ranging from 58 to 134 ppm (393 to 909 mg/m^3).[19] The maximum levels observed were 41 mg TCA and 116 mg TCE per liter of urine. Seventy-two percent of these workers reported subjective complaints.

Muenzer and Heder[20] reported that 124 of 200 dry cleaning plant employees had TCA in their urine. Seventy-one individuals had more than 10 mg per liter. Liver function tests were comparable between exposed and unexposed (control) groups. The general room air in the work places contained between 200 to 300 ppm (1,357 to 2,035 mg/m^3). An association between workroom air concentrations and TCA levels was not made.

Ikeda et al.[21] reported evidence that TCA and TCE concentrations in the urine increased in proportion to environmental concentrations of PERC up to 50 ppm (339 mg/m^3). In this study, urine samples were collected from 34 male industrial workers who had been exposed to PERC vapors for 8 hours per day, 6 days per week. Concentrations of PERC in the work place ranged from 10 to 400 ppm (68 to 2,713 mg/m^3). The plateau observed in the urinary excretion curve for TCA suggested to the investigators that the capacity of humans to metabolize

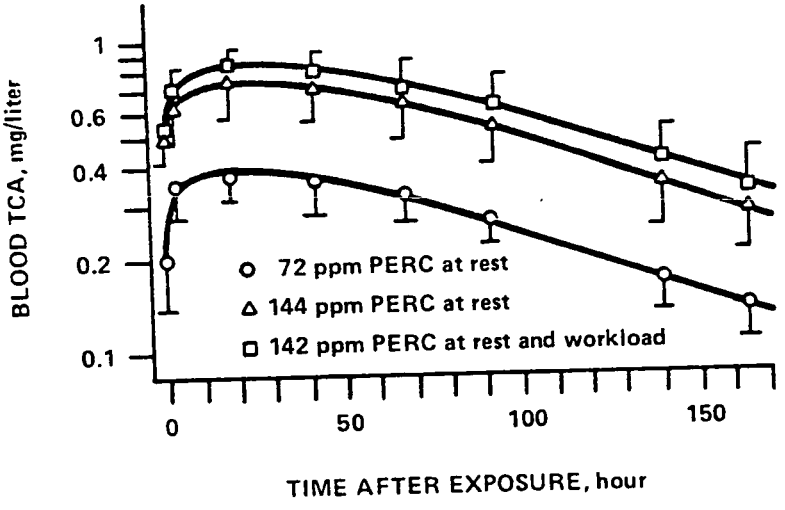


Figure 10-5. Trichloroacetic acid (TCA) in blood following exposure to PERC for 4 hours. Each point represents the geometric mean ± the standard deviation of six subjects.[8]

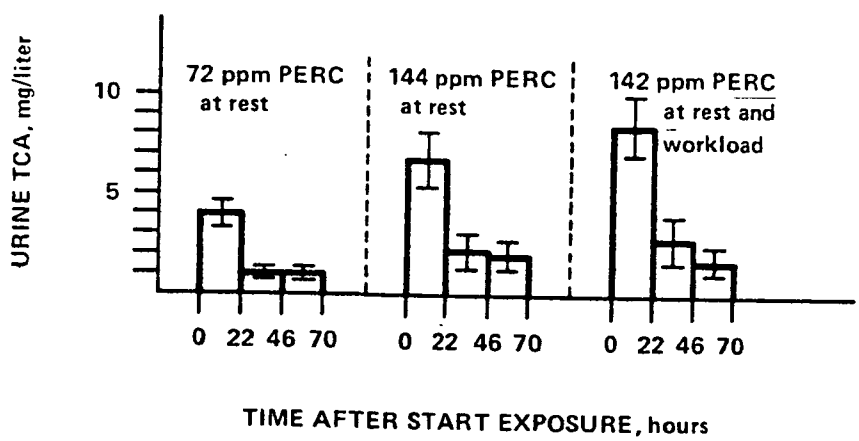


Figure 10-6. Urinary excretion of trichloroacetic acid(TCA) following exposure to PERC for 4 hours. Each point represents the mean ± the standard deviation of six subjects.[8]

PERC is limited. The maximum level of TCA observed was approximately 50 mg per liter of urine. For TCE, the maximum concentration reported was approximately 25 mg per liter. Trichloroethanol was measured indirectly by oxidation of urine with chromic oxide.

In another study, Ikeda and Ohtsuji[22] reported a wide variation in the TCA and TCE levels in urine from occupationally exposed workers. One group of four had been exposed to a concentration range of 20 to 70 ppm (136 to 475 mg/m^3), while 66 workers in another group had been exposed to between 200 and 400 ppm (1,357 and 2,713 mg/m^3). The urine from the smaller group contained between 4 and 35 mg TCA and 4 to 20 mg TCE per liter of urine. In the larger group, TCA levels were 32 to 97 mg per liter and TCE levels ranged from 21 to 100 mg per liter.

High levels of TCA (>60 mg/liter of urine) also were reported by Weiss[23] and by Haag[24] in studies of individuals exposed occupationally.

The findings, if confirmed, that TCE may be a metabolite of PERC are of toxicological importance since this compound has been reported to be neuro- and cardiotoxic.[25] Further research in this area is suggested.

10.1.3 Estimates of Biological Half-Life

Monster[8] determined from the concentration curves of PERC in blood and exhaled air after exposure (Figure 10-3) that PERC was eliminated from the body at three different rate constants with corresponding half-lives of 12 to 16, 30 to 40, and 55 hours, respectively, and indicating three major body compartments for PERC. The predominant half-life, derived from the data of Stewart et al.,[3] was determined to be 65 hours.

Trichloroacetic acid in blood was reported by Monster[8] (Figure 10-3) to have a predominant half-life (60 hours after exposure) of 75 to 80 hours.

Ikeda[26] and Ikeda and Imamura[27] reported that the mean biological half-life for PERC urinary metabolites is 144 hours. A possible sex difference, indicated from exposures of 9 males and 4 females, is yet to be confirmed.

The estimated biological half-life of PERC stored in adipose tissue is 71.5 hours.[12]

10.1.4 Interaction of PERC with Other Compounds

In a study designed to determine the effects of alcohol and diazepam (Valium®) on 12 individuals exposed to 25 and 100 ppm (170 and 678 mg/m^3) PERC for 5.5 hours, Stewart and co-workers[6] found altered blood levels of the halocarbon. Administration of alcohol to individuals during exposure to 25 ppm (170 mg/m^3) significantly increased blood levels of PERC ($p<0.01$). There was no effect during exposure at 100 ppm (678 mg/m^3). Diazepam and alcohol each raised both blood and breath levels of PERC during exposure at 25 ppm (170 mg/m^3). Results are shown in Table 10-2. It was concluded that neither diazepam nor alcohol exacerbated or enhanced the effects of PERC as measured by behavioral and neurological tests.

10.2 METABOLISM

The hepatotoxic, carcinogenic, and mutagenic potentials of a number of chlorinated ethylene compounds[28-34] have generated considerable interest in the metabolic pathways of these compounds. Certain relatively inert chemicals are activated by biotransformation to carcinogenic intermediate metabolites which induce the carcinogenic lesion. Examining metabolic pathways is especially meaningful if it appears likely that a compound is a pro-carcinogen. The relationship of the metabolism of the various chlorinated ethylenes, including tetrachloroethylene, to their toxicity, and possibly to an assessment of their carcinogenicity, is thus an important consideration.

TABLE 10-2. ALCOHOL AND DIAZEPAM EFFECTS UPON TETRACHLOROETHYLENE BLOOD AND BREATH LEVELS, 5-1/2 HOUR EXPOSURES[6]

PERC in Chamber, PPM	PPM PERC in blood			PPM PERC in Breath					
	@ 2 hours into exposure			@ 2 hours into exposure			@ 30 minutes post exposure		
	PERC alone	PERC + alcohol[a]	PERC + diazepam[b]	PERC alone	PERC + alcohol[a]	PERC + diazepam[b]	PERC alone	PERC + alcohol[a]	PERC + diazepam
25	1.65	2.92**	1.76	11.03	12.35*	11.72	6.40	7.49**	6.96*
	(35)	(15)	(23)	(35)	(15)	(23)	(35)	(14)	(22)
100	8.25	7.95	8.47	33.2	32.3	35.5	17.62	13.83**	17.35
	(63)	(29)	(41)	(68)	(28)	(44)	(64)	(29)	(42)

[a]Alcohol blood levels of 30 to 100 mg percent.

[b]Diazepam Blood levels of 7 to 30 mcg percent.

*Significantly different from PERC alone at $p<.05$.

**Significantly different from PERC alone at $p<0.1$.

(n) Number of determinations

The cytochrome P-450 dependent mixed function oxidases of mammalian liver microsomes have been demonstrated to oxidize the carbon-carbon double bond in olefins to an epoxide ring.[35-38] Depending upon the configuration of the oxirane compound, the epoxide ring tends to be chemically quite unstable. This activated intermediate metabolite may thus interact covalently with a variety of groups in compounds of biological concern. When these compounds are nucleic acids and proteins that are essential to cellular function, the reaction may result in alteration of cellular metabolism, and cellular necrosis, or in carcinogenic or mutagenic lesions.[39]

The formation of an epoxide intermediate for a chloroethylene compound was originally postulated by Powell[40] in 1945. Later, Yllner[41] (1961) and Daniel[42] (1963) speculated that PERC might be oxidized to an epoxide as an intermediate metabolite during its biotransformation. Recent interest in this hypothesis has resulted from findings that vinyl chloride is carcinogenic in man and animals,[30-32,43] and the observation that this in turn is likely due to the formation of an epoxide intermediate, chloroethylene oxide. This mechanism was proposed by Van Duuren[44] in 1975. A similar metabolic pathway and the production of epoxide intermediates for structural homologs of vinyl chloride has also been proposed by Van Duuren[44,45] and by Corbett.[46] The mechanism has gained support from findings of covalent binding of ^{14}C-labeled vinyl chloride and trichloroethylene to tissue macromolecules, catalyzation by rat liver microsomal preparations,[47-49] and by the formation of an alkylating metabolite, having an absorption spectrum identical with that of chloroethylene oxide, when vinyl chloride is passed through a mouse liver microsomal preparation.[50]

Tetrachloroethylene epoxide has been synthesized by Kline et al.[51] Previously, trichloroethylene epoxide had been synthesized by Kline and Van Duuren[52] and by Derkosch.[53] Detection of, and thus proof of the existence of, any chloroethylene epoxide in vivo has proven to be extremely difficult, primarily due to instability, high reactivity, and short half-life. However, a number of such epoxides have now been synthesized and characterized by Kline et al.[51] The stability of several of these epoxides, including tetrachloroethylene epoxide, was examined under physiological conditions. The compounds all gave good pseudo- first-order kinetics when hydrolysis rates were measured at 37°C in buffered aqueous solution of pH 7.4.

Yllner[41] studied the metabolism of ^{14}C-labeled PERC in mice exposed for 2 hours by inhalation to doses of 1.3 mg/g. Seventy percent of the absorbed radioactivity was expired in air, 20 percent was excreted in the urine, and less than 0.5 percent was eliminated in the feces. Of the total urinary activity, 52 percent was identified as trichloroacetic acid, 11 percent was present as oxalic acid, and a trace as dichloroacetic acid. No labeled monochloroacetic acid, formic acid, or trichloroethanol was found. However, 18 percent of the radioactivity was not extractable with ether, even after hydrolysis of the urine.

Daniel[42] fed ^{14}C-labeled PERC to rats and found that excretion was largely of unchanged compound through the lungs (half-time of expiration was 8 hours). Only 2 percent of the radioactivity was excreted in the urine, and equimolar proportions of trichloroacetic acid and inorganic chloride were the only metabolites detected.

Trichloroacetic acid has since been observed to be a urinary metabolite of tetrachloroethylene in experimental animals and humans.[17,22,26,54-58]

These studies demonstrate the metabolic formation of products in which transfer of chlorine atoms from one carbon atom to another had taken place. The most likely pathway for such product formation would be via epoxidation of the double bond. The resulting chloro-oxirane compound is known to be unstable and rearranges spontaneously quite rapidly. However, the stability of symmetric oxiranes such as the one formed from PERC is greater than that of the asymmetric oxiranes such as those formed from vinyl chloride, vinylidene chloride, and trichloroethylene. Henschler and his colleagues[59-62] have studied the chemical reactivity, metabolism, and mutagenicity of the chlorinated ethylene series, including vinyl chloride, trichloroethylene, and tetrachloroethylene. These investigators have demonstrated a rather interesting correlation between biological activity and chemical structure: those chlorinated ethylenes that are symmetrical such as cis-and trans-1,2-dichloroethylene and tetrachloroethylene are relatively stable and not mutagenic. In contrast, the asymmetrical ethylenes, vinyl chloride, vinylidene chloride, and trichloroethylene, are unstable and mutagenic. Although they recognized that oxiranes (epoxides) may be formed by all six of the chlorinated ethylenes, they concluded that the asymmetrical oxiranes are far less stable than the symmetrical ones, are more highly electrophilic, and may react directly with nucleophilic constituents of cells more readily, thereby exerting mutagenic or carcinogenic effects. The results of the mutagenic tests conducted by these investigators correlate with this structure-activity relationship.

Evidence for the involvement of the microsomal mixed-function oxidase system in the metabolism of PERC was shown by Moslen et al.[54] Rats pretreated with phenobarbital or Arochlor-1254 (polychlorinated biphenyls)--inducers of the hepatic mixed function oxidase system--showed a significant increase in

total trichlorinated urinary metabolites and trichloroacetic acid excretion following a single oral administration of 0.75 ml/kg PERC. Hepatotoxicity of PERC was enhanced by Arochlor-1254 pretreatment as evidenced by doubling of SGOT levels, and by the appearance of focal areas of vacuolar degeneration and necrosis of the liver. Cornish et al.[63] did not observe a potentiation of tetrachloroethylene toxicity following intraperitoneal injection of 0.3 to 2.0 ml/kg PERC to rats pretreated with phenobarbital. However, elevation of SGOT was noted at all dose levels in this study.

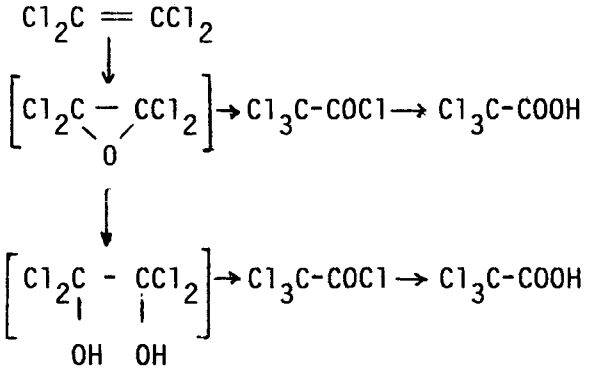
Vainio et al.[64] looked at the effects of PERC on liver metabolizing enzymes in vivo--in the rat. Oral administration of 2.6 mmol/kg PERC was associated with a statistically significant lowering of levels of 3,4-benzpyrene hydroxylation and p-nitroanisole-o-methylation. These findings could be attributed to competitive inhibition.

Plevova et al.[65] showed that 6 hours of inhalation of 12 mg/liter tetrachloroethylene 20 hours prior to 2 ml/kg i.p. pentobarbital would lengthen pentobarbital sleeping time by 30 percent. This effect was possibly mediated through hepatic drug metabolizing enyzme activity. Also, changes in spontaneous motor activity induced by intraperitoneal injection of pentobarbital, diazepam, amphetamine, and partly by chlorpromazine were enhanced by previous inhalation of PERC. This was probably due to an effect on metabolism rates.

Although, as mentioned previously, trichloroacetic acid has been observed by several investigators to be a urinary metabolite of tetrachloroethylene, the excretion of total trichloro compounds, as measured by the Fujiwara colorimetric reaction after oxidation, exceeded that of trichloroacetic acid--in some cases this was assumed to be trichloroethanol.[20,21] In other studies that portion which was not trichloroacetic acid could not be demonstrated to be

trichloroethanol.[16] In one report ethylene glycol was claimed to be a prominent metabolite in the rat.[54]

Leibman and Ortiz[66,67] proposed a scheme for possible pathways of PERC metabolism. The formation of tetrachloroethylene epoxide by the hepatic mixed function oxidase system may be followed by hydration of the epoxide to tetrachloroethylene glycol. Due to the symmetric arrangement of the epoxide and the glycol intermediates, rearrangement of both would yield trichloroacetyl chloride, which hydrolyzes rapidly to trichloroacetic acid.



Incubation of PERC and rat liver supernatant with a nicotinamide-adenine dinucleotide phosphate (reduced) generating system confirmed the production of trichloroacetic acid. Nicotinamideadenine dinucleotide, reduced (NADH) did not promote the formation of trichloroacetic acid. Expoxide hydrase inhibition, produced by the addition of cyclohexane to the incubation mixture, did not have any effect upon trichloroacetic acid formation. Leibman and Ortiz concluded that, if the epoxide-diol pathway is operative, trichloroethylene oxide is not a substrate for hydration by epoxide hydrase, or that the epoxide and glycol rearrange to trichloroacetyl chloride at similar rates.

Bonse et al.[59] also found trichloroacetic acid to be the only detectable metabolite in isolated rat liver perfused with PERC. The trichloroacetic acid metabolite was found free in the circulating perfusate and could also be extracted from the liver tissue after acid hydrolysis.

A study by Sakamoto[68] supports the conclusions that the metabolism of PERC is mediated via the formation of an epoxide intermediate, and that the observed toxicity of PERC may be largely due to the formation of tetrachloroethylene oxide. In this study, tetrachloroethylene epoxide administered to guinea pigs intraperitoneally resulted in the detection of TCA and, to a much lesser extent, TCE in the urine. The tetrachloroethylene oxide appeared to be more toxic than PERC.

Considerable evidence exists that variations in exposure profiles, including different dose levels, dosing periods, and durations of exposure, as well as concomitant exposure to other chemicals, modify the pharmacokinetics and metabolism in the body. However, there is little evidence to support a generalization that a total shift to a more hazardous metabolite or pharmacokinetic pattern will result from exposure at high-dose levels. Gehring et al.[69] showed that with high-dose levels of vinyl chloride a greater percentage of the chemical was either excreted unchanged or retained in the body without undergoing metabolism. Although major differences in the kinetics of retention and elimination were seen, there was no qualitative change in metabolites as the dose was changed.

Pegg et al.[70] saw no difference in the urinary metabolites when PERC was administered to rats either orally or by inhalation. However, at higher

doses, as seen in the study with vinyl chloride, a greater proportion of PERC was expired unchanged with either route of administration.

Kraybill[71] and Page,[72] in recent reviews of carcinogenicity testing methods and applications of these results, illustrate that extrapolation from high dose levels may, in some cases, underestimate the actual effect that occurs at low dose levels. This might happen when exposure levels exceed the capacity of the body to absorb, or when an inactive chemical species is metabolized to an activated carcinogenic intermediate by a system of finite capacity. Sequential increases in exposure levels may not result in incremental increases in effect.

10.3 SUMMARY

In summary, based on animal experiments and/or exposures of human volunteers (which are discussed in this document), a few conclusions on the pharmacokinetics and metabolism of PERC may be stated:

1. Tetrachloroethylene is readily absorbed following inhalation. It is also absorbed to a minor extent through the skin, and it is absorbed if ingested.
2. Tetrachloroethylene is distributed via the bloodstream throughout the body. It accumulates in fat tissue, lungs, liver, kidney, spleen, and lean muscle. Repeated daily exposures will result in accumulation of tetrachloroethylene until equilibrium with the inspired air is reached.
3. Tetrachloroethylene is eliminated primarily in the unchanged form (parent molecule) in expired air rather than as urinary metabolites. Approximately two weeks' time is required to completely rid the body of tetrachloroethylene following a single exposure.

4. It is established that tetrachloroethylene can be metabolized to trichloroacetic acid, which is excreted in the urine. Other minor metabolites which have been proposed are: trichloroethanol, oxalic acid, dichloroacetic acid, and ethylene glycol. Less than 10% of the tetrachloroethylene absorbed in humans is believed to be metabolized.

5. The formation of an epoxide intermediate metabolite via oxidation of tetrachloroethylene by the microsomal mixed function oxidase system has been proposed. This epoxide, due to its relative instability, may react with compounds of biological interest which may explain the carcinogenicity of tetrachloroethylene.

10.4. REFERENCES FOR CHAPTER 10

1. Stewart, R. D. Acute tetrachloroethylene intoxication. J. Amer. Med. Assoc. 208(8):1490-1492, 1969.

2. Hake, C. L., R. D. Stewart, A. Wu, and S. A. Graff. Experimental human exposures to perchloroethylene. I. Absorption and excretion. Toxicol. Appl. Pharmac. 37:175, 1976 (abstr)

3. Stewart, R. D., E. D. Baretta, H. C. Dodd, and T. R. Torkelson. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health. 20:224-229, 1970.

4. Stewart, R. D., H. H. Gay, D. S. Erley, C. L. Hake, and A. W. Schaffer. Human exposure to tetrachloroethylene vapor. Arch. Env. Health. 2:40-46, 1961.

5. Stewart et al. Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene. Ind. Med. Sur. 30:327-330, 1961.

6. Stewart, R. D., C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. V. Salama. Effects of Perchloroethylene/Drug Interactions on Behavior and Neurological Function. Final Report. National Institute for Occupational Safety and Health, Cincinnati, Ohio, April 1977.

7. Stewart, R. D., C. L. Hake, H. V. Forster, A. J. Lebrun, J. E. Peterson and A. Wu. Tetrachloroethylene--development of a biologic standard for the industrial worker by breath analysis. Report No. NIOSH MCOW-ENVM-PCE-74-6, 1974. 172 pp.

8. Monster, A. C., G. Boersma, and H. Steenweg. Kinetics of tetrachloroethylene in volunteers; influence of exposure concentration and work load. Int. Arch. Occup. Environ. Health. 42::303-309, 1979.

9. Bolanowska, W., and J. Golacka. Absorption and elimination of tetrachloroethylene in humans under experimental conditions. Medycyna Pracy. 23(2):109-119, 1972. (English translation)

10. Monster, A. C. Difference in uptake, elimination and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. Int. Arch. Occup. Environ. Health. 42:311-317, 1979.

11. Monster, A. C., and J. M. Houtkooper. Estimation of individual uptake of trichloroethylene, 1,1,1,-trichloroethane and tetrachloroethylene from biological parameters. Int. Arch. Occup. Environ. Health. 42:319-323,1979.

12. Guberan, E., and J. Fernandez. Control of industrial exposure to tetrachloroethylene by measuring alveolar concentration: theoretical approach using a mathematical model. Brit. J. Ind. Med. 31:159, 1974.

13. Fernandez. J., E. Guberan, and J. Caperos. Experimental human exposures to tetrachloroethylene vapor and elimination in breath after inhalation. Amer. Ind. Hyg. Assoc. 37:143-150, 1976.

14. Stewart, R. D., and H. C. Dodd. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. J. Ind. Hyg. 25:439-446, 1964.

15. Riihimäki, V., and P. Pfäffli. Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health. 4:73-85, 1978.

16. Hake, C. L., and R. D. Stewart. Human exposure to tetrachloroethylene: inhalation and skin contact. Environ. Health Persp. 21:231-238, 1977.

17. Ogata, M., Y. Takatsuka, and K. Tomokuni. Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. Brit. J. Industr. Med. 28:386-391, 1971.

18. National Institute of Occupational Safety and Health. Health Hazard Evaluation Report No. 73-86-114, 1974.

19. Medek, V., and J. Kovarik. The effect of perchloroethylene on the health of workers. Pracovni Lekarstvi. 25(8):339-341, 1973.

20. Muenzer, M., and K. Heder. Results of an industrial hygiene survey and medical examinations of drycleaning firms. Zbl. Arbeitsmed. 22:133-138, 1972.

21. Ikeda, M. H. Ohtsuji, T. Imamura, and Y. Komoike. Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroecetic acid as a measure of exposure to trichloroethyle-e and tetrachloroethylene. Brit. J. Ind. Med. 29:329-333, 1972.

22. Ikeda, M., and H. Ohtsuji. A comparative study on the excretion of Fujiwara reaction positive substances in the urine of humans and rodents given trichloro or tetrachloro derivatives of ethane or ethylene. Brit. J. Ind. Med. 29:94-104. 1972.

23. Weiss, G. A course of observations of trichloroacetic acid excretion in occupationally caused perchlorocthylene poisoning. Zentr. Arbeitsmed. Arbeitschutz. 19:143-146, 1969 (In German).

24. Haag, T. P. Concerning the question of the determination and decomposition of perchloroethylene. Arch. fuer Toxikol. 17:204-205, 1958.

25. Mikisková, H. and A. Mikiska. Trichloroethanol in trichloroethylene poisoning. Brit. J. Md. Med. 23:116-125, 1966.

26. Ikeda, M. Metabolism of trichloroethylene and tetrachloroethylene in human subjects. Environ. Health Persp. 21:239-245, 1977.

27. Ikeda, M., and T. Imamura. Biological half-life of trichloroethylene and tetrachloroethylene in human subjects Int. Arch. Arbeitsmed. 31:209-224, 1973.

28. Bioassay of Tetrachloroethylene for Possible Carcinogenicity. DHEW Pub. No. (NIH) 77-813. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. 1977

29. Bioassay of Trichloroethylene for Possible Carcinogenicity. DHEW Publication No. (NIH) 76-802. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. 1977.

30. Viola, P. L., A. Brigotti, and A. Caputo. Oncogenic response of rat skin, lungs and bones to vinyl chloride. Cancer Res. 31:516, 1971.

31. Maltoni, C., and G. Lefemine. Carcinogenicity bioassays of vinyl chloride. I. Environ. Res. 7:387. (1974).

32. Creech, J. L., Jr., and M. N. Johnson. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. J. Occup. Med. 16:150, 1974.

33. Waxweiler, R. J. et al. Neoplastic risk among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci. 271:39. 1976.

34. Vinyl Chloride Related Compounds. Environmental Health Perspectives. U.S. Department of Health, Education and Welfare. Public Health Service (NIH), NIEHS. Vol. 21. 333 p. December 1977.

35. Liebman, K. C., and E. Ortiz. Styrene epoxide - an intermediate in microsomal oxidation of styrene to its glycol. Pharmacologist 10:203, 1968.

36. Watabe, T., and E. W. Maynert. Role of epoxides in the metabolism of olefins. Pharmacologist. 10:203. 1968.

37. Liebman, K. C., and E. Ortiz. Epoxide intermediates in microsomal oxidation of olefins to glycols. J. Pharmacol. Explt. Therap. 173:242, 1970.

38. Maynert, E. W., R. L. Foreman, and T. Watabe. Epoxides as obligatory intermediates in the metabolism of olefins to glycols. J. Biol. Chem. 245:5254. 1970.

39. Jerima, D. M., and J. W. Daly. Arene Oxides: A new aspect of drug metabolism. Science. Vol. 185. p 573. 1974.

40. Powell, J., Trichloroethylene: absorption, elimination, and metabolism. Br. J. Ind. Med. 2:142-145.

41. Yllner, S., Urinary metabolites of C^{14}-tetrachloroethylene in mice. Nature 191:820-821, 1961.

42. Daniel, J. The metabolism of ^{36}Cl-labeled trichloroethylene and tetrachloroethylene in the rat. Biochem. Pharmacol. 12:795-802, 1963.

43. Lee, F. I. and D. S. Harry. Angiosarcoma of the liver in a vinyl chloride worker. Lancet 1:1316, 1974.

44. Van Duuren, B. On the possible mechanism of carcinogenic action of vinyl chloride. N. Y. Acad. Sci. 246:258-267, 1975.

45. Van Duuren, B. Chemical structure, reactivity and carcinogenicity of halohydrocarbons. Environ. Health Perspec. 21:17-23, 1977.

46. Corbett, T. Inhalation anesthetics--More Vinyl Chloride. Environ. Res. 9:211-214, 1975.

47. Kappus, H., H. Bolt, A. Buchter, and W. Bolt. Rat liver microsomes catalyse conalent binding of ^{14}C-vinyl chloride to macromolecules. Nature 257:134-135.

48. Van Duuren, B. L. and S. Banergee. Covalent interaction of metabolites of the carcinogen trichloroethylene in rat hepatic microsomes. Cancer Res. 36:2419, 1976.

49. Allemand, H., D. Pessayre, V. Desatoire, C. Degott, G. Feldmann, and J. P. Benhamou. Metabolic activation of trichloroethylene into a Chemically active metabolite toxic to the liver. J. Pharmacol. Exp. Therap. 204:714-723. 1978.

50. Barbin, A., H. Bresil, A. Croisey, P. Jacquignon, C. Malaveille, R. Montesano, and H. Bartsch. Liver microsome mediated formation of alkylating agents from vinyl bromide and vinyl chloride. Biochim. Biophys. Res. Comm. 67:596. 1975.

51. Kline, S. A., J. J. Solomon, and B. L. Van Duuren. Synthesis and reactions of chloroalkene epoxides. J. Org. Chem. 43:3596-3600, 1978.

52. Kline S. A. and B. L. Van Duuren. Reactions of epoxy-1,1,2-trichloroethane with nucleophiles. J. Heterocyclic Chem. 14: 455-458. 1977.

53. Derkosch. Cited in: CRC Crit. Rev. Toxicol. 4:395-409. 1976.

54. Moslen, M. T., E. S. Reynolds, and S. Szabo. Enhancement of the metabolism and hepatotoxicity of trichloroethylene and perchloroethylene. Biochem. Pharmacol. 26:369-375. 1977.

55. Dmitrieva, N. V. Contribution to the metabolism of tetrachloroethylene. Gig Tr. Prof. Zabol. 11:54-56. 1967. (English translation).

56. Tada, O. and K. Nakaaki. Urinary excretion of alkali- pyridine reactants in humans exposed to perchloroethylene vapor. Rodo Kagaku. 45:588. 1969. Chem. Abstr. 72:47126. 1970.

57. Boillat, M. A. The value of the determination of trichloroacetic acid in the urine for the detection of trichloroethylene and perchloroethylene poisoning. An inquiry in several works. Praventivmedizin -- Revue de Med. Prev. 15(6):447-456. 1970.

58. Barchet et al. Chemical investigations for environmental protection. Deutsch Lebensm - Rundsch. 68:69. 1972. Cited. in: Chem. Abstr. 77:32869. 1972.

59. Bonse, G., Th. Urban, D. Reichert, and D. Henschler. Chemical reactivity, metabolic oxirane, etc. Biochem. Pharmacol. 24(19): 1829-1834. 1975.

60. Greim, H. G. Bonse, Z. Radwan, D. Reichert, and D. Henschler. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacology. 24(21):2013-2017. 1975.

61. Henschler, D., G. Bonse, and H. Greim. Carcinogenic potential of chlorinated ethylenes -- tentative molecular rules. Proc. Third WHO-IARC Meeting, Lyon, November 3. 1975.

62. Bonse, G. and D. Henschler. Chemical reactivity, biotransformation, and toxicity of polychlorinated aliphatic compounds. CRC Crit. Rev. Toxicol. 4:395-409. 1976.

63. Cornish, H. H., B. P. Ling, and M. C. Barth. Phenobarbital and organic solvent toxicity. Amer. Ind. Hyg. Assoc. 34:487-492. 1973.

64. Vainio, H. M. G. Parkki, and J. Marniemi. Effects of aliphatic chlorohydrocarbons on drug metabolizing enzymes in rat liver in vitro. Xenobiotica 6(10):599-604. 1976.

65. Plevova, J., E. Frantik, and D. Chladkova. Problem of interaction between drugs and some air pollutants. Proc. Eur. Soc. Toxicol. 16:303-306. 1975.

66. Leibman, K. C. and E. Ortiz. Microsomal metabolism of chlorinated ethylenes Paper presented at the Sixth International Congress on Pharmacology. 1975.

67. Leibman, K. C. and E. Ortiz. Metabolism of halogentaed ethylenes. Environ. Health Persp. 21:91-97. 1977.

68. Sakamoto, N. Metabolism of tetrachloroethylene in guinea pigs. Sangyo Igaku. 18(1):11-16. 1976.

69. Gehring, P., P. Wantanabe, J. Young, and J. Lebeau. Metabolic thresholds in assessing carcinogenic hazard. In: Chemicals, Human Health, and thr Environment. A collection of four scientific papers., Volume 2, Dow Chemical Company. Midland, Michigan. pp 56-70. 1976.

70. Pegg, D. G., J. A. Zemple, W. H. Braun, and P. J. Gehring. Disposition of [C^{14}] tetrachloroethylene following oral and inhalation exposure in rats. Toxicol. Res. Lab. Health and Environmental Research, Dow Chemical, U.S.A. Midland, Michigan. Meeting abstract Toxicol. Appl. Pharmacol. 45(1):276. 1978.

71. Kraybill, H. and M. Mehlman. Conceptual appoaches to the assessment of nonoccupational environmental cancer. In: Environmental Cancer, Chapter 2. H. Kraybill and M. Mehlman, eds. Hemisphere Publishing Co. Washington, D.C. 1977. pp 27-62.

72. Page, N. Concepts of a Bioassay Program in Environmental Carcinogenesis, Chapter 4. In: Environmental Cancer, H. Kraybill and M. Mehlman, eds. Advances in Modern Toxicology, Volume 3. Hemisphere Publishing Co., Washington; John Wiley and Sons. New York. 1977. pp 87-171.

11. THE CARCINOGENIC POTENTIAL OF TETRACHLOROETHYLENE

Two long-term animal bioassays have been conducted to assess the carcinogenic potential of tetrachloroethylene (PERC). In one, in which mice and rate were exposed by gavage to PERC, the National Cancer Institute (NCI) reported the induction of a highly significant number of hepatocellular carcinomas in male and female mice, but concluded that the test with rats was inconclusive due to excessive mortality. These results which have been described in great detail[1], were also reported in the Federal Register in October 1977.

In the other study, in which Sprague-Dawley rats were exposed by inhalation to PERC, the Dow Chemical Company reported no evidence for the carcinogenicity of the chemical.[2,3]

In a short-term assay using the Strain A mouse lung adenoma system, injections of PERC did not increase the average number of lung tumors per mouse as compared to control animals.[4]

Preliminary results of a mouse skin bioassay conducted by Van Duuren and co-workers at the New York University Institute of Environmental Medicine indicate that PERC may be carcinogenic.[5]

A recently published study by Price et al.[6] demonstrates <u>in vitro</u> carcinogenesis by PERC. Malignant transformation of mammalian cells was observed. This study provides important data to confirm the carcinogenicity of PERC and to support the results of the NCI bioassay.

The results of mutagenicity studies of PERC in bacterial systems are somewhat conflicting.

An extensive literature review did not produce any other toxicity studies which reveal such highly significant evidence for carcinogenicity as the NCI bioassay or the in vitro cell transformation study. There are other major carcinogenicity studies now underway (Appendix A). However, until these ongoing assays are complete, only the studies mentioned above can be utilized to show carcinogenic potential of PERC.

11.1 NCI BIOASSAY

Tetrachloroethylene was one of several halogenated hydrocarbon compounds selected for bioassay by the National Cancer Institute because of chemical structure and lack of adequate toxicity data as well as large production and extensive use.[1,7]

Each of these compounds, including PERC, was studied separately in male and female Osborne-Mendel rats and male and female $B_6C_3F_1$ mice. Each experiment consisted of high- and low-dose treatment groups of 50 animals each, an untreated control group, and a vehicle control group. The untreated control and vehicle control groups comprised 20 animals of each species/sex combination. The halocarbons were administered to the animals in a corn oil vehicle by gastric intubation (stomach tube) 5 days a week for 78 weeks. The vehicle control animals were intubated with pure corn oil of the amount given the high dose animals.

The National Cancer Institute concluded that, under the conditions of the bioassay, PERC is carcinogenic in mice. The results do not provide evidence that PERC causes cancer in rats. A significant association between increased dosage and accelerated mortality was observed in rats treated with PERC. Early mortality may have obscured a carcinogenic effect in these animals.

11.1.1 Animals and Chemicals Used in Test

The $B_6C_3F_1$ mouse, a hybrid of the C57 B1/6 female and C3H/He male (Charles River, Wilmington, Massachusetts), was selected because of previous extensive use in NCI bioassay.[1,7,8,9] The Osborne-Mendel rat (Battelle Memorial Institute, Columbus, Ohio) was chosen because previous studies by FDA scientists[10] and by Reuber and Glover[11] had shown this strain was sensitive to various chlorinated compounds such as DDT and carbon tetrachloride.

In the bioassay program, however, the NCI strain of Osborne-Mendel rat appeared to have low sensitivity not only to PERC but to other chlorinated hydrocarbon compounds which caused liver cancer in mice, but not in the rats.[12-16] Possibly this is an indication of innate species differences in sensitivity to chlorinated aliphatic compounds.

The U.S.P. grade PERC used in the NCI bioassay was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. Purity was checked by gas chromatography and infrared spectroscopy. The results indicated a compound with a purity over 99 percent but with at least one minor impurity not identified in the report.

11.1.2 Selection of Dose Levels and Chronic Study

The experimental design of the NCI bioassay is outlined in Table 11-1. The lowest doses of PERC in single-dose, range-finding studies were selected as the highest level for an 8-week subchronic study. The primary objective of the subchronic study was to determine the maximal tolerable dose for the chronic test.

TABLE 11-1. Experimental Design-NCI Carcinogen Bioassay of Tetrachloroethylene

Experimental Design		Experimental Groups	Dose Levels mg/kg/day*
Mice ($B_6C_3F_1$)			
Route of Exposure:	Intragastric intubation	Males:	
Treatment mixture:	6-11% tetrachloroethylene in corn oil	Controls	0
Frequency of exposure:	once daily, 5 x week	Low Dose	536
Duration of exposure:	78 weeks	High Dose	1072
Additional Observation:	12 weeks	Females:	
Total period:	90 weeks	Controls	0
Microscopic examination:	about 30 tissues**/all animals	Low Dose	386
		High Dose	772
Rats (Osborne-Mendel)			
Route of Exposure:	Intragastric intubation	Males:	
Treatment mixture:	50-60% tetrachloroethylene in corn oil	Controls	0
Frequency of exposure:	once daily, 5 x week	Low Dose	471
Duration of exposure:	78 weeks	High Dose	941
Additional Observation:	32 weeks	Females:	
Total period:	110 weeks	Controls	0
Microscopic examination:	about 30 tissues**/all animals	Low Dose	474
		High Dose	949

*Time-weighted average doses. Actual doses listed below:

mice (M) 11 weeks 450/900 mg/kg/day
67 weeks at 550/1100 mg/kg/day
mice (F) 11 weeks 300/600 mg/kg/day
67 weeks at 400/800 mg/kg/day
rats (M) 19 weeks 500/1000 mg/kg/day
27 weeks at 700/1400 mg/kg/day
32 weeks (1 week no dosing followed by 4 weeks dosing)
3 weeks at 600/1200 mg/kg/day
rats (F) 16 weeks 500/1000 mg/kg/day
6 weeks at 700/1400 mg/kg/day
21 weeks at 500/1000 mg/kg/day
32 weeks (1 week no dosing followed by 4 weeks dosing)

**brain, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, trachea, esophagus, thymus, salivary gland, lymph nodes, heart, nasal passages, lung and bronchi, spleen, liver, kidney, stomach, small intestine, large intestine, gall-bladder (mice) and bile duct, pancreas, urinary bladder, prostate or uterus, seminal vesicles and testes with epididymus or ovary, skin with mammary gland, muscle, nerve, bone marrow

From the results of the subchronic study, two dose levels were chosen for administration to groups of 50 each of both sexes of Osborne-Mendel rats and $B_6C_3F_1$ mice. Twenty animals of each sex of both species constituted the vehicle control and untreated control groups. Animals were dosed once a day, 5 days/week, with PERC administered in corn oil by stomach tube. The initial age of the weanling animals was 25 days for the mice and 35 days for the rats. Dosing continued for 18 months. Animal weights and food consumption per cage were obtained weekly for the first 10 weeks and monthly thereafter. Doses were increased after a few weeks and the animals appeared to be tolerating the chemical. Later, the amount of PERC administered to high dose female rats was decreased to the original level due to signs of toxicity. The low dose consistently remained one-half of the high dose.

At the end of 90 weeks (mice) or 110 weeks (rats), surviving animals were killed, necropsied, and submitted to an extensive gross and microscopic examination. Specified organs plus any other tissue containing visible lesions were fixed in 10 percent buffered formalin embedded in paraplast, and sectioned for slides. Hematoxylin and eosin staining (H and E) used routinely, but other stains were employed when needed. Diagnoses of any tumors and other lesions were coded according to the Systematized Nomenclature of Pathology (SNOP) of the College of American Pathologists, 1965. Animals dying or killed prior to the scheduled termination date were examined in the same manner.

11.1.3 Results of NCI Bioassay

The occurrence of tumors in test animals is summarized in Table 11-2. Both sexes of mice treated with PERC experienced a highly significant

TABLE 11-2. SUMMARY OF TUMOR-OCCURRENCE
NCI TETRACHLOROETHYLENE BIOASSAY

Species	Tumor	Males			Females		
		Control	Low	High	Control	Low	High
Rat	Mammary adenoma fibroadenoma	0	0	0	3	8	8
	Mammary adenocarcinoma	0	0	0	1	1	2
	Pituitary adenomas	0	1	0	4	9	6
	Thyroid adenoma and carcinoma	1	0	1	0	0	2
	Hemangiosarcoma	1	2	1	0	1	0
	Metastases	2	0	0	0	7	2
	Total primary tumors	7	5	6	10	25	27
	Number of animals examined	20	49	50	20	50	50
	Animals with tumors	5	5	5	7	17	15
Mouse	Liver hepatocellular carcinoma	2	32	27	0	19	19
	Malignant histiocytic lymphoma	2	0	0	4	0	1
	Lung adenoma	0	3	0	0	0	1
	Metastases	0	3	0	0	1	1
	Total primary tumors	6	36	28	5	20	21
	Number of animals examined	20	49	47	20	48	48
	Animals with tumors	6	33	27	5	19	19

excess of hepatocellular carcinoma as compared to untreated controls or vehicle controls. In addition, control groups from four studies--tetrachloroethylene, methyl chloroform, 1,1-dichloroethane, and chloroform--were combined to form a pooled group of untreated controls and a pooled group of vehicle controls. Both sexes of the treated mice showed a significant excess of liver cancer as compared to either of the pooled control groups. An even greater degree of confidence would be obtained if the historical data from the entire colony were used, as opposed to the matched controls or the pooled control groups from four studies. The observed tumor incidences of 12 and 10 percent in the matched male and female control mice compare favorably with incidences observed in over 2,000 colony controls of the same strain used in similar NCI experiments.[9]

11.1.4 Comments

In reviewing these NCI test results, the response of male mice appeared to be greater than that of the female mice not only in total incidence of hepatocellular carcinomas but also in shorter latency. These sex differences may have been more apparent than real, however, inasmuch as spontaneous hepatocellular carcinomas normally are not only of higher incidence in male controls but also appear earlier and metastasize with greater frequency.[9]

For male mice, the first of the hepatocellular carcinomas to be detected at necropsy was found in week 27 in the low dose group, compared to week 40 in the high dose group and weeks 90 and 91 in the vehicle and untreated control groups. The probability of hepatocellular carcinoma by week 91 was estimated to be 1.00 for a high-dose male mouse. For

female mice, the first hepatocellular carcinoma to be detected at necropsy was found in week 41 in the low dose group, compared to week 50 in the high dose group and week 91 in the untreated control. The probability of observing hepatocellular carcinoma by week 91 was estimated to be 0.938 for a high-dose female mouse.

No other types of tumors were significantly increased ($p = 0.05$) in mice.

The NCI report acknowledges that there were several design features that may have exerted a modifying or contributing role in the experiment. In employing high-dose levels the NCI followed the recommendations of expert panels on carcinogenesis testing[9] so as to provide maximum sensitivity in the screening assay. "Maximum tolerated" doses were chosen after an 8-week range-finding study. However, some subsequent minor adjustments were made in dose levels.

Toxic tubular nephropathy was observed at high incidences in all treated groups of mice. Not any of the control animals had this condition.

Mice developed loss of hair, skin sores, and a hunched appearance after a few weeks exposure. (Abdominal distension was noted in the second year of the study which was probably due to developing liver pathology.) Although toxicity was clinically evident, mortality by 90 weeks was not sufficient to reduce seriously the effective number of animals. Early mortality was observed in mice and may indicate that the optimum dose was exceeded, but liver tumors were found in substantial numbers of the mice that died early in the experiment.

Clinical signs of toxicity were observed in all exposed groups of rats, beginning in the first year and increasing in frequency progressively

thereafter. Among the signs observed were rough haircoat, skin sores, reddish discharge from eyes, and a hunched appearance. An apparent exposure-related chronic toxic nephropathy occurred in exposed groups of rats. The animals were afflicted with chronic respiratory disease. Survival of PERC-exposed rats was poor, and was significantly associated with dose levels. No hepatocellular carcinomas, like those diagnosed in mice, were observed in any of the exposed rats. No significant changes in the structure of the liver were observed. The NCI investigations concluded that the high mortality among the rats detracted from the usefulness of the experiment in detecting carcinogenic potential with that species.

Groups of animals to which other volatile chemicals had been administered were housed in the same rooms with PERC-exposed and control animals. Although the ventilation in the room conformed to the recommendations of the Institute of Laboratory Animal Resources,[17] it is possible that the animals were also subjected to very low-level exposures of several other chemicals.

Tissues of the fetus or newborn animal are generally regarded as more sensitive to chemical carcinogenesis than those of older offspring. It should be noted that several expert committees have recommended that exposure begin prior to conception, continue during pregnancy, with exposure to offspring for life, especially for those chemicals to which the human fetus may be exposed.[18-20] Since exposure to the chemical began when the animals were young adults, no assessment for transplacental carcinogenesis can be made. The FDA[18] further recommended that studies

not be terminated until cumulative mortality has reached 75 percent in a group showing negative results. The NCI tests were terminated at 90 weeks for mice and at 110 weeks for rats. It is possible that late developing tumors might have been observed had the animals survived longer or if the study had continued for a longer period of observation. The FDA[18] also considers that sample sizes greater than 40 to 50 per group are required for testing "weaker" carcinogens. The NCI study does not follow these guidelines.

While these deficiences in basic design and performance detract somewhat from the confidence that one might attach to the NCI study, the differences observed in liver cancer rates between exposed and control mice are statistically significant. At this point one must conclude that a carcinogenic potential in the mouse has been demonstrated for tetrachloroethylene under the test conditions. It then becomes necessary to examine several scientific issues to assess the probability that tetrachloroethylene would represent a cancer risk in man under normal conditions of exposure.

11.2 SCIENTIFIC ISSUES CONCERNING THE RELEVANCE OF THE NCI BIOASSAY TO NORMAL HUMAN EXPOSURE

11.2.1 Species Differences

Differences in species response to chemical carcinogens might be attributed to differing metabolic pathways and to an inability of some species to convert effectively the test chemical to an active carcinogen. The high sensitivity of the $B_6C_3F_1$ mouse and the low sensitivity of the NCI strain of Osborne-Mendel rat not only to PERC but to carbon tetrachloride, chloroform, trichloroethylene, and most of the chloroethane

compounds as well, [12-15] indicate innate species differences in sensitivity to chlorinated aliphatic compounds. Banerjee and Van Duuren[21] have demonstrated differences in the metabolism of trichloroethylene by the $B_6C_3F_1$ mouse and the Osborne-Mendel rat used in the NCI study. Their in vitro findings of a higher degree of binding of trichloroethylene to microsomes in mice than in rats agree well with the test results of the NCI bioassay for trichloroethylene, which were similar to those for tetrachloroethylene--hepatocellular carcinoma in the mice, no significant tumors in the rat.

A toxic chemical must make contact with a vulnerable target tissue in order to produce its toxic effect. This effect, including carcinogenicity, may well depend upon the effectiveness of biotransformation mechanisms in activating as well as inactivating reactive metabolites including a possible epoxide. A reactive epoxide may be inactivated by a hepatic epoxide hydrase. Oesch et al.[22] has demonstrated such hydrase activity using styrene oxide as the substrate. In addition, they compared the levels of humans with those of certain laboratory animal species. According to their results, the hydrase activity in humans appears to be four times that of mice, two times that of rats, about the same as that of guinea pigs, and considerably lower--about one-third - that of rhesus monkeys.

Henschler[23] claims that the difference in response of rats and mice might be attributed to the comparatively low activity of epoxide hydrase in mice. In other words, the mouse may have a decreased ability to detoxify an epoxide.

11.2.2 Route of Exposure

In the NCI study, PERC was administered by gastric intubation. Ambient air exposures are predominantly by inhalation. Based on the appearance of tumors outside the intestinal tract in the test animals, assumptions of absorption of PERC, and then of systemic exposure of other tissues to the chemical can be made. The amount absorbed and the relative distributions to other organs were not measured and would be difficult to estimate. The liver would be the main organ responsible for biotransformation--both activation and deactivation--following absorption and distribution of PERC after either oral or inhalation exposure. Thus the kinetic relationships are likely to be of a similar qualitative nature, and results obtained with one route may feasibly be applicable to the other. The inhalation studies recently initiated by NCI may provide useful data in assessing that route of exposure as a modifier of potential carcinogenicity of PERC. Results of the inhalation study by the Dow Chemical Company are difficult to interpret (Section 11.3).

11.2.3 Dose Levels

Dose levels, which were selected from subchronic testing results, were to be the highest consistent with long-term survival of the animals--referred to as "maximum tolerated doses"--and one-half of the maximum tolerated dose. This is in accordance with methods proposed by Weisburger and Weisburger.[24] These high dose levels were used to increase the probability of a tumorigenic response by the test system. However, the objections to such high levels are: (1) that they may introduce toxic conditions which interfere with survival and the carcinogenic process, and (2) they may introduce atypical metabolites from routes not utilized until saturation of the usual metabolic pathways.

As mentioned previously, the doses used in the NCI study were too high, and the survival of the test animals, especially of the rats, was poor. Consequently, the ability of the test to detect carcinogenicity in the rat was comparatively low.

11.2.4 Exposure to Other Chemicals

The animals in the NCI bioassay may have been exposed to low levels of known carcinogens by way of contaminants in the PERC, the air, water, or feed. These contaminants may have exerted possible additive or modifying effects. The PERC-treated mice, as well as both vehicle and untreated controls, were housed in the same room as mice receiving 1,1,2,-tetrachloroethane, allyl chloride, chloroform, chloropicrin, 1,2-dichloroethane, 1,1-dichloroethane, 3-sulfolene, iodoform, methylchloroform, 1,1,2-trichloroethane, hexachloroethane, carbon disulfide, trichlorofluoromethane, carbon tetrachloride, trichloroethylene, 1,2-dibromoethane, and dibromochloropropane.

11.2.5 Significance of Mouse Liver Cancer as an Indicator of Carcinogenic Potential to Man

Indeed, the relevance of liver cancer induction in the mouse as a predictor of carcinogenic potential in man is unquestionably one of the most controversial issues in cancer research. Many eminent scientists have disagreed about the validity of predicting carcinogenic activity in man from results obtained in the mouse. Some argue that additional evidence is necessary. Recent discovery of a high incidence of spontaneous liver tumors in untreated $B_6C_3F_1$ mice which live longer than bioassay lifetimes, indicates factors other than the test chemical may influence the incidence of hepatomas in mice. A mechanism may be responsible for the effect in mice exposed to high levels of chemical which is less likely to occur in man exposed at low levels.

However, others point to the many results which were obtained first in the mouse that were later confirmed in other animal species and even in humans. For years the mouse was accepted as the species of choice by cancer researchers.[25]

The experimental method is used for predictive tests capable of detecting the carcinogenic effects of an agent in laboratory animals, and for epidemiologic analysis in which 'after-the-fact' observations of a large, exposed population are made. Consideration of the long-term animal test for which results are available is recommended.

11.3 DOW CHEMICAL COMPANY ASSAY

Many tumors were found in groups of 96 male and 96 female Sprague-Dawley rats exposed to 300 or 600 ppm (2,034 or 4,068 mg/m^3) PERC in air 5 days a week for 12 months;[2,3] however, for most tumors there was no statistically significant tumor incidence between exposed and control rats.[3] Some tumors were found in higher incidence in control animals. In exposed animals, unilateral adrenal pheochromocytoma was seen at higher incidence in female rats at the lower exposure level only. Pheochromocytoma is a tumor which gives rise to high blood pressure and hyperglycemia due to release of epinephrine and norepinephrine into the blood. Increased mortality occurred in the male rats exposed to 600 ppm (4,068 mg/m^3). Earlier onset of advanced chronic renal disease appeared to be a contributing factor in the increased mortality rate of this group which also experienced a statistically significant increase of kidney tumor or tumor-like change. Thus, PERC appears to have induced kidney disease, or at least to have accelerated a spontaneous process, which contributed to increased mortality.

Both groups of female rats exposed to tetrachloroethylene showed liver atrophy, and high-exposure-level females experienced an increased incidence of fluid filled cysts in the liver.

The authors state that there was no evidence of a tumorogenic response to PERC because the incidence of tumors was similar for exposed and control rats. A complete report of this study is now available,[4] although only a portion of this study has been published and appeared only in abstract form.

Dose levels employed in this experiment were not high enough to provide maximum sensitivity, especially when the number of animals studied is considered.

The control animals were housed in the same room as the treated animals. Contamination of the air within the room by a low concentration of PERC exhaled by the treated animals may have occurred throughout the 12-month exposure period. Thus, the control rats may well have been exposed to a low level of PERC, especially since it is a volatile compound. As no environmental measurements were reported, these levels cannot be estimated.

11.4 INTRAPERITONEAL ADMINISTRATION OF PERC

Theiss et al.[4] injected 6- to 8-week-old male A/St mice intraperitoneally (i.p.) with doses of 80 mg/kg, 200 mg/kg, or 400 mg/kg PERC. The i.p. injections were given three times a week until 14 injections at 80 mg/kg or 24 injections of 200 or 400 mg/kg were completed. The survivors were sacrificed 24 weeks after the initial injection of PERC. The treated animals did not experience any significant increase in the average number of lung tumors per mouse when compared to controls.

11.5 APPLICATION TO SKIN

Van Duuren and his co-workers[5] conducted mouse skin bioassays of several halohydrocarbons including PERC in ICR/Ha Swiss mice. Groups of 30 female mice received skin applications of PERC for about one year.

When 160 mg of PERC in 0.2 ml acetone was applied to the dorsal skin of test animals and was followed 14 days later by thrice weekly application of 50 µg of phorbol myristate acetate in 0.2 ml acetone, four of the 30 mice developed skin papillomas. The total number of papillomas was 7. Of ninety mice receiving only repeated applications of 5.0 µg phorbol myristate acetate, six developed skin papillomas. A total of 7 papillomas was observed. Two of these mice developed squamous cell carcinoma. Nine of 120 mice receiving repeated applications of 2.5 µg phorbol myristate acetate developed a total of 10 papillomas. One mouse developed squamous cell carcinoma.

When PERC was applied to the dorsal skin three times weekly in doses of 55 or 20 mg in 0.2 ml acetone, one mouse receiving the lower dose developed squamous cell carcinoma. The final results of this study are not statistically significant. However, the investigators conclude that the evidence is suggestive of weak carcinogenic activity on mouse skin.

There are other major carcinogenicity studies now under way (see Appendix A).

11.6 CELL TRANSFORMATION

Using a highly sensitive <u>in vitro</u> cell system, Price et al.[2] demonstrated the transformation of Fischer rat embryo cells (F1706) to tumor-producing cells upon exposure to PERC. The transformation was phenotypically characterized by the appearance of progressively growing

foci of cells lacking in contact inhibition and orientation, and by the growth of macroscopic foci in semi-solid agar. When these morphologically altered cells were injected subcutaneously into newborn Fischer rats (1 x 10^6 cells), tumors developed at the inoculation sites in all animals in less than 2 months. No spontaneous transformation was observed in either the media or acetone controls. On the basis of their results, Price et al. concluded that PERC has a carcinogenic potential.

Three other chlorinated hydrocarbon solvents, trichloroethylene, methyl chloroform, and methylene chloride, also were tested in this system. These compounds also induced transformation. Tetrachloroethylene was considered more toxic than its trichloroethylene analog in this system. The positive control, methylcholanthrene, was more effective in transformation than any of the four chlorocarbons studied.

11.7 MUTAGENICITY

The data currently available are somewhat conflicting as to whether or not PERC is mutagenic in bacterial systems.

Henschler and his co-workers[23,26-31] found that PERC, as well as the cis- and trans-isomers of 1,2-dichloroethylene, was not mutagenic when tested in the metabolizing *in vitro* system with *E. coli* K_{12}. The mutagenicity of vinyl chloride, vinylidene chloride, and trichloroethylene in the above test system was attributed to their initially forming asymmetric unstable oxiranes, whereas the non-mutagenic effect demonstrated for tetrachloroethylene, and cis- and trans-1,2-dichloroethylene was rationalized on the basis of the somewhat more stable symmetrical configuration of the oxiranes formed from these compounds.

Similar negative findings after incubation with a microsomal activation system have been obtained in other bacterial assays using Salmonella typhimurium strains TA 1538 and TA 1535. Because of primary toxicity of some of the compounds (cell death), comparison of the compounds using Salmonella typhimurium was said not to be possible.[23,30]

These reports do not indicate any attempt to provide a systematic validation of the E. coli K_{12} test system using a wide range of positive compounds. The fact that several known carcinogens and mutagens including chloroform and carbon tetrachloride were nonmutagenic to Salmonella strains TA 1538 and TA 1535 indicates that the results of these bacterial mutagenicity assays with PERC should be interpreted with caution.

Cerna and Kypenova[32] indicate finding elevated mutagenic activity in Salmonella with PERC as well as with cis-1,2-dichloroethylene--both symmetrically substituted compounds. Tetrachloroethylene induced both base substitution as well as frameshift mutation. The results were statistically significant for PERC mutagenic activity without metabolic activation in tester strain TA 100. In the host-mediated assay using tester strains TA 1950, TA 1951, and TA 1952, PERC induced significant increases in the number of revertants. These results require confirmation.

The National Institute for Occupational Safety and Health (NIOSH) tested PERC for mutagenic activity in Salmonella tester strains TA 1535, TA 1537, TA 98, and TA 100. The NIOSH results were negative in all four strains.[33]

Rampy et al.,[4] in a chronic study, did not find chromosome or chromatid aberrations in male or female rat bone marrow cells after the animals had been exposed to 300 or 600 ppm (2,035 or 4,070 mg/m^3) PERC by inhalation for 6 hours per day, 5 days per week for one year.

11.8 TERATOGENICITY

Schwetz et al.[34] exposed 17 pregnant Sprague-Dawley rats and 17 pregnant Swiss Webster mice by inhalation to 300 ppm (2,035 mg/m^3) PERC for 7 hours per day on days 6 through 15 of gestation. Caesarean sections were performed on days 21 and 18, respectively, in the rats and mice. While all fetuses and dams were examined grossly for visible abnormalities, a subgroup of each litter was randomly selected for visceral exam, and a second subgroup from each litter was fixed in formalin. These were sectioned, stained, and examined microscopically.

The authors reported that exposure to PERC caused little or no maternal, embryonic, or fetal toxicity. However, following exposure to 300 ppm (2,035 mg/m^3) PERC, a statistically significant reduction in the mean body weights of maternal rats was observed. Also the mean relative weight of the liver of maternal mice was increased. Exposure to PERC was associated with a significant decrease in the fetal body weight of mice, and with a statistically significant increase of resorptions of fetuses in rats. Subcutaneous edema occurred at an incidence significantly greater among the litters of mice exposed to PERC than among control litters. Among litters of mice the incidence of delayed ossification of skull bones and the incidence of split sternebrae were significantly increased compared to those of controls.

An examination of the tables of data suggests other possible fetal effects among the mouse and rat litters although these were not found to be significant by the investigators at $p = 0.05$.

These studies would have detected major teratogenic effects. However, they were not sufficiently sensitive or adequately designed to detect weak

teratogens. According to Page and Arthur,[16] teratogenic neurological effects would not have been detected by this study.

The study certainly suggests the teratogenic potential of PERC. Further research is needed, especially to assess the occurrence of subtle latent effects including neurological effects, behavioral effects, and transplacental carcinogenesis. The National Institute for Occupational Safety and Health has undertaken a behavioral teratology study (see Appendix A). In addition, NIOSH has contracted for a study to evaluate the potential teratogenicity and the mutagenicity of tetrachloroethylene. (Appendix A).

However, based upon weak evidence from animal studies, there is sufficient reason to be concerned about the teratogenic potential of PERC.

11.9 SUMMARY

11.9.1 Evidence for Carcinogenicity

Currently, the most important study on which to base suspicion of carcinogenic potential is the NCI bioassay. Other studies which are under way may well provide comparable results (see Appendix A). Highly significant positive results were obtained, but only in the mouse and only with regard to liver cancer. Based on the results of Van Duuren and his colleagues, PERC cannot be considered a remarkable skin carcinogen. However, the occurrence of squamous cell carcinoma in 1 of 30 mice following skin application of PERC may be considered to indicate possible carcinogenic potential of the compound.

Tetrachloroethylene has been tested for *in vitro* transforming potential in a cell system which has been previously shown to be sensitive to transformation by chemical carcinogens. Malignant transformation of mammalian

cells was observed. The results of this study certainly suggest the carcinogenic potential of PERC.

The available data concerning mutagenicity in microbial systems are conflicting. There are results which indicate that the chemical is mutagenic, and there are other results which indicate that PERC is nonmutagenic when tested in the bacterial systems.

Structural similarity to vinyl chloride and other chloroethylenes puts PERC under suspicion for possession of carcinogenic potential even without experimental results. The metabolism of PERC to an epoxide intermediate (oxirane) with alkylating potential is possible.

There are no available epidemiological data to associate tetrachloroethylene with cancer in humans. Retrospective mortality studies are currently being conducted (see Appendix B) by NIOSH and NCI.

Since we can learn that an agent can cause cancer in mammalian species from two main sources--epidemiologic observations and long-term animal bioassays--and since we have no epidemiological evidence available, the assessment for carcinogenicity must be based largely on the animal bioassay results. We also have in vitro test results and considerations of biochemical activity. The bioassay does not provide information on the response at low levels of exposure. Mutagenicity or transformation tests were inconsistent or did not show strong responses.

TABLE 11-3. A COMPARISON OF NCI CARCINOGENESIS BIOASSAY TESTS OF TRICHLOROETHYLENE (TCE), TETRACHLOROETHYLENE (PERC), METHYL CHLOROFORM (MCh), CHLOROFORM ($CHCl_3$), AND CARBON TETRACHLORIDE (CCl_4).[16]

Chemical/expt'l group		Dose levels[1] (mg/kg)		Percent alive at 78 weeks		Hepatocellular carcinomas in mice	
		Rats	Mice	Rats	Mice	Percent incidence[2]	Time to 1st tumor (wks)
TCE	Males						
	Low dose	549	1169	60	80	52	81
	High dose	1097	2339	24	48	65	27
	Females						
	Low dose	549	869	40	82	8	90
	High dose	1097	1739	46	45	23	91
PERC	Males						
	Low dose	471	536	43	53	65	27
	High dose	941	1072	14	25	56	40
	Females						
	Low dose	474	386	50	25	40	41
	High dose	949	772	42	17	40	50
$CHCl_3$	Males						
	Low dose	90	138	78	86	36	80
	High dose	180	277	54	81	98	54
	Females						
	Low dose	100	238	56	86	80	66
	High dose	200	477	50	72	95	67
MCh	Males						
	Low dose	750	2807	2	42	0	-
	High dose	1500	5615	4	28	2	50
	Females						
	Low dose	750	2807	18	56	0	
	High dose	1500	5615	24	28	0	

(continued)

TABLE 11-3 (continued).

CCl_4	Males						
	Low dose	47	1250	68	22	100	48
	High dose	94	2500	68	4	98	26
	Females						
	Low dose	80	1250	76	25	100	16
	High dose	159	2500	42	9	96	19

[1]Chemicals were administered by stomach intubation at predicted maximum tolerated dose levels for 78 weeks and observed for an additional 12 weeks (mice) or 32 weeks (rats).

[2]Incidence in all animals at end of experiment, i.e., 90 weeks for mice and 110 weeks for rats. Colony control incidence (n = 2208) of hepatocellular carcinoma in $B_6C_3F_1$ mice: Males = 8.7%; Females = 1.7% (Page 1977).

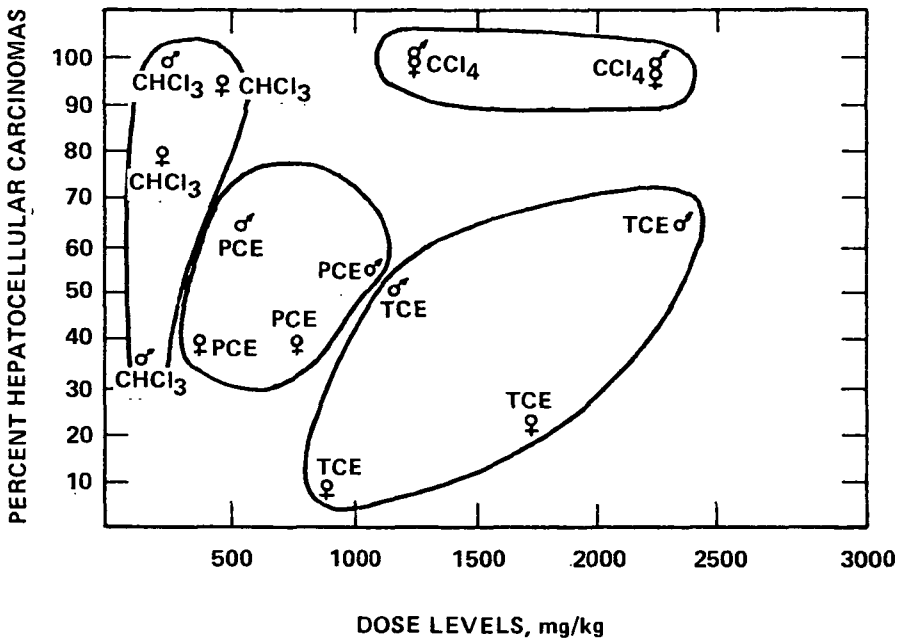


Figure 11-1. Relationship of hepatocellular carcinoma incidence with dose levels for trichloroethylene (TCE), tetrachloroethylene (PCE), chloroform ($CHCl_3$), and carbon tetrachloride (CCl_4).[16]

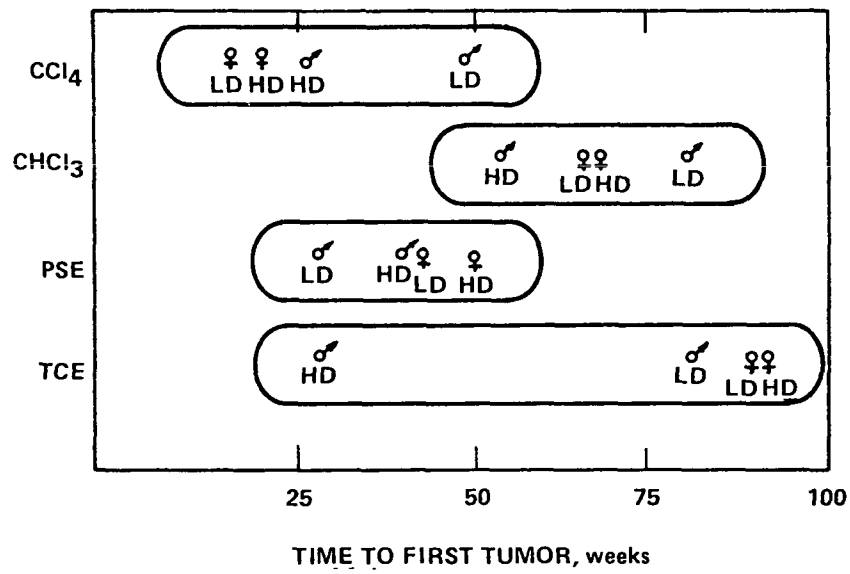


Figure 11-2. Initial tumor appearance with TCE, PCE, $CHCl_3$, and CCl_4.[16] LD= low dose; HD= high dose

11.10 REFERENCES FOR CHAPTER 11

1. Bioassay of Tetrachloroethylene for Possible Carcinogenicity. National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Dept. of Health, Education, and Welfare. DHEW Publication No. (NIH) 77-813, 1977.

2. Price, P. J., C. M. Hassett, and J. I. Mansfield. Transforming activities of trichloroethylene and proposed industrial alternatives. In Vitro 14:(3):290-293, 1978.

3. Rampy, L. W., J. F. Quast, B. K. J. Leong and P. J. Gehring. Results of long-term inhalation toxicity studies on rats of 1,1,1-trichloroethane and perchloroethylene formulations. Toxicology Research Laboratory Dow Chemical, U.S.A. Poster presentation, International Congress of Toxicology, Toronto, Canada, April, 1977.

4. Rampy, L. W., J. F. Quast, M. F. Balmer, B. K. J. Leong, and P. J. Gehring. Results of a long-term inhalation-toxicity study on rats of a perchloroethylene (tetrachloroethylene) formulation. Toxicology Research Laboratory. Health and Environmental Research, The Dow Chemical Company, Midland, Michigan, 1978.

5. Theiss, J. C., G. D. Stoner, M. B. Shimkin, and E. K. Weisburger. Tests for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37:2717-2720, 1977.

6. Van Duuren, B. L. personal communication.

7. Weisburger, E. K. Carcinogenicity studies on halogenated hydrocarbons. Environmental Health Perspectives 21:7-16, 1977.

8. Innes, J. R. M. et al. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Nat. Cancer Inst. 42:1101, 1969.

9. Page, N. Concepts of a Bioassay Program in Environmental Carcinogenesis. Chapter 4. In: Environmental Cancer, H. Kraybill and M. Mehlman, eds. Advances in Modern Toxicology, Vol. 3, Hemisphere Publishing Co., Washington, John Wiley and Sons, New York, 1977. pp. 87-171.

10. Fitzhugh, O. G., and A. A. Nelson. The chronic oral toxicity of DDT (2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane). J. Pharmacol. Exptl. Therap. 89:18- 1947.

11. Reuber, M. D. and E. L. Glover. Cirrhosis and carcinoma of the liver in male rats given subcutaneous carbon tetrachloride. J. Nat. Cancer Inst. 44:419, 1970.

12. Carcinogenesis Bioassay of Trichloroethylene. National Cancer Institute Carcinogenesis Technical Report Series No. 2, HEW Publication No. (NIH) 76-802, February, 1976.

13. Bioassay of Hexachloroethane for possible carcinogenicity. U.S. Dept. of Health, Education, and Welfare. Public Health Service, NIH, National Cancer Institute DHEW Publication No. (NIH) 78-1318, 1978.

14. National Cancer Institute. Bioassay of 1,1,2-Trichloroethane for Possible Carcinogenicity. U.S. Dept. of Health, Education, and Welfare, PHS, NIH, NCI. DHEW Pub. No. (NIH) 78-1324, 1978.

15. National Cancer Institute. Bioassay of 1,1,2,2-Tetrachloroethane for Possible Carcinogenicity. U.S. Dept of Health, Education, and Welfare, PHS, NIH, NCI. DHEW Pub. No. (NIH) 78-827, 1978.

16. Page, N. P., and J. L. Arthur. Special Occupational Hazard Review of Trichloroethylene. U.S. Dept. of Health, Education, and Welfare, PHS, CDC, NIOSH, DHWE (NIOSH) Pub. No. 78-130.

17. Institute of Laboratory Animal Resources. Long-term holding of laboratory rodents. ILAR News 19:L1-L25, 1976.

18. Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation. Panel on Carcinogenesis report on cancer testing in the safety of food additivies and pesticides. Toxicol. Appl. Pharmacol. 20:419-438, 1971.

19. Tomatis, L., C. Partensky, and R. Montesano. The predictive value of mouse liver tumor induction in carcinogenicity testing -- literature survey. Int. J. Cancer 12:1-20, 1973.

20. Canadian Ministry of Health and Welfare. The testing of chemicals for carcinogenicity, Mutagenicity, and Teratogenicity, 1973.

21. Banerjee, S., and B. L. Van Duuren. Covalent binding of the carcinogen trichloroethylene to hepatic microsomal proteins, and to exogenous DNA in vitro. Cancer Res. 38:776-780, 1978.

22. Oesch, F., H. Thoenen, and H. Fahrlaender. Epoxide hydrase in human liver biopsy specimens: assay and properties. Biochem. Pharmacol. 23:1307-1317, 1974.

23. Henschler, D., E. Eder, T. Neudecker and M. Metzler. Short Communication: Carcinogenicity of trichloroethylene: Fact or artifact? Arch. Toxicol. 37:233-236, 1977 (see other 1977 publication).

24. Weisburger, J., and E. Weisburger. Tests for chemical carcinogenesis. In: Methods In Cancer Research, H. Busch, ed., Vol. 1. Academic Press, Inc., New York, 1967. pp. 307-398.

25. Saffiotti, U. Experimental approaches to the identification of environmental carcinogens. In: Environmental Determinants of Human Cancer S. Epstein, ed. Charles C. Thomas, Publ. Springfield, Illinois. 1977.

26. Bonse, G., Th. Urban, D. Reichart, and D. Henschler. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem. Pharmacol. 24:1829-1834, 1975.

27. Griem, H., G. Bonse, Z. Radwan, D. Reichert, and D. Henschler. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24:2013-2017, 1975.

28. Henschler, D., G. Bonse, and H. Griem. Carcinogenic potential of chlorinated ethylenes-tentative molecular rules. Proc. Third WHO-IARC Meeting, Lyon, November 3, 1975.

29. Bonse, G., and D. Henschler. Chemical reactivity biotransformation, and toxicity of polychlorinated aliphatic compounds. CRC Crit. Rev. Toxicol., October 1976. pp, 395-409.

30. Henschler, D. Metabolism and mutagenicity of halogenated olefins--A comparison of structure and activity. Environ. Health Persp. 21:61-64, 1977.

31. Fishbein, L. Industrial mutagens and potential mutagen, I. Halogenated aliphatic derivatives. Mutat. Res. 32:267-308, 1976.

32. Cerna, N. and H. Kypenova. Mutagenic activity of chloro ethylenes analyzed by screening system test. Mutat. Res. 46(3):214-215, 1977.

33. Taylor, G. Memorandum to Office/Division Directors, NIOSH, Mutagenicity Task Force Members. National Institute for Occupational Safety and Health, Morgantown, West Virginia, December 9, 1977.

34. Schwetz, B. A., B. K. Leong, and P. J. Gehring. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32:84-96, 1975.

APPENDIX A

ONGOING STUDIES CONCERNING THE CARCINOGENESIS AND/OR THE TERATOGENESIS OF TETRACHLOROETHYLENE

There are a few ongoing studies of the carcinogenic or teratogenic potential of PERC. The results of these studies will be evaluated when they become available.

A.1 Carcinogenesis Bioassay of Perchloroethylene

Wheeler, R. Tracor Jitco, Inc., Rockville, MD.

Sponsored by NCI

A 2-year chronic gavage study of PERC (C04580 in the Carcinogenesis Bioassay Data System) will be undertaken in 4 strains of rats and in $B_6C_3F_1$ mice. Rat strains to be used are: Fischer 344, Long Evans, Wistar, and Sherman.

There will be 50 rats/strain/sex/dose level. Dose levels will be the maximum tolerated dose and one-half the maximum tolerated dose. Dose levels will be selected on the basis of prechronic tests, including clinical chemistry, histopathology, and other toxicological parameters.

In the mouse test, 30/sex will receive the maximum tolerated dose; 50/sex will receive one third the maximum tolerated dose and 90/sex will receive one ninth the maximum tolerated dose. Lower dose levels will also be included. The vehicle will be corn oil. The objectives of the mouse study are to determine a dose response curve and to check results of a different testing laboratory.

A set of vehicle controls (50 rats/sex) will be in the same room as the treated animals. A separate set of vehicle controls (50/sex) and the untreated

controls (50/sex) will be kept in a room separate from the chemically treated group. In the mouse study, vehicle controls of 50/sex and separate untreated controls of 50/sex will be used.

Body weight, food consumption, and clinical signs will be monitored throughout the chronic test. All animals will be monitored throughout the chronic test. All animals will be sacrificed for histopathological evaluation at the end of 2 years.

The objectives of this NCI study are: (1) to assess the carcinogenicity of PERC in rat strains other than Mendel, (2) to investigate whether hepatotoxicity is a necessary precursor of hepatocarcinogenicity in the mouse, and (3) to correlate dosage with blood levels of PERC in various strains and species.

A.2 Carcinogenesis Bioassay of Tetrachloroethylene.

Lindberg, D. Tracor Jitco, Inc., Rockville, MD

(Battelle Columbus Laboratories is to begin the 2-year chronic studies in October, 1978)

Sponsored by NCI

Tetrachloroethylene (C04580 in the Carcinogenesis Bioassay Data System) will be tested for 2 years by inhalation in the Fischer 344 rat, the $B_6C_3F_1$ mouse, and the Syrian Golden Hamster. Prechronic testing has been completed and was used to determine the maximum tolerated dose. During the chronic phase, 50 animals/species/sex/dose level will be exposed to the maximum tolerated dose and to one half the maximum tolerated dose.

Controls will be pooled with those for two other chemicals being tested under the subcontract. For the three chemicals there will be 90 untreated

animals/species/sex. In addition, there will be a positive chemical control to test the species and strain for sensitivity to a known carcinogen, dimethylnitrosamine. Fifty animals/species/sex/dose level will be used in the positive chemical control test.

All animals will be sacrificed at the end of the chronic test for histopathological evaluation; no clinical chemistry, teratogenesis, or mutagenesis evaluations will be undertaken.

A.3 Carcinogenesis Study of Perchloroethylene.

Van Duuren, B. L., Department of Environmental Medicine,
New York University School of Medicine
Sponsored by the National Science Foundation

Tetrachloroethylene has been tested as an initiator, promoter, and complete carcinogen using two-stage skin tests in female ICR/Ha mice. Long-term tests began in the fall of 1977 and continued for the lifespan of the mice. It was communicated by Dr. Van Duuren in the fall of 1978 that, under the conditions of this test, the evidence indicating cancer in mice was weak.

A.4 Teratological Study of Perchloroethylene in Rats and Rabbits.

Beliles, Niemeier, and Brusick, Litton Industries, Kensington, MD.
Sponsored by NIOSH

Charles River rats and New Zealand rabbits are exposed to PERC for 7 hours per day in closed inhalation chambers beginning 3 weeks prior to impregnation and continuing through gestation. Animals are sacrificed 1 day prior to parturition. Both dams and fetuses will undergo histopathological and morphological examinations for toxic and teratogenic effects of the compound.

A.5 Toxicology of Perchloroethylene in Rats exposed *in utero*.

Nelson, B. K.

NIOSH (in house research, Cincinnati, OH)

Two groups of female Sprague-Dawley rats will be exposed to PERC in closed inhalation chambers for 7 hours per day. One group will be exposed from days 7 to 13 of gestation; the second group will be exposed from days 14 through 21. Subgroups will be exposed to three different dose levels.

Behavioral studies will be carried out on the pups until they are 50 days old. Studies include measurement of reflexes, sense of smell, activity, and learning. Periodically, rats will be randomly selected and sacrificed for neurochemical and pathological analysis of brain tissues. At the end of the behavior studies, all remaining rats will be sacrificed and studied at necropsy.

APPENDIX B

EPIDEMIOLOGY

The National Institute for Occupational Safety and Health has contracted for a retrospective cohort study of mortality of dry cleaner workers exposed to PERC for at least 1 year prior to 1960. The study cohort is being selected from records maintained by several labor unions. The contract is monitored by the Biometry Section of the NIOSH Industry-Wide Studies Branch. A final report is expected at the end of calendar year 1979.

A retrospective cohort mortality study of laundry and dry cleaning workers who had been exposed to various solvents has been initiated by the National Cancer Institute. Mortality statistics, obtained from historical dues records of two union locals in St. Louis, Missouri during the period 1957 to 1977, are being evaluated. The study is being conducted under the auspices of the Environmental Epidemiology Branch of the National Cancer Institute. Preliminary findings concerning the causes of death of 330 workers by the proportionate mortality method indicate an increased risk for malignant neoplasms within this occupational group.