J. Barton

TRICHLOROETHYLENE. I. AN OVERVIEW

E. M. Waters, H. B. Gerstner, J. E. Huff

Toxicology Information Response Center, Biomedical Sciences Section, Information Center Complex/Information Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee

Trichloroethylene (TCE) has been an industrial chemical of some importance for the past 50 years. First synthesized by Fischer in 1864, TCE has enjoyed considerable industrial usage as a degreaser and limited medical use as an inhalation anesthetic and analgesic.

This TCE overview provides a narrative survey of the reference literature. Highlights include history, nomenclature, physical and chemical properties, manufacture, analysis, uses, metabolism, toxicology, carcinogenic potential, exposure routes, recommended standards, and conclusions.

Chemically, TCE is a colorless, highly volatile liquid of molecular formula C_2HCl_3. Autoxidation of the unstable compound yields acidic products. Stabilizers are added to retard decomposition. TCE's multitude of industrial uses center around its highly effective fat-solvent properties.

Metabolically, TCE is transformed in the liver to trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide; these breakdown products are excreted through the kidneys.

Most toxic responses occur as a result of industrial exposures. TCE affects principally the central nervous system (CNS). Short exposures result in subjective symptoms such as headache, nausea, and incoordination. Longer exposures may result in CNS depression, hepatorenal failure, and increased cardiac output. Cases of sudden death following TCE exposure are generally attributed to ventricular fibrillation. Current interest in TCE has focused on recent experimental data that implicate TCE as a cause of hepatocellular carcinoma in mice. No epidemiological data are available that demonstrate a similar action in humans. The overall population may be exposed to TCE through household cleaning fluids, decaffeinated coffee, and some spice extracts.

The NIOSH recommended standard for TCE is 100 ppm as a time-weighted average for an 8-hr day, with a maximum allowable peak concentration of 150 ppm for 10 min.

Preparation of this review was supported by the Toxicology Information Program/National Library of Medicine. The Oak Ridge National Laboratory is operated by Union Carbide Corporation Nuclear Division for the Energy Research and Development Administration under contract W-7405-eng-26.

The authors express appreciation to J. P. Hutson and S. A. Black, Toxicology Information Response Center, for assistance in the preparation of this overview and to G. U. Ulrikson, Oak Ridge National Laboratory, and H. M. Kissman, National Library of Medicine, for professional advice and support.

Trichloroethylene II. An Abstracted Literature Collection, 1907 to 1976, by E. M. Waters and S. A. Black, combined with Part I, is available through the National Technical Information Service, Springfield, Va. 22161; order number ORNL/TIRC-76/2; $20.00. (1673 refs., 265 pp.)

Requests for reprints should be sent to E. M. Waters, Toxicology Information Response Center, Biomedical Sciences Section, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830.

Journal of Toxicology and Environmental Health, 2:671–707, 1977

Those who cannot remember the past not only relive it; they tend to impose it, mistakes and all, on others.—Eliot Wigginton, *The Foxfire Book*, Anchor Books, 1972.

INTRODUCTION

An important industrial chemical for the last 50 years, trichloroethylene (TCE) has been the subject of much research—gaining momentum in the most recent decade; more than 1,600 total references have been collected from the literature (Waters and Black, 1976). Several authors have reviewed in some detail the pharmacology and toxicology of TCE (notably Defalque, 1961; Smith, 1966; Huff, 1971).

Defalque (1961) concluded from his analysis of the pre-1961 TCE literature that many research projects were apparently poorly designed; early experiments should be viewed with caution because of the less-than-pure grade of TCE used. In the mid-1960s TCE contained substantial amounts of 1,1,2,2-tetrachloroethane (NIOSH, 1973).

Even the most recent literature offers contradictory conclusions about the toxic effects of TCE. Specifically, more thorough experimental investigations appear necessary before the detailed toxicologic profile of TCE can be elucidated or before the possible carcinogenic potential of TCE for humans can be decided unequivocally.

TCE nomenclature and other identifying parameters are listed in Table 1. Known by many names, TCE possesses a single Class 1 chemical name, approximately five common or generic names, and more than 36 brand and trade names.

The major objective of this overview on the impact of TCE is to provide a brief but inclusive survey of the reference literature. Highlights include a chronologic history, nomenclature, physical and chemical properties, manufacture, analysis, uses, metabolism, toxicology, carcinogenic potential, exposure routes, recommended standards, and conclusions.

HISTORY

Synthesized in 1864, patented in 1906, and introduced as a narcotic in 1911, TCE subsequently became a seemingly indispensable multi-use solvent. Table 2 displays chronologically the primary use patterns of TCE from discovery by Fischer in the late 19th century through the proposed ban for use in foods.

LITERATURE SURVEY

TCE literature statistics (see Table 3) reflect consistent growth in reports published (Waters and Black, 1976). A noticeable increase began to

TABLE 1. Trichloroethylene Nomenclature and Other Information

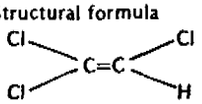
Chemical name	Ethene, trichloro- [Chemical Abstracts Service (CAS) preferred name, 9th Collective Index; and IUPAC]
Common names	Ethylene, trichloro- (CAS preferred name, 8th Collective Index) Acetylene trichloride Ethinyl trichloride Trichloroethylene TCE
Brand and trade names	Algylen, Aramenth, Blacosolv, Chlorylen, Circosolv, Dow-Tri, Fleck-Flip, Gamalgene, Landin, Lethurin, Narcogen, Narcosoid, Nialk, Perm-A-Clor, Petzinol, Philex, Threthylen, Trethylene, TRI, Triad, Trial, Triasol, Trichloran, Trichloren, Triclene, Tri-Clene, Trielene, Trielin, Trilene, Triline, Trimar, Trisan, Vestrol, Vitran, Westrosol
CAS registry number 79-01-6	Wiswesser line notation (WLN) GYGUIG
National Cancer Institute Number CO4546	Empirical formula C_2HCl_3
Percentage composition Carbon 18.28% Hydrogen 0.77% Chlorine 80.95%	Structural formula  Molecular weight 131.40

TABLE 2. History of Trichloroethylene

1864	First prepared by Fischer
1906	First patent held by Konsortium für Elektrochemische Industrie, Nürnberg
1911	Narcotic properties discovered by Lehman
1914–1918	Limited use as a degreaser and solvent
1915	Trigeminal analgesia reported by Plessner
1920s	More widespread use in metal degreasing
1930s	Use spreads to dry-cleaning industry
1933	Jackson successfully anesthetizes dogs
1940s	Use in Great Britain as inexpensive, nonexplosive anesthetic
1945	Use as anesthetic spreads to the United States, does not gain widespread popularity
1960s	"Carbona-cult" solvent-sniffing
1966	Use as a solvent curtailed in Los Angeles County, California, as a result of evidence implicating TCE in severe smog formation
1975	Preliminary report indicating carcinogenicity
1975	Invocation of Delaney clause sought to ban all uses in foods
1976	FDA drafting order to ban TCE
1976	Other chlorinated solvents proposed as substitutes: methyl chloroform, perchloroethylene, methylene chloride.

TABLE 3. Trichloroethylene Literature Survey

Years covered	Total number of reports	Percentage of total
1970 to present	563	33.6
1965 to 1969	361	21.6
1960 to 1964	190	11.4
1955 to 1959	165	9.9
1950 to 1954	131	7.8
1945 to 1949	69	4.1
1864 to 1944	194	11.6
Totals	1,673	100.0

occur in 1967, peaked in 1972, and now seems to have plateaued at an apparently constant rate. Nearly 34% of all TCE papers appearing since 1864 have been published between 1970 and the present.

Current emphasis on the workplace environment is mirrored by the significant increase in the number of reports in the occupational health and safety category. An apparent lack in the present TCE literature is in epidemiological studies. From these trends a reasonable prediction can be made for increased investigative reports in the areas of toxicology, biological studies, and occupational health and safety.

PHYSICAL AND CHEMICAL PROPERTIES

Trichloroethylene, an unsaturated chlorinated hydrocarbon with molecular formula C_2HCl_3 and $Cl_2C{=}CHCl$, exists as a colorless, mobile liquid with a sweetish odor resembling that of chloroform. The important physical properties of TCE are presented in Table 4. TCE is highly volatile with an evaporation rate three times that of ethyl ether; both hug surfaces, but ethyl ether is an explosive and flammable hazard, whereas at room temperatures TCE is neither flammable nor explosive, and at higher temperatures it is only moderately flammable. TCE is practically insoluble in water but readily miscible with a variety of organic solvents such as ether, chloroform, and alcohol.

Being unstable, TCE is susceptible to autoxidation, which can be prevented by the addition of stabilizers. The usual stabilizer choice for clinical grade TCE is thymol (0.01%) or ammonium carbonate (0.02%) (Aviado, 1972), while industrial grades may contain any one of a number of patented stabilizers. In 1963 Kirk and Othmer stated that the earlier stabilizers were usually single substances with antioxidant characteristics (simple amines), capable of fixing hydrochloric acid (epoxy compounds), or metal deactivators (ethanolamine and aniline). Newer stabilizers tend to

TABLE 4. Physical Properties of Trichloroethylene

Boiling point, 760 mmHg, °C	86.7[a]	
Melting point, °C	−87.1[a]	
Vapor pressure, mmHg, 20°C	57.8[a]	
Vapor density, boiling point, 1 atm, g/liter	4.45[a]	
Autoignition temperature, °C	410[a]	
Decomposition temperature, °C	700[a]	
Flash point	None by standard methods[b]	
Specific gravity, 20/4°C	1.46[a]	
Surface tension, 30°C, dyne/cm	29[a]	
Odor threshold, ppm	21.4[b]	
Solubility in water, g/100 g H_2O, 20°C	0.11[a]	
Distribution coefficients of solubility at 20° and 37°C[c]		
Water/air	3	1.6
Blood/air	18–22	8–10
Plasma/air	16–20	–

[a]Kirk and Othmer, 1963.
[b]NIOSH, 1973.
[c]Powell, 1947.

be synergistic mixtures of organic compounds, for example diisopropylamine plus an alkyl-*p*-hydroxyanisole.

Decomposition

In the presence of light (particularly ultraviolet light) and moisture, TCE decomposes to form acidic products. Table 5 summarizes various degradation conditions and reaction products. TCE in liquid or vapor form decomposes in contact with hot metal or a naked flame, forming phosgene ($COCl_2$; $O{=}CCl_2$) and hydrochloric acid. In the presence of strong alkali, dichloroacetylene (C_2Cl_2; $ClC{\equiv}CCl$) may be formed. Dichloroacetylene

TABLE 5. Degradation Products of TCE under Various Conditions

Conditions	Reaction products
Autoxidation	Acidic products including hydrogen chloride
Hot vapor in contact with a naked flame (air and moisture present)	Phosgene, hydrogen chloride
Strong alkali, e.g., sodium hydroxide	Dichloroacetylene
At 300°–600°C in contact with metals such as aluminum and magnesium (air and moisture present)	Phosgene, hydrogen chloride
Mammalian metabolism	Trichloroacetic acid, trichloroethanol, trichloroethanol glucuronide
Biodegradation	Carbon dioxide, water, chloride ions

reacts violently with air to produce two noxious gases, phosgene and carbon monoxide. TCE reacts with metals such as magnesium or aluminum at temperatures of 300°–600°C to form phosgene and hydrochloric acid. Unfortunately, conditions favorable to the decomposition of TCE are often found in the vicinity of arc welding and degreasing operations (Smith, 1966). Industries, businesses, and individuals using or planning to use TCE should be made acutely aware of these potential decomposition products and the concomitant hazards.

MANUFACTURE

The solvent properties of TCE were not realized until the early 1900s. Subsequent to this observation, TCE manufacture was begun on a large scale. U.S. production rose to a peak of 610 million pounds in 1970, falling to a level of 452 million pounds in 1973 and 435 million pounds in 1974 (*Chem. Eng. News*, 1975). World production in 1973 was estimated to be 2,260 million pounds (McConnell et al., 1975). Legislative action following TCEs implication as a contributor to Los Angeles County's photochemically reactive smog has resulted in its replacement by other solvents—methylene chloride, tetrachloroethylene, and 1,1,1-trichloroethane (*Chem. Eng. News*, 1969).

Most industrially produced TCE is manufactured from 1,1,2,2-tetrachloroethane, derived from either ethylene or acetylene. The industrial processes for TCE production are well established and have changed little in the past two decades. An outline of TCE manufacture is presented in Fig. 1. The initial reaction step involves chlorination of the starting material (ethylene or acetylene) to sym-tetrachloroethane, followed by selective dehydrochlorination of the latter. Dehydrochlorination can be accomplished by two different methods: alkaline hydrolysis of sym-tetrachloroethane with a suspension of calcium hydroxide in water, or pyrolysis (thermal decomposition) of sym-tetrachloroethane by a modified process in the presence of a silica gel or an activated charcoal catalyst impregnated with barium chloride, copper chloride, or a mixture of other chlorides at temperatures between 300° and 500°C (Kirk and Othmer, 1963).

ANALYSIS

Analysis and quantification of trichloroethylene and the principal metabolites—trichloroacetic acid and trichloroethanol—are accomplished by several means, including spectrophotometric colorimetry (Stack et al., 1961), neutron activation (Morgan and Duxbury, 1965), spark source mass spectroscopy (Cooper et al., 1971), infrared spectroscopy (Stewart et al., 1974a), and gas chromatography coupled with electron capture (Castello, 1971) or flame ionization detectors (Buchet et al., 1974; Bzdega, 1974).

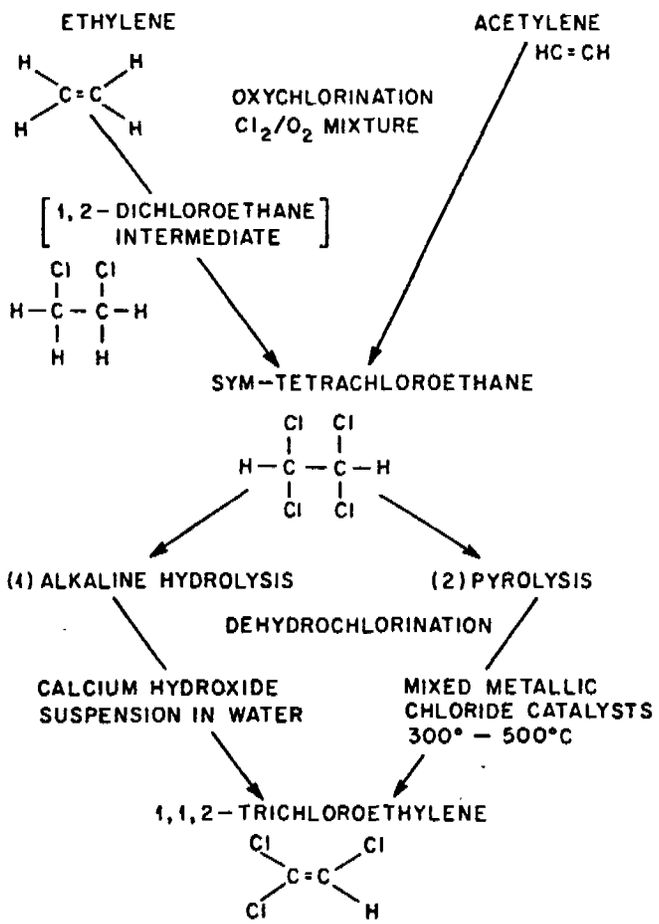


FIGURE 1. Summary of TCE manufacture.

A detailed account of gas sampling techniques and analytical methodology is found in the National Institute of Occupational Safety and Health criteria document (NIOSH, 1973).

Analytic techniques are available for TCE detection in air, tissues, urine, and other media. For instance, TCE may be determined in wastewater by gas chromatography (Austern et al., 1975), nephelometry (Effenberger and Deyl, 1958), and potentiometry (Deyl and Effenberger, 1958).

USES

Trichloroethylene is used as an industrial solvent, as a household cleaner and solvent, and as an inhalation analgesic and anesthetic.

Medical

TCE has been employed in anthelmintic preparations and for bactericidal and fungicidal purposes. During the 1940s TCE enjoyed considerable popularity as an analgesic and anesthetic, particularly in obstetrics; however, this popularity declined because of the subsequent synthesis of more effective and versatile halogenated anesthetic agents.

Anesthetic. The use of TCE as an anesthetic has largely been abandoned because it does not produce sufficient skeletal muscle relaxation for many surgical procedures. To determine TCE use statistics in hospitals with more than 100 beds, NIOSH surveyed 1,254 hospitals and found that 63 (5%) used TCE (*Med. World News*, 1975). Another source (*Chem. Eng. News*, 1975) quotes a maximum figure of 60,000 patients a year receiving TCE during anesthetic procedures.

Induction and recovery are slow because of the high solubility of this compound in blood (Aviado, 1972). TCE is believed to stimulate the pulmonary stretch receptors governing lung deflation, probably resulting in the shallow, accelerated breathing that is characteristic of TCE anesthesia (Whitteridge and Bulbring, 1944). It causes a dose-dependent depression of cardiac contractility; spontaneous cardiac arrhythmias have been reported but the experimental evidence is contradictory (Aviado, 1972). TCE is reported to sensitize the heart to catecholamines, particularly epinephrine, resulting in ventricular fibrillation. It is still used for short operative procedures in obstetrics, dentistry, burn dressing, and cystoscopy.

Many of the early poisoning incidents during TCE anesthesia resulted from using a closed-system rebreathing apparatus where soda lime acted as a carbon dioxide absorber; however, later investigations revealed that passage of TCE over soda lime results in the production of dichloroacetylene, a neurotoxic agent.

TCE is contraindicated in anemia, toxemia of pregnancy, and diseases of the heart, lungs, and kidneys. It is not advocated for use in children or together with epinephrine because of the high risk of ventricular fibrillation (Osol and Pratt, 1973).

Analgesic. Plessner (1915) reported trigeminal desensitization following TCE anesthesia, and for a short time TCE use was advocated in the treatment of trigeminal neuralgia. The analgesic properties are attributed to a defatting action on the myelin nerve sheaths.

As an analgesic for women in labor, TCE is suitable where less than 10 min of light anesthesia is needed. Self-administration for obstetrical analgesia has proved to be effective and safe.

The availability of pure TCE preparations and the development of special inhaler devices have enhanced the use of vapors for obstetrical analgesia; however, the onset of analgesia is slow and TCE is potentially cardiotoxic and hepatotoxic (Swinyard, 1975).

For dental extractions, incision of furuncles, and other short operative procedures, TCE has the advantage of being a satisfactory analgesic that is

readily portable, inexpensive, and not unpleasant to inhale, coupled with a wide margin of safety between analgesic effect and toxic doses. Excessive salivation, however, may be troublesome in dental procedures (Osol and Pratt, 1973).

Veterinary medicine. TCE is used as an inhalation anesthetic for animals such as pigs, dogs, and cats; as a disinfectant and detergent for skin, minor wounds, and surgical instruments; and as a solvent for the removal of grease from fur, hair, and wounds of animals (Stecher, 1968).

Agriculture

TCE has been cancelled for use in fumigant mixtures or as a solvent with other ingredients on grains (*Farm chemicals handbook*, 1976).

Food Production

Until recently, TCE was used in the decaffeination of coffee and the extraction of spice oleoresins. Under Section 121.1041, the Food and Drug Administration has established tolerances of 25 ppm for TCE in decaffeinated ground coffee, 10 ppm in decaffeinated instant coffee, and 30 ppm in spice oleoresins (FDA, 1974). As a result of recent studies at the National Cancer Institute, the FDA is drafting an order to ban TCE.

Industrial Uses

By far the most prolific use of TCE has been as a fat solvent for degreasing metal parts prior to painting, anodizing, and electroplating. As much as 90–95% of all TCE produced in the United States is used in degreasing operations (*Chem. Eng. News*, 1975). Historically, TCE has had a multitude of uses: mordant and dye fixative, cleaning solvent, and stain remover; caulking substance for shipbuilding; desizer for textiles; drying agent in varnishes; solvent for rubber; antifoaming agent; solvent in insecticides; and defatting agent for skins and hides. A representative selection of commercial products containing TCE is displayed in Table 6 (Braddock, 1976). A listing of TCE-containing products available prior to 1971 has been published (Huff, 1971).

METABOLISM

"Toxicants have undoubtedly been metabolized by living systems since the first cells were formed in the primordial ooze" (Norton, 1975). Bodily defense mechanisms for toxic substances can be divided into four groups: elimination in unchanged form (in expired air, urine, feces, perspiration, vomitus, hair, and milk); chemical structural modification (usually for increased water solubility to facilitate excretion by the kidneys); structure modification for detoxification regardless of whether water solubility is increased or not; and host defense mechanisms (immunity, tolerance, and encapsulation or trapping) (Norton, 1975).

TABLE 6. A Representative Selection of Commercial Products Containing TCE[a]

Adhes-Off
(Harvey Labs Inc.)
Trichloroethylene
Petroleum base

Balkamp Klean and Prime
(Balkamp Inc., Mfr. Loctite Corp.)
Trichloroethylene

Bowes Buffing Solution
(Bowes Corp.)
Xylol
Trichloroethylene

Carboff
(Holcomb Corp.)
Cresol > 10%
Methylene Chloride > 10%
Trichloroethylene 1–10%

Carbona Cleaning Fluid
(Carbona Products Co.)
Trichloroethylene 44%
Petroleum solvent 56%

Carbona No. 10 Special
Spot Remover
(Carbona Products Co.)
Trichloroethylene 40%
1,1,1-Trichloroethane 10%
Petroleum solvent 50%

Crater 2X Fluid
(Texaco Inc.)
Petroleum lubricating oil
Trichloroethylene
Pine tar

Crater 5X Fluid
(Texaco Inc.)
Petroleum lubricating oil
Trichloroethylene
Pine tar

Detrex-Eaton Dux
(Detrex Chem. Ind. Inc.)
Piccotex 120 solution (synthetic resin)
Wax (paraffin)
Trichloroethylene

Glamorene Dry Cleaner for Rugs
(Glamorene Products Corp.)
Chlorinated hydrocarbon (TCE)
Petroleum distillate
Wood flour

Instant Chimney Sweep
(Miracle Adhesives Corp.)
Trichloroethylene 34%/wt.
Propellant Freon 25%/wt.

Kwik Kleen Dry Shampoo
(Royal Bond, Inc.)
Trichloroethane

Lacco Chlorosan
(Los Angeles Chemical Co.)
Orthodichlorobenzene 59.5%
Trichlorobenzene 6.3%
Trichloroethylene 6.4%
Pine oil 4.4%

Lash Bath
(Revlon Inc.)
Naphtha
Trichloroethylene

Mildew Stop Spray
(Cardinal Products Corp.)
Propellant [Freon 11-12(50/50)] 55.0%
1,1,1-Trichloroethene[b] 25.9%
Isopropyl alcohol (anhydrous) 17.8%
Perfume oil 0.4%

Pedi-Skin Adherent No. 2
(Pedinol Pharmacal Inc.)
Resins
Trichloroethylene

Perm-A-Chlor NA
(Detrex Chem. Ind. Inc.)
Trichloroethylene

TFE Dri-Glide Teflon Aerosol
(Cling-Surface Co.)
Methylene chloride 30%
Toluene 7%
Trichloroethylene 14%
Blended Freon 11-12 40%

Thoro Dry Cleaner
(Thoro Products Co.)
Chloroform
Ether
Methanol
Trike (trichloroethylene)
Naphtha base

Trichlor
(PPG Industries, Inc.)
Trichloroethylene 100%

[a] Braddock, 1976.
[b] Label information.

Classically, enzymatic metabolic reactions have been considered to take place by four chemical pathways—oxidative, reductive, hydrolytic, and synthetic (conjugation)—which most often occur in the soluble, mitochondrial, or microsomal fractions of the liver. The first three are classed as phase I reactions, whereas conjugation occurs in phase II.

A summary scheme outlining the proposed intermediary metabolism of trichloroethylene is diagramed in Fig. 2. Various reference works (Daniel, 1963; Leibman, 1965; Byington and Leibman, 1965) have been consulted to piece together this essentially complete and generally accepted detoxification sequence.

Absorption

TCE is absorbed into the animal system by a variety of routes—inhalational, oral, and dermal. Each exposure avenue presents a distinct

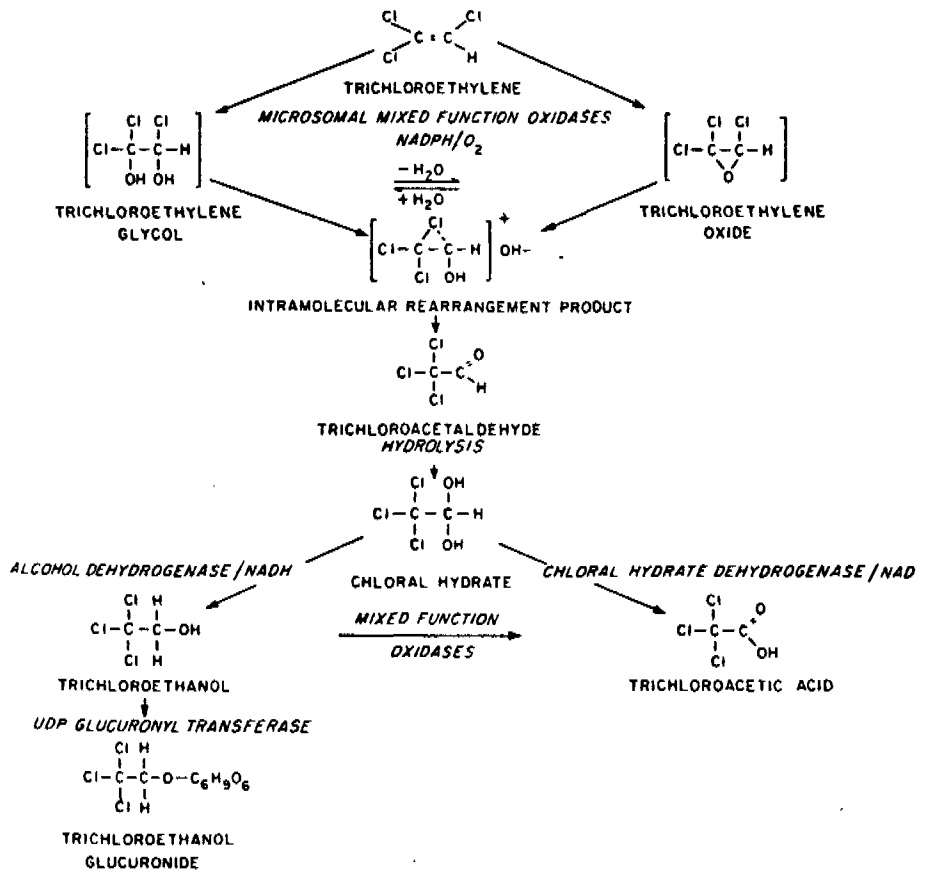


FIGURE 2. Proposed intermediary metabolism of TCE.

problem for workers as well as consumers; however, except for experimental trials, most exposures to TCE are by a combination of all three routes.

Inhalation. By far, inhalation is the most important entry route for solvents and vapors, being the cause of most acute and chronic symptomatology related directly and indirectly to TCE exposure. TCE vapors are readily absorbed through the respiratory epithelium, absorption being greatest during the first minutes of exposure, then decreasing rapidly until equilibrium with the blood is reached.

Oral. TCE passes easily across the gastrointestinal wall, as illustrated by the numerous cases of poisoning following oral ingestion of TCE (Gibitz and Plochl, 1973; Migdal et al., 1971; Vignoli et al., 1970; Wiecko, 1966; Vyskocil and Polak, 1963).

Dermal. Following immersion of a person's thumb in TCE for 30 min, Stewart and Dodd (1964) detected TCE in the alveolar air, indicating that absorption through intact skin is possible. The mean peak of TCE breath concentration was 0.5 ppm; thus, cutaneous exposure to TCE is unlikely to result in absorption of dangerous quantities of TCE.

Distribution

Following absorption, TCE disappears rapidly from the blood. Pulmonary arterial blood shows a higher TCE concentration than pulmonary venous blood, which suggests that a large percentage (72–85%) is exhaled unchanged via the lungs (Daniel, 1963).

Because of high fat solubility, the TCE that is not immediately metabolized may be retained in fatty tissues. By inhalation experiments with guinea pigs, Fabre and Truhaut (1952) studied TCE and trichloroacetic acid distribution in a number of tissues. In all cases, the tissue concentration of trichloroacetic acid was greater than that of TCE.

Table 7 shows the time-dependent tissue distribution of TCE and trichloroacetic acid (TCAA) in guinea pigs. As the exposure time increases, the concentration of TCAA in all tissues begins to decline as TCAA is further metabolized or excreted. No significant patterns emerge with regard to dose or time of exposure. Body fat, adrenals, and ovaries show high concentrations of TCE, whereas adrenals and spleen show significantly higher concentrations of TCAA than other organs; ovaries and urine hold intermediate levels. Because of the limited number of animals used and the older and less specific analytical techniques available at that time, too much emphasis should not be placed on these results.

In further experiments with rats, Fabre and Truhaut (1952) found 41.3 mg% TCE in blood cellular components and 2.5 mg% TCE in blood plasma following inhalation of 10 mg/liter TCE in air. These authors proposed that lipids in the erythrocyte membrane may facilitate transport of TCE. Before this, Powell (1947) suggested that hemoglobin in the erythrocytes is responsible for uptake and transport of TCE by blood.

By examining autopsy tissue from persons with unknown exposure to

TABLE 7. Distribution of TCE and TCAA in Guinea Pigs[a]

Organ	Concentration (mg/100 g fresh tissue)							
	TCE[b]	TCAA[b]	TCE[c]	TCAA[c]	TCE[d]	TCAA[d]	TCE[e]	TCAA[e]
Adrenals	–	–	3.4	12	2.2	11	3.8	10
Blood	1.3	3.6	1.0	3.8	0.5	3.1	0.8	2.7
Brain	0.5	3.2	0.7	3.0	0.9	2.5	1.0	3.0
Fat	3.1	4.4	3.5	–	3.9	3.5	3.8	–
Kidney	2.2	4.0	0.8	3.4	1.4	2.1	1.8	–
Liver	0.8	2.8	0.5	2.0	1.0	1.2	0.6	1.1
Lungs	0.8	4.2	1.2	3.3	0.7	3.2	0.8	3.2
Muscle	–	–	0.5	–	0.2	–	0.2	–
Ovaries	–	–	2.3	7.0	2.3	8	–	–
Spleen	1.7	9.3	1.9	9.0	1.3	8.6	0.9	7.8
Urine	–	–	3.5	5.0	3.1	4.8	2.6	4.7

[a] Fabre and Truhaut, 1952.
[b] Inhalation of 9 mg/liter, 4 hr daily for 5 days; total 20 hr.
[c] Inhalation of 6 mg/liter, 4.5 hr daily for 13 days; total 58.5 hr.
[d] Inhalation of 6 mg/liter, 5 hr daily for 19 days; total 95 hr.
[e] Inhalation of 7 mg/liter, 5 hr daily for 23 days; total 115 hr.

TCE, McConnell et al. (1975) confirmed the presence of TCE in most organs. Profile details are summarized in Table 8. Tissue analysis was incomplete in six out of eight cases; no significant patterns of distribution or accumulation appear, and therefore no absolute conclusion can be drawn concerning the extent of population exposure to TCE.

Biotransformation

TCE is more or less water-insoluble and, like most foreign compounds, is converted enzymatically to more water soluble metabolites; much of the intermediary metabolism of TCE has been elucidated.

Referring to Fig. 2, the first metabolic step involves oxidation of TCE through intermediates to chloral hydrate. Leibman (1965) and Byington and Leibman (1965) determined that this step is mediated by a reduced nicotinamide adenine dinucleotide phosphate/oxygen ($NADPH/O_2$)-dependent reaction taking place in liver microsomes. Chemically, chloral hydrate formation requires migration of a chlorine atom from the 2-carbon to the 1-carbon position.

Using ^{36}Cl-labeled TCE fed to rats (single doses of 8.6, 7.5, and 4.0 μCi ^{36}Cl-labeled TCE), Daniel (1963) studied the metabolism of TCE by determining the specific activity of TCAA and trichloroethanol (see Table 10). The specific activity of these two compounds was essentially the same as that of the administered TCE, which indicates (1) an intramolecular rearrangement of TCE and (2) no exchange of chloride ions with the body chloride-ion pool.

TABLE 8. Concentration of TCE in Human Tissues[a]

Subject	Age/Sex	Tissue	Concentration (μg/kg wet tissue)
A	76/F	Body fat	32
		Kidney	<1
		Liver	5
		Brain	1
B	76/F	Body fat	2
		Kidney	3
		Liver	2
		Brain	<1
C	82/F	Body fat	1.4
		Liver	3.2
D	48/M	Body fat	6.4
		Liver	3.5
E	65/M	Body fat	3.4
		Liver	5.2
F	75/M	Body fat	14.1
		Liver	5.8
G	66/M	Body fat	4.6
H	74/F	Body fat	4.9

[a]McConnell et al., 1975.

The existence of an epoxide intermediate had been hypothesized by Powell (1945) 18 years previously. Further, Daniel (1963) suggested that the epoxide intermediate spontaneously rearranges, forming trichloroacetaldehyde and subsequently chloral hydrate. Leibman (1965) speculated that the same nonspecific microsomal enzymes that are responsible for the conversion of TCE to chloral hydrate mediate the conversion of other olefinic compounds, such as dihydronaphthalene, aldrin, and isodrin, to their respective glycols or epoxides.

Chloral hydrate, being rapidly metabolized, has a short biological half-life in humans [not detected in plasma 5–30 min after ingestion of 30 mg/kg (Marshall and Owens, 1954)], dogs (10 min using 250 mg/kg (Scansetti et al., 1959)], and mice [10–20 min in brain tissue (MacKay and Cooper, 1962)]. Leibman (1965) recognized two possible pathways: (1) reduction of chloral hydrate to trichloroethanol by liver alcohol dehydrogenase (NADH coenzyme), or (2) oxidation via "chloral hydrate dehydrogenase" (NAD coenzyme) to TCAA.

Trichloroethanol is most often conjugated with glucuronic acid before being excreted in the urine (Muller et al., 1974). As with most detoxification reactions, glucuronide formation takes place mainly in the liver.

Thus, the principal urinary metabolites of TCE are trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid.

TABLE 9. Biological Half-Life of Trichloroethanol and TCAA in Humans[a]

Compound	Exposure	Half-life (hr)	
		Trichloroethanol	TCAA
Trichloroethylene	100 ppm/6 hr/10 days	13.3	85.57
Trichloroethylene	50 ppm/6 hr/5 days	12.4	99.02
Chloral hydrate	15 mg/kg	14.3	62.45
Trichloroethanol	10 mg/kg	13.2	65.39
Sodium trichloroacetate	3 mg/kg		50.60

[a]Muller et al., 1974.

Elimination

After inhalation exposure, much of the absorbed TCE is exhaled unchanged, following an exponential course. The remainder is gradually metabolized and excreted in the urine (Soucek and Vlachova, 1960). The biological half-lives of trichloroethanol and TCAA are shown in Table 9. Trichloroethanol exhibits a relatively short biological half-life in humans (approximately 13 hr) compared with a value of 50–99 hr for TCAA. Excretion of trichloroethanol glucuronide by the kidneys is rapid, whereas that of TCAA is slow, probably because of the high protein-binding affinity of the acid (Muller et al., 1974).

Following oral administration of ^{36}Cl-labeled TCE (8.6, 7.5, and 4.0 μCi) to rats, respiratory excretion accounted for 72–85% of the dose and urinary excretion for 11–21% (Daniel, 1963). Urinary metabolites were measured as trichloroethanol (75%) and TCAA (25%). Radioactivity was detectable for 18 days after dosing. The results are shown in Table 10. Increasing the dose of TCE causes increased exhalation of radioactivity with a decrease in urinary excretion, suggesting a possible saturation of the biochemical pathways responsible for TCE metabolism.

Soucek and Vlachova (1960) exposed human volunteers to 500–850 μg

TABLE 10. Excretion of ^{36}Cl-labeled TCE in Rats[a]

Radioactivity dose (μCi)	Radioactivity (%)		
	Exhaled	Urine	Feces
8.6	84.8	10.7	0.5
7.5	82.3	13.8	0
4.0	72.1	20.6	0

[a]Daniel, 1963.

TCE/liter air for 5 hr and measured urinary excretion of TCE metabolites. Excretion kinetics appeared to be biphasic, with an initial fast phase followed by a slow phase. Trichloroethanol and TCAA were detected for more than 16 days after exposure. Seventy-three percent of the retained TCE was excreted in urine; the metabolite profile in urine was 4% monochloroacetic acid, 19% TCAA, and 50% trichloroethanol.

Interaction with Ethyl Alcohol

Of particular industrial, social, and health interest is the interaction between TCE and ethyl alcohol. Intolerance of or sensitivity to ethanol is a well-documented symptom of TCE exposure (Stewart et al., 1974b; Jindrichova, 1970), often manifest as red flushes on the face and upper parts of the body. Muller et al. (1975) demonstrated that concurrent administration of ethyl alcohol and TCE (100 ppm for 6 hr) to human volunteers resulted in a 2½-fold increase in the concentration of TCE in blood (from a control level of 1.0 μg/ml to 2.5 μg/ml) and a 3- to 4-fold increase in the TCE concentration in exhaled breath (from 10 ppm to 35 ppm). Although the rate of excretion of unchanged TCE in exhaled breath increased, the blood concentration of TCE rose, suggesting a lower rate of TCE metabolism in the presence of ethyl alcohol with a subsequent buildup of TCE concentration in the blood.

Because the oil:water distribution for TCE is 900:1, lipophilic brain components may facilitate an accumulation of TCE in the CNS; thus, TCE concentrations in the CNS may approach subhypnotic levels, leading to the early onset of symptoms of intoxication (Muller et al., 1975). Studying the interaction between ethanol and TCE, Stewart et al. (1974b) confirmed increased levels of TCE in blood and exhaled air.

Muller et al. (1975) suggested that the mixed function oxidases capable of metabolizing ethanol are also responsible for metabolizing TCE, leading to competitive inhibition between TCE and ethanol for the enzyme and resulting in a subsequent buildup of TCE concentrations in the blood.

TOXICOLOGY

Toxicological investigations of TCE encompass a diverse array of experimental animals and protocols. The results often parallel this diversity. Hence interspecies and human extrapolation has proved difficult. The following discussion concerns industrial toxicology, experimental toxicology, and comments on the toxicity of TCE-extracted soybean meal and addiction to TCE.

Industrial Toxicology

Because of the industrial and medical use of TCE, the NIOSH conducted a survey in 1975, which indicated that each year nearly

300,000 industrial workers are exposed to TCE, often in massive doses, and approximately 5,000 operating room personnel and dentists have regular contact (*Med. World News,* 1975). Corbett (1972) reported a higher rate of miscarriages among operating room nurses compared with the general nursing population; although not directly implicated, TCE may be a contributing factor.

Reports of industrial exposures are often sketchy and contradictory; information is rarely given on important details such as (1) degree of TCE exposure; (2) grade of TCE used and possible contamination with breakdown products—phosgene, chlorine, and hydrogen; (3) existing pathological conditions in the workers; and (4) conditions under which TCE is being used. Roche (1953), for instance, stated that in many incidences accidental overheating of the degreasing tank may lead to the formation of phosgene. Also, noxious substances such as perchloroethylene may be present as contaminants.

This section is divided into (1) general, acute, and chronic case reports emphasizing signs and symptoms, and (2) the effect of TCE on organs and systems—particularly the cardiovascular and nervous systems; also affected are the skin and blood chemistry.

Case reports following acute exposure. Numerous cases of acute exposure to TCE are cited in the literature (Longley and Jones, 1963; Masoero and Lavarino, 1955; Vallee and Leclercq, 1935). Cotter (1950), for instance, reported signs and symptoms such as nausea, vomiting, and mental agitation, with subsequent abdominal cramps, diarrhea, and pain in the lower back of ten workers exposed during cleanup of an accidental spill. In another case, a worker was overcome by TCE fumes while cleaning an out-of-use degreaser; in addition to narcotic effects, he sustained first and second degree burns of the skin and first degree chemical burns to both eyes (Maloof, 1949). However, autopsy findings for an individual who allegedly died from TCE poisoning showed no pathological abnormalities; death was reportedly caused by ventricular fibrillation (Bell, 1951).

Hepatorenal failure was considered the cause of death of a man who accidentally drank a large quantity of TCE. Before death, nephrosis and acute pancreatitis developed; necrosis of the liver was noted at autopsy (Kleinfeld and Tabershaw, 1954).

Case reports following chronic exposure. Signs and symptoms resulting from long-term exposure to TCE are many in number and myriad in type. Dizziness, headache, fatigue, nausea, vomiting, fainting spells, burning of the eyes, and intolerance to alcohol are well-characterized manifestations of TCE exposure, having been reported by many authors (Schiøtz, 1938; Alexander, 1948; Forssman, 1950; Hickish et al., 1956; Mazza and Cascini, 1956; Doskar and Gabriel, 1965; Lilis et al., 1969; Jindrichova, 1970. In general, these TCE-induced symptoms are alleviated when the subject is removed from the source of exposure or contact.

Cases of sudden death attributed to chronic TCE exposure are not uncommon. Kleinfeld and Tabershaw (1954) describe five TCE-associated deaths attributed to ventricular fibrillation; four of the men had worked in a degreasing plant. At autopsy, except for congestion of the viscera, no gross anatomical changes were observed.

James (1963) described the sudden death of a man who had been employed as a degreaser for 9 yr in an electroplating factory. Symptoms of paresis of the olfactory nerves and gastric disturbances developed during these years. Death occurred 17 hr after the last known exposure. Autopsy revealed old as well as recent lung hemorrhages and fatty degeneration of the liver. Death was attributed to ventricular fibrillation.

Effects. Observations of the effects of TCE on specific organs and systems following acute exposure are reported in the literature. Initial effects are on the nervous system and are characterized by inebriation, lack of coordination, and dizziness. The cardiovascular system, the skin, and the blood chemistry may be affected to some degree.

TCE affects principally the nervous system, especially depressing all functions of the CNS—in decreasing order from the cortex to the medulla (Irish, 1963).

Sagawa et al. (1973) found transverse lesions of the spinal cord following accidental exposure to anesthetic levels of TCE. Vegetative nervous system alterations and neurologic psychiatric symptoms (Grandjean et al., 1955), perceptive deafness with labyrinthine disorders (Szulc-Kuberska, 1972), and increased reflex activity and hypotension (Mazz[illegible] and Cascini, 1956) have been reported.

More than 60% of workers exposed to TCE and examined exhibited increased cardiac output. Lilis et al. (1969) attributed this effect to elevated epinephrine levels; at the same time, virtually no electrocardiogram (ECG) changes were observed. Vyskocil (1953) reported bradycardia and disturbances of heart muscle conduction in persons with long-term employment in a dry-cleaning establishment.

An extremely effective degreaser, TCE consistently exacerbates existing lesions, rashes, or minor skin conditions. Schirren (1971), for example, observed eczematous skin lesions on hands due to leaching of skin oils, cracking of skin, and lowering of resistance to infection.

The delicate homeostatic chemical balance is routinely disrupted by TCE. Examining workers exposed to TCE for periods ranging from 5–10 months, Takamatso (1962) detected hypoalbuminuria and hypoglobulinemia. Nomura (1962) also reported similar changes in blood chemistry in workers exposed to TCE during degreasing operations, including increased γ-globulin fractions, decreased albumin fractions (hypoalbuminemia), and a positive 24-hr cephalin-cholesterol flocculation test (CCFF); all changes were interpreted as indicative of liver damage. Liver function tests conducted on 12 women, each with 2 yr exposure, revealed dyspeptic syndromes and serum protein changes in six of the subjects; two

displayed slight hyperbilirubinemia (Capellini and Grisler, 1958). Normal range values were seen for total serum proteins, total albumin and esterified cholesterol, alkaline phosphatase, blood glucose, and urea levels. Seventy workers exposed chronically to TCE exhibited dysproteinemia, decreased serum albumin, decreased and inverted albumin to globulin ratio, positive thymol turbidity tests, and positive cephalin-cholesterol tests amounting to slight liver damage (Graovac-Leposavic et al., 1964).

Yamaga and Saruta (1953) reported a low erythrocyte count, monocytosis, eosinophilia, low blood urea, high serum alkaline phosphatase, and urinary urobilinogen in workers handling TCE for 7 months.

Experimental Toxicology

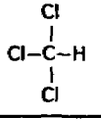
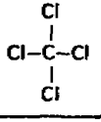
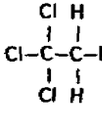
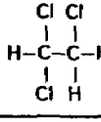
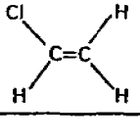
This section presents experimental data obtained after exposure of various animal species (including humans) to TCE under controlled conditions. Effects of TCE on the liver, renal system, nervous system, and behavioral and psychological functions point to the necessity for further clarity.

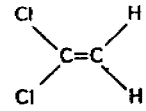
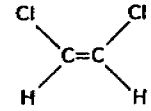
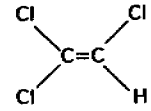
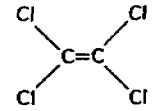
Liver. Much attention has been directed toward the hepatotoxic properties of the chlorinated hydrocarbons. Chloroform and carbon tetrachloride show marked hepatotoxicity, whereas evidence for the hepatotoxicity of TCE is largely inconclusive. Table 11 was compiled to illustrate the comparative toxicities of nine chlorinated methane, ethane, and ethylene derivatives and to correlate possible structural similarities with lethality.

Early experiments on TCE toxicity indicated some degree of liver damage. In two groups of dogs exposed to 750 ppm TCE for 8 hr/day, 6 days/wk for 3 wk, and 500–570 ppm TCE for 6 hr/day, 5 days/wk for 8 wk, Seifter (1944) found anemia, weight loss, nausea, vomiting, lethargy, diarrhea, glycogen depletion, and degeneration of parenchymatous liver cells. [Here we reiterate the warning of Defalque (1961) concerning the relatively impure nature of the TCE available at that time.]

More recent work has indicated little or no hepatotoxic effects following TCE exposure. Rats exposed to TCE for 30 min/day for 120 days showed liver damage amounting to histological changes, decreased total serum proteins and albumin levels, and increased α-, β-, and γ-globulins and cholesterol (Fonzi et al., 1967). Wirtschafter and Cronyn (1964) injected rats with 0.004 mol TCE/kg (approximately 0.5 g/kg) and found mild degenerative liver changes within 12–24 hr. Histological examination revealed granularity and clumping around the central veins. At 24 hr, necrosis had not occurred and no lipids were present, while rats inhaling 0.25, 0.5, 0.8, and 1.20 g TCE/liter for 15-90 hr showed increased intracellular lipid levels but no liver necrosis (Verne et al., 1959). Gehring (1968) observed no increase in serum glutamic pyruvic transaminase (SGPT) levels following a single exposure of mice to TCE at an LD_{50} level (5,500 ppm). Experimental exposures approaching lethal dose

TABLE 11. Comparative Toxicity of TCE and Related Compounds

Compound and parent alkane	Oral LD_{50} (mg/kg)	Inhalation LC_{50} (ppm)	Lowest published toxic concentration (ppm)	Structural formula
Chloroform (Methane derivative)	Rat: 800[a] Rat: 2,180[b]	Mouse: 5,687/7 hr[b] Mouse: 28[a] Rabbit: 59[a] Dog: 100[a]	Human: 10/yr[a] Systemic effects	
Carbon tetrachloride (Methane derivative)	Mouse: 12,800[b] Rat: 1,770[a] Rat: 7,460[b] Rabbit: 6,380[a]	Mouse: 9,526/8 hr[a] Mouse: 9,528/7 hr[b] Rat: 23,900/30 min[b]	Human: 20 CNS: toxic effects	
1,1,1-Trichloroethane (Ethane derivative)	Guinea pig: 9,470[a] Rabbit: 5,660[a]	Rat: 14,000/7 hr[b] Rat: 18,000/3 hr[b]	Human: 350[a] Psychotrophic effects Human: 920/70 min[a] CNS: toxic effects	
1,1,2-Trichloroethane (Ethane derivative)	Rat: 580[a]			
Monochloroethylene (Vinyl chloride monomer) (Ethylene derivative)		Mouse: 27,419[c] Rat: 47,640[c] Guinea pig: 236,215[c] Rabbit: 236,215[c]	Human: 20[a] CVS: toxic effects	

1,1-Dichloroethylene (Vinylidene chloride) (Ethylene derivative)		Rat: 6,350[d] Rat: 600, fasted[e] Rat: 15,000, unfasted[e]	
1,2-Dichloroethylene (Ethylene derivative)		Human: 613[a] CNS: toxic effects	
1,1,2-Trichloroethylene (Ethylene derivative)	Rat: 5,200[f] Rat: 4,920[a] Dog: 5,900[g]	Human: 160/83 min[a] CNS: toxic effects Human: 110/8 hr[a]	
1,1,2,2-Tetrachloroethylene (Ethylene derivative)	Mouse: 8,850[b] Mouse: 10,900[b]	Human: 230[a] Systemic effects Human: 280/2 hr[a] Eye: toxic effects Human: 600/10 min[a] CNS: toxic effects	

[a]Christensen and Luginbyhl, 1975.
[b]Spector, 1956.
[c]Prodan et al., 1975.
[d]Siegel et al., 1971.
[e]Jaeger et al., 1974.
[f]National Clearinghouse for Poison Control Centers, 1967.
[g]Stecher, 1968.

levels were necessary before significant elevations of SGPT were observed. One hour after exposure of mice to an anesthetic mixture of TCE and air (1.8% v/v), Heim and co-workers (1966) observed disturbances in intermediary liver metabolism and elevated blood sugar levels, but no significant changes in liver lipid concentrations. Mice fed various concentrations of TCE in olive oil showed mild degenerative liver changes (Jones et al., 1958).

Exposure of one dog, three rabbits, and three rats to TCE (0.5–0.1% v/v, 18 hr/day, for 90 days) produced a slowing growth rate; however, liver, renal, and hematopoietic functions were judged normal (Nowill et al., 1954). No gross abnormalities were observed at autopsy. Prendergast and co-workers (1967) obtained similar results following continuous (24 hr/day) exposure of rats, guinea pigs, dogs, rabbits, and monkeys for 90 days or exposure for 8 hr/day, 5 days/wk for 6 wk. Growth depression was the only visible effect. Hematological functions were within normal limits.

Still other researchers have observed no liver damage following TCE exposure. Ikeda et al. (1969) injected rats every second day with TCE for 40 doses—0.5 ml/kg three times and 1.5 ml/kg 37 times. No significant changes were observed in liver and blood lipids, phospholipids, total cholesterol, triglycerides, free fatty acids, glycogen, or glucose. Kylin and co-workers (1963) found no liver damage in rats following a single 4-hr exposure to 3,200 ppm TCE as assessed by serum ornithine carbamoyl transferase (SOCT) activity and histological examination. Mice exposed to 1,600 ppm for longer periods showed only transient liver damage. Kylin et al. (1963) assessed the relative hepatotoxicities of TCE, tetrachloroethylene, and chloroform at a ratio of 1:10:20.

Renal system. Conflicting results are reported with respect to renal damage following TCE exposure. Plaa and Larson (1965) injected mice ip with TCE (0.6 ml/kg) and using phenosulfonaphthalein excretion, sugar urine assays, and histopathological examination, found no indication of kidney damage. Similarly, Nowill et al. (1954), in experiments with various animal species (one dog, three rabbits, three rats), found no evidence of TCE nephrotoxicity.

In contrast, Bartonicek and Soucek (1959), Cagianelli et al. (1965), and Kiseleva and Korolenko (1971) reported definite kidney abnormalities following exposure to TCE. Kiseleva and Korolenko (1971) reported cytotoxicity to liver and kidneys following anesthesia of dogs with 1.5% v/v TCE. Twenty-four hours after anesthesia, proximal renal tubules exhibited a loss in Krebs cycle enzyme activity. Six rabbits injected parenterally with 33–55 g TCE for 55–100 days resulted in two deaths, both attributed to renal failure (Bartonicek and Soucek, 1959). Kalashnikova et al. (1974) maintained rats on a high-protein or high-carbohydrate diet with simultaneous exposure to 5 mg/liter TCE, 5 hr/day for 7 days. Rats on a high-protein diet appeared weaker; focal dystrophic

changes in renal tubules were detected. Cagianelli et al. (1965) also found histological evidence of glomerular nephrosis in kidneys of rats subjected twice daily to sprays of TCE.

Nervous system. As previously stated, TCE affects principally the nervous system, causing depression of the CNS.

Baker (1958) found no evidence of neuropathological changes in dogs that had died after a single exposure to 30,000 ppm TCE. Further, Baker (1958) observed pathological changes indicating selective destruction of cerebellar Purkinje cells in dogs exposed to various concentrations of TCE vapors for up to 162 hr.

Behavioral and psychological effects. Since TCE is a CNS depressant, behavioral effects following inhalation are to be expected, the degree and duration depending on exposure levels and biological individuality. Behavioral studies must and do play an important role in setting safe hygienic standards for industrial exposure. Because sensitivities among workers vary, many have failed to show behavioral disturbances following TCE exposure.

Stewart et al. (1970) exposed human volunteers to 200 ppm TCE daily for various periods of time. The subjects showed difficulty in performing a modified Romberg test; other performance and neurological tests yielded normal results. In a study by Salvini et al. (1971), six male volunteers exposed to an average 110 ppm TCE during two 4-hour exposures separated by a 90-min interval showed a significant decrease in perception, manual dexterity, complex reaction times, and Wechsler memory scale. Salvini et al. (1971) expressed the opinion that a workplace threshold limit value of 100 ppm is too high. Nakaaki et al. (1973) reported only a slight decline in psychophysical functions and a small reduction in performance in human subjects exposed to 100 ppm TCE.

Grandjean (1963) exposed rats for 6 hr to doubling doses of 400, 800, and 1,600 ppm TCE; exposure to 400 ppm resulted in no significant decrease in performance during a 4-hr swimming test. Exposure to 800 ppm caused an immediate decrease in motor performance, but normal activity was regained after 1 hr. Exposure to 1,600 ppm impaired motor activity, which persisted for 80 min. Evidently, however, recovery was uneventful and complete after removal from exposure. Using chronic exposure, Baettig and Grandjean (1963) observed no behavioral peculiarities in rats exposed to 360–420 ppm TCE, 8 hr/day, 5 days/wk for 46 wk. In another experiment, Baettig (1964) found that rats exposed to 400 ppm TCE over 43 wk showed more physical activity in a maze than the control group.

Toxicity of TCE-Extracted Soybean Meal

In cattle and chickens fed on soybean meal defatted with TCE, cases of aplastic anemia have been reported. Pritchard et al. (1956) observed aplastic anemia, atrophy of the testes, and depression of secondary sexual

characteristics in chickens fed a diet composed of 72.9% soybean meal extracted with TCE. Hager (1926) and Rundles (1958) described evidence in cattle of enigmatic anemia, fever, weight loss, reduced milk flow, epistaxis, bloody diarrhea, and death due to internal hemorrhaging. Extensive losses of cattle occurred in Europe between 1923 and 1925 from feeding the meal. In 1952, manufacturers in the United States voluntarily withdrew such meals from the market (Huff, 1971).

The toxic factor in TCE-extracted soybean meal is believed to be formed by the interaction of TCE with a component of the meal. McKinney et al. (1959) synthesized a substance [*S*-(1,2-dichlorovinyl)-L-cysteine (DCVC)] extremely toxic to cattle, which may be formed by the reaction of TCE with cysteine during the defatting process.

Addiction

Addiction to TCE has been attributed to the euphoric "high" effects produced by inhalation of the vapors. Together with other manifestations of TCE addiction, cases of sudden death have been reported in the literature. In 1945, Rickles reported disorientation and bouts of maniacal behavior following oral administration of TCE. Similarly, Ikeda et al. (1971) observed disorientation, hallucinations, and delusions of persecution following inhalation of TCE vapors.

A 16-yr-old male youth who had been employed as a degreaser for 2 yr had become addicted to TCE. He was found dead with his head over a bucket containing TCE (Teare, 1948); superficial burns were present on the left side of his face. Autopsy findings revealed the cause of death as hemorrhagic edema of the lungs. Musclow and Awen (1971) described the death of another 16-yr-old male youth who had reportedly practiced glue-sniffing for 2 yr. Death followed a glue-sniffing episode, apparently due to TCE poisoning. Autopsy findings revealed pulmonary edema; congestion of spleen, liver, and kidneys; edema of the brain; and slight fatty degeneration of liver, myocardium, and renal tubules. At post-mortem, the blood was quite fluid and devoid of any clots.

O'Connor (1954) described the case of a 25-yr-old man who had been addicted to TCE for several years. Following a heavy session of TCE usage, he attacked and killed his mother. When apprehended by police, he became violent and had to be strapped to a couch before being removed to a hospital. The maniacal phase continued for three more hours.

Renal failure, acute centrilobular necrosis of the liver, together with ECG and EEG abnormalities were detected in two male youths after repeated episodes of Carbona sniffing (this cleaning fluid contains 40–44% TCE; see Table 6); both had a history of drug abuse. On admission to a hospital, SGOT and SGPT levels were elevated but returned to normal within 17 days. Subjective symptoms included headache, anorexia, and vomiting (Baerg and Kimberg, 1970).

CARCINOGENIC POTENTIAL

On March 21, 1975, the National Cancer Institute issued a memorandum warning that preliminary tests on mice implicated TCE as the cause of hepatocellular carcinoma with some metastases (*Chem. Eng. News*, 1975). The reaction from industry was one of shock and concern; as a result, the Manufacturing Chemists Association swiftly developed a program for long-term inhalation studies to further investigate the carcinogenic potential of TCE.

Results of four studies done in 1944, 1951, 1955, and 1967 aimed at assessing carcinogenic potential of TCE are shown in Table 12. None of these results, performed on a variety of experimental animals and at different levels of TCE, revealed evidence of carcinogenicity.

TABLE 12. Summary of Carcinogenic Data

Species	No.	Exposure	Results	Reference
		Inhalation		
Dogs	16	150–750 ppm in air 20–48 hr/wk for 7–16 wk	No tumors; no deaths	Seifter, 1944[a]
		Inhalation		
Rats	12	3,000 ppm, 27 exposures	Three rats died; no tumors	Adams et al., 1951[a]
Guinea pigs	11	100 ppm, 132 exposures		
Monkeys	2	200 ppm, 148 exposures		
Rabbits	4	200 ppm, 178 exposures		
		Inhalation		
Cats	8	200 ppm 75 min/day for 6 months	No tumors; no deaths	Mosinger and Fiorentini, 1955[a]
		Intragastric		
Mice	28	0.1 ml in 40% oil solution 2/wk	No tumors; no deaths	Rudali, 1967[a]
		Intragastric		
Mice	50	2,339 mg/kg (M) 5/wk for 78 wk	Hepatocellular carcinoma; metastases, mainly lung	NCI, 1976
	50	1,739 mg/kg (F) 5/wk for 78 wk		
	50	1,169 mg/kg (M) 5/wk for 78 wk		
	50	869 mg/kg (F) 5/wk for 78 wk		
		Intragastric		
Rats	100	1,097 mg/kg (M and F) 5/wk for 78 wk	No hepatocellular carcinoma; many deaths from toxic doses during experiment	NCI, 1976
	100	549 mg/kg (M and F) 5/wk for 78 wk		

[a] Survey of compounds which have been tested for carcinogenic activity, 1957 to 1971.

A recent study (NCI, 1976) involved gastric intubation of TCE into male and female Osborne-Mendel rats and B6C3F1 mice.

In rats, dose levels of 1,097 and 549 mg TCE/kg dissolved in corn oil were administered five times a week for 78 wk. All surviving rats were sacrificed at 110 wk and subjected to extensive pathological examination. Chronic respiratory disease occurred in most rats regardless of treatment group or sex; however, the only treatment-related lesion was chronic neuropathy, present in rats of both sexes at high and low dose levels. The investigators speculate that intercurrent disease or a greater sensitivity of the Osborne-Mendel rat strain to the toxic effects of TCE may be responsible for the high mortality rate. The data are summarized in Table 13A. As seen from Table 11, these experimental doses approached one-fifth to one-tenth the LD_{50} value. Vehicle-treated (corn oil) as well as positive CCl_4-treated control rats were utilized. Data outlining the incidence of liver tumors in colony- and CCl_4-treated control rats are shown in Table 13B; data outlining tumor incidence in matched control and TCE-treated rats are shown in Table 13C. Matched control rats showed a 20% incidence of hepatocellular carcinoma in males and a 35% incidence in females. Both values are greater than the occurrence of hepatocellular carcinoma in TCE-treated males and females whereas the positive controls—CCl_4-treated rats—showed a 4–5% incidence of liver tumors. The

TABLE 13A. Incidence of Mortality in Matched Control and TCE-Treated Rats[a]

	Control	Low dose	High dose
Males	17/20	42/50	47/50
Females	12/20	35/48	37/50

[a]NCI, 1976.

TABLE 13B. Incidence of Liver Tumors—Colony Control and CCl_4-Treated Rats[a]

Animal group	Hepatocellular carcinoma	Neoplastic nodule	Percentage (approximate)
Males			
Controls	1/99	0/99	0.5
Low dose	2/50	2/50	4.0
High dose	2/50	1/50	3.0
Females			
Controls	0/98	2/98	1.0
Low dose	4/49	2/49	6.0
High dose	1/49	3/49	4.0

[a]NCI, 1976.

TABLE 13C. Tumor Incidence—Rats with Tumors[a]

	Males			Females		
	Control	Low dose	High dose	Control	Low dose	High dose
Before 110 wk	4/17	5/42	4/47	4/12	6/35	4/37
At 100 wk	1/3	2/8	1/3	3/8	6/13	8/13
Total	5/20	7/50	5/50	7/20	2/48	12/50
Percentage	20	14	10	35	25	24

[a]NCI, 1976.

decreased rate of hepatocellular carcinoma with increased dose of TCE may be explained by the greater number of deaths caused by the toxic effects of TCE before sufficient time has elapsed for tumors to develop. However, the high mortality rate coupled with the large number of liver tumors strongly suggests that additional factors such as disease are interacting to produce the ambiguous results. Further studies of the carcinogenic potential of TCE in rats are necessary.

The B6C3F1 mice were subjected to a similar experimental protocol. Mice received TCE by gastric intubation at dose levels of 2,339 and 1,169 mg TCE/kg for males and 1,739 and 869 mg TCE/kg for females five times a week for 78 wk. Surviving mice were sacrificed at 90 wk and subjected to pathological examination. During the first weeks of treatment, alopecia, sores on the tail and other parts of the body, and hunched appearance were noted. After 50 wk, bloating and distention of the abdomen were apparent. Following 27 wk of treatment, hepatocellular carcinomas were diagnosed in some males receiving the high doses of TCE. Mortality rates were high in males and lower in female (Table 14A). Again, the mortality rate in matched-control male mice was higher than in the TCE-treated mice. Almost all (179/182) male and female mice fed CCl_4 developed hepatocellular carcinoma. Sixty-four percent of the males fed TCE at the high dose level (2,339 mg/kg) and 52% fed at the lower dose level (1,169 mg/kg) developed hepatocellular carcinoma. For females fed 1,739 and 869 mg/kg, the incidence was 23 and 8%.

TABLE 14A. Incidence of Mortality in Matched-Control and TCE-Treated Mice[a]

Animals	Control	Low dose	High dose
Males	12/20	14/50	28/50
Females	0/20	8/50	8/47

[a]NCI, 1976.

TABLE 14B. Comparison of Hepatocellular Carcinoma Incidence in Colony Controls (Vehicle-Treated) and CCl_4-Treated Mice[a]

		CCl_4	
Animals	Control	Low dose	High dose
Males	5/77	49/49	47/48
Females	1/80	40/40	43/45

[a]NCI, 1976.

TABLE 14C. Incidence of Hepatocellular Carcinoma in TCE-Treated Mice[a]

Group	Males	Females
Controls	1/20 (5%)	0/20 (0%)
Low dose	26/50 (52%)	4/50 (8%)
High dose	31/48 (64%)	11/47 (23%)

[a]NCI, 1976.

The reason for using lower dose levels for females (approximately three-fourths of the dose administered to males) was not mentioned. Under these different dosage regimens, the percentage of hepatocellular carcinoma for females is significantly lower than for males. This could be an effect of dose or reflect sex-related differences in the ability of TCE to induce hepatocellular carcinoma. These experiments implicate TCE as a carcinogen in mice, but more conclusive animal experimentation must be accomplished—coupled with human epidemiology—to justify this indictment.

The International Agency for Research on Cancer (IARC), in evaluating the carcinogenic potential of TCE, presented only prepublication results from the above study, and in the absence of epidemiological data following industrial exposure to TCE, no conclusions were drawn (IARC, 1976).

Methods of evaluating possible carcinogenic risk are again at issue; this time representatives of the two major U.S. producers of TCE—Dow Chemical Company and PPG Industries, Inc.—have stated that the doses employed in the 1975 preliminary study are roughly equivalent to that of a person drinking 6 ounces of TCE every day, a situation which these producers consider bears no relation to actual exposure levels. The estimated fatal oral dose of TCE in humans is 3-5 mg/kg—about 210-350 mg for a 150-pound person (Irish, 1963).

NCI acknowledges the high dosage levels, but considers these levels necessary to elucidate mechanisms of toxic action as well as to detect other untoward effects.

So far, no proven cases of human cancer due to TCE have been reported; moreover, no detailed epidemiological surveys have been made—these should be undertaken with utmost haste.

The major route of oral TCE exposure to the general population has been from use in decaffeinating coffee. Even though TCE is no longer used for coffee decaffeination, some TCE-decaffeinated coffee may still be available to the public. In an experimental study of decaffeinating agents, Jans (1972) fed TCE-decaffeinated coffee to golden hamsters and rats daily for 2 yr and for three generations. No pathogenic effects, growth problems, alteration of reproduction, teratogenic, carcinogenic, or co-carcinogenic effects were observed.

Van Duuren (1975) reviewed the mechanism of carcinogenic action of vinyl chloride (monochloroethylene) and speculated that the carcinogenic entity of this compound is monochloroethylene epoxide. Vinyl chloride is probably metabolized by the same mixed function microsomal oxidases as TCE, and because TCE epoxide is a probable intermediate in the biological detoxification, TCE, by analogy, may be carcinogenic. Van Duuren (1975) predicted this probability nearly 2 months before the announcement by the NCI that TCE may be carcinogenic. The extrapolation from vinyl chloride monomer to TCE was based on the structure-activity relation of the intermediates to carcinogenic moieties. Leibman (1965) stressed that epoxides are unstable and quickly metabolized. Whether this substance can initiate cancerous growth remains speculative until corroborative data are developed.

EXTRAPOLATION OF ANIMAL DATA TO HUMANS

The use of animals to assess the potential toxicity of drugs and chemicals in humans has become a standard and valuable procedure. For example, compounds that are toxic to one species tend to be toxic to others. Nevertheless, numerous exceptions prevent an absolute correlation between animal toxicity data and the corresponding hazards for humans. This does not, however, limit the value of toxicity studies in animals; success depends on the judicious interpretation of animal test results and knowledgeable extrapolation to humans (Hiatt and Huff, 1975).

POTENTIAL AVENUES OF EXPOSURE

Environmental and human exposure to hazardous and potentially hazardous agents is on the increase. This is inevitable as more and more chemicals are introduced into the end-product armamentarium. Unfortunately, many chemicals have been introduced without adequate toxicologic testing. In fact, "generally recognized as safe until proved hazardous" seems to be the prevailing attitude, rather than "recognized as hazardous until proved safe." This is particularly apropos for attempts to

set safe standards or remove hazardous agents from environmental and human contact—vinyl chloride monomer, heptachlor, chlordane, dieldrin (and congeners), chlordecone, asbestos, heavy metals, and polychlorinated or brominated biphenyls are examples.

Although the most serious cases of human exposure to TCE are limited to a relatively small industrial population, the general population has encountered and may still encounter TCE in decaffeinated coffee, some spice extracts, and household cleaning agents. The current maximum allowable concentrations of TCE permitted by the FDA are 10 ppm in instant coffee, 25 ppm in ground coffee, and 30 ppm in spice extracts (FDA, 1974). In response to the announcement by the NCI that TCE may be carcinogenic, General Foods Corporation, producers of Sanka and Brim brands of decaffeinated coffee, is now using methylene chloride for caffeine extraction, for which the FDA has established a 10-ppm tolerance. However, substitutes for TCE should be scrutinized also by long-term feeding studies.

TABLE 15. Concentrations of TCE in Foodstuffs[a]

Foodstuff	Concentration (μg/kg)
Dairy produce	
Fresh milk	0.3
Cheshire cheese	3
English butter	10
Hens' eggs	0.6
Meat	
English beef (steak)	16
English beef (fat)	12
Pigs' liver	22
Oils and fats	
Margarine	6
Olive oil (Spanish)	9
Cod liver oil	19
Vegetable cooking oil	7
Beverages	
Canned fruit drink	5
Light ale	0.7
Instant coffee	4
Tea (packet)	60
Wine (Yugoslav)	0.02
Fruits and vegetables	
Potatoes (NW England)	3
Apples	5
Pears	4
Grains	
Fresh bread	7

[a]McConnell et al., 1975.

TCE residues may be present in foods as a result of environmental contamination. McConnell et al. (1975) surveyed a variety of everyday foodstuffs for TCE content and obtained the results displayed in Table 15. Tea, meat products, and butter contained significant quantities of TCE.

Environmental contamination with TCE arises primarily as a result of losses during degreasing operations. While most solvents are recovered for further use, the need for constant production indicates the extent of loss. McConnell et al. (1975) reported that derivatives of methane, ethane, and ethylene are widely distributed in the atmosphere at a concentration on the order of 1 ppb. Water contamination is also widespread, but minute. The mean half-lives of chlorinated ethylenes are in the range of 6–12 wk; degradation products are simple inorganic species such as CO_2, water, and chloride ions. Further, no evidence indicates persistence of chlorinated ethylenes in the environment or accumulation in the food chains.

RECOMMENDED STANDARDS FOR OCCUPATIONAL EXPOSURE

The NIOSH (1973) recommended standard for employees exposed to TCE is stated as follows:

> Section 1—*Environmental (Workplace air)*
>
> (a) Concentration
>
> (1) Occupational exposure to trichloroethylene shall be controlled so that workers will not be exposed to trichloroethylene at a concentration in excess of 100 ppm determined as a time-weighted average (TWA) exposure for an 8-hour workday, as measured by a minimum sampling time of 10 minutes.
>
> (2) No worker shall be exposed to a peak concentration of trichloroethylene in excess of 150 ppm, as measured by a maximum sampling time of 10 minutes.

The Occupational Safety and Health Administration has given notice of the setting of a new standard for TCE exposure. The proposed new standard retains the current 8-hr time-weighted average limit for exposure to airborne concentrations of TCE at 100 ppm but reduces the ceiling limit from 200 to 150 ppm (*Fed. Regist.*, 1975). In addition, the acceptable maximum peak of 300 ppm for 5 min in any 2-hr period would be deleted. Moreover, the proposed standard would add detailed requirements on measuring employee exposures, methods of compliance, respiratory protections, hazardous and emergency situations, protective equipment, housekeeping, training, signs and labels, medical surveillance, and record keeping (*Fed. Regist.*, 1975).

CONCLUSIONS

Trichloroethylene is a useful but potentially hazardous industrial chemical. Extensive searching of the massive literature base (~1,700 references) has revealed gaps and contradictions in the state of the knowledge. Renewed interest in TCE centers around recent experimental data, which implicate TCE as a cause of hepatocellular carcinoma in mice.

The toxic action of TCE on the nervous system, heart, liver, and kidneys still awaits further elucidation. Epidemiological data need to be collected to establish whether any relationship exists between TCE and liver cancer in humans. In the meantime, attempting to minimize worker exposure to all hazardous chemicals including TCE and providing comprehensive medical supervision of workers are worthy and necessary goals. Some suggest lowering the present threshold limit value.

Current awareness of the vast array of hazardous and potentially hazardous substances to which we are exposed has focused attention on various compounds, including TCE. Apparently, lessons taught us by asbestos, vinyl chloride, and chlordecone are neither easily learned nor remembered. No sooner is one chemical spotlighted and removed from use than another of equally unknown hazard often becomes a less-than-completely-tested surrogate. The substitution of methylene chloride and perchloroethylene for TCE is a case in point.

REFERENCES

Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D. and Irish, D. D. 1951. Vapor toxicity of trichloroethylene determined by experiments on laboratory animals. *Arch. Ind. Hyg. Occup. Med.* 4:469–481.

Alexander, M. 1948. Injury to health due to trichloroethylene exposure. *Dtsch. Gesundheitsw.* 3:237–239.

Austern, B. M., Dobbs, R. A. and Cohen, J. M. 1975. Gas-chromatographic determination of selected organic compounds added to waste water. *Environ. Sci. Technol.* 9(6):588–590.

Aviado, D. M. 1972. *Krantz and Carr's pharmacologic principles of medical practice*, 8th ed., pp. 251 and 1241. Baltimore: Williams & Wilkins.

Baerg, R. D. and Kimberg, D. V. 1970. Centrilobular hepatic necrosis and acute renal failure in "solvent sniffers." *Ann. Intern. Med.* 73(5):713–720.

Baettig, K. 1964. Comparison of the effects of trichloroethylene with the effects of drugs on exploratory behavior in the rat. *Int. Congr. Occup. Health, 14th, Madrid, 1963.* 2:887–889.

Baettig, K. and Grandjean, E. 1963. Chronic effects of trichloroethylene on rat behavior. *Arch. Environ. Health* 7(6):694–699.

Baker, A. B. 1958. The nervous system in trichloroethylene (poisoning), an experimental study. *J. Neuropathol. Exp. Neurol.* 17:649–655.

Bartonicek, V. and Soucek, B. 1959. Metabolism of trichloroethylene in rabbits. *Arch. Gewerbepathol. Gewerbehyg.* 17:283–293.

Bell, A. 1951. Death from trichloroethylene in a drycleaning establishment. *N.Z. J. Med.* 50:119–126.

Braddock, J. 1976. Production descriptions gleaned from the *Clinical toxicology of commercial products* data base. Personal communication.

Buchet, J. P., Lauwerys, R., Roels, H., Defeld, J. M. and Bauer, H. 1974. Gas-chromatographic

determination of the urinary metabolites of trichloroethylene. Trichloroacetic acid and trichloroethanol. *Arch. Mal. Prof.* 35(3):395–402.

Bvington, K. H. and Leibman, K. C. 1965. Metabolism of trichloroethylene in liver microsomes. II. Identification of the reaction product as chloral hydrate. *Mol. Pharmacol.* 1(3):247–254.

Bzdega, J. 1974. Field determination of trichloroethylene vapors by a continuous method. *Med. Pr.* 25(4):385–387.

Cagianelli, M. A., Menchini, G., Menchini, G. F. and Bianchi, F. 1965. Histological and humoral aspects of chronic experimental trichloroethylene intoxication. *Boll. Soc. Med.-Chir. Pisa* 33(4):558–570.

Capellini, A. and Grisler, R. 1958. Liver function in workers constantly exposed to trichloroethylene. *Med. Lav.* 49:167–172.

Castello, G. 1971. Analysis of traces of contaminants in breathing oxygen with a helium detector and an electron capture detector. *J. Chromatogr.* 58(1):117–125.

Chem. Eng. News. Sept. 15, 1969. Trichloroethylene: Not to blame in smog, p. 19.

Chem. Eng. News. May 19, 1975. Reactions grow to trichloroethylene alert, pp. 41–43.

Christensen, H. E. and Luginbyhl, T. T., eds. 1975. *Registry of toxic effects of chemical substances*, pp. 295, 314, 510, 534, 536, 538. Rockville, Md.: DHEW, NIOSH.

Cooper, C. V., White, L. D. and Kupel, R. E. 1971. Qualitative detection limits for specific compounds utilizing gas chromatographic fractions, activated charcoal, and a mass spectrometer. *Am. Ind. Hyg. Assoc. J.* 32(6):383–386.

Corbett, T. H. 1972. Anesthetics as a cause of abortion. *Fertil. Steril.* 23:866–869.

Cotter, L. H. 1950. Trichloroethylene poisoning. *Arch. Ind. Hyg. Occup. Med.* 1:319.

Daniel, J. W. 1963. The metabolism of Cl^{36}-labeled trichloroethylene and tetrachloroethylene in the rat. *Biochem. Pharmacol.* 12(8):795–802.

Defalque, R. J. 1961. Pharmacology and toxicology of trichloroethylene. A critical review of the world literature. *Clin. Pharmacol. Ther.* 2(5):665–688.

Deyl, Z. and Effenberger, M. 1958. Potentiometric determination of trichloroethylene in industrial waters. *Voda* 37:90–92.

Doskar, J. and Gabriel, J. 1965. Precision casting process. VII. Hygienic conditions and working protection. *Giesserei Prax.* (18):376–378.

Effenberger, M. and Deyl, Z. 1958. The nephelometric determination of trichloroethylene in industrial wastes. *Sb. Vys. Sk. Chem.-Technol. Praze Oddil Fak. Technol. Paliv Vody* 2(1):225–236.

Fabre, R. and Truhaut, R. 1952. Toxicology of trichloroethylene. II. Results of experimental animal studies. *Br. J. Ind. Med.* 9:39–43.

Farm chemicals handbook. 1976. Willoughby, Ohio: Meister.

FDA (Food and Drug Administration). 1974. *Code of Federal Regulations*, Title 21, 121.1041.

Fed. Regist. 1975. Occupational exposure to trichloroethylene. *Fed. Regist.* 40(203):49032–49045.

Fonzi, S., Focardi, L. and Raddi, R. 1967. Trichloroethylene as a hepatotoxic substance. Experimental study in chronic poisoning. *Lav. Um.* 19(Suppl. 12):94–110.

Forssman, S. 1950. Occupational poisoning by trichloroethylene. *Arh. Hig. Rada Toksikol.* 1:257–262.

Gehring, P. J. 1968. Hepatotoxic potency of various chlorinated hydrocarbon vapors relative to their narcotic and lethal potencies in mice. *Toxicol. Appl. Pharmacol.* 13(3):287–298.

Gibitz, H. J. and Plochl, E. 1973. Oral trichloroethylene intoxication in a four-and-one-half-year-old boy. *Arch. Toxikol.* 31(1):13–18.

Grandjean, E. 1963. The effects of short exposures to trichloroethylene on swimming performances and motor activity of rats. *Am. Ind. Hyg. Assoc. J.* 24(4):376–379.

Grandjean, E., Munchinger, R., Turrian, V., Haas, P. A., Knoepfel, H. K. and Rosenmund, H. 1955. Investigations into the effects of exposure to trichloroethylene in mechanical engineering. *Br. J. Ind. Med.* 12:131–142.

Gradovac-Leposavic, Lj., Milosavljevic, Z. and Ilic, V. 1964. Liver function in workers exposed to trichloroethylene. *Arh. Hig. Rada Toksikol.* 15(1):93–97.

Hager, G. 1926. Duren disease and its cause. *Landwirtsch. Vers. Stn.* 104(3/4):221–226.

Heim, F., Estler, C. J., Ammon, H. P. T. and Haehnel, U. 1966. Liver metabolites of white mice during acute trichloroethylene poisoning. *Med. Pharmacol. Exp.* 15(2):116–122.

Hiatt, V. and Huff, J. E. 1975. The environmental impact of cadmium: An Overview. *Int. J. Environ. Stud.* 7:277–285.

Hickish, D. E., Smith, J. H. and Bedford, J. 1956. Exposure to trichloroethylene during an industrial degreasing operation. *Br. J. Ind. Med.* 13:290–293.

Huff, J. E. 1971. New evidence on the old problems of trichloroethylene. *Ind. Med. Surg.* 40(8):25–33.

IARC (International Agency for Research on Cancer). 1976. *Monograph on the evaluation of carcinogenic risk of chemicals to man. Trichloroethylene* (draft copy). Lyon, France.

Ikeda, T., Nagano, C. and Okada, A. 1969. Hepatotoxic effect of trichloroethylene and perchloroethylene in the rat and mouse. *Igaku To Seibutsugaku* 79(3):123–129.

Ikeda, M., Ohtsuji, H., Kawai, H. and Kuniyoshi, M. 1971. Excretion kinetics of urinary metabolites in a patient addicted to trichloroethylene. *Br. J. Ind. Med.* 28(2):203–206.

Irish, D. D. 1963. Halogenated hydrocarbons: 1. Aliphatic. In *Industrial hygiene and toxicology*, 2d ed., ed. F. A. Patty, vol. 2, *Toxicology*, eds. D. W. Fassett and D. D. Irish, pp. 1309–1313. New York: Interscience.

Jaeger, R. J., Conolly, R. B. and Murphy, S. D. 1974. Effect of 18 hour fast and glutathione depletion on 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats. *Exp. Mol. Pathol.* 20:187–198.

James, W. R. L. 1963. Fatal addiction to trichloroethylene. *Br. J. Ind. Med.* 20:47–49.

Jans, R. 1972. Residues of chlorinated solvents in decaffeinated coffee. *Ann. Falsif. Expert. Chim.* 65(100):157–209.

Jindrichova, J. 1970. Poisoning by trichloroethylene in the production of brake linings. *Prac. Lek.* 22(3):103–107.

Jones, W. M., Margolis, G. and Stephen, C. R. 1958. Hepatotoxicity of inhalation anesthetic drugs. *Anesthesiology* 19:715–723.

Kalashnikova, V. P., Vissarionova, V. Ya., Bondarev, G. I., Skirko, B. K. and Karantirova, O. V. 1974. Influence of different diets on the cause of chronic experimental trichloroethylene poisoning. *Vopr. Pitan.* 6:43–47.

Kirk, R. E. and Othmer, D. F., eds. 1963. *Encyclopedia of chemical technology*, 2d ed., vol. 5, pp. 183–915. New York: Interscience.

Kiseleva, A. F. and Korolenko, A. M. 1971. Histoenzymic changes in liver and kidneys during the experimental effect of anesthetic doses of fluorothan and trylen. *Eksp. Khir. Anesteziol.* 16(5):81–84.

Kleinfeld, M. and Tabershaw, I. R. 1954. Trichloroethylene toxicity. Report of five fatal cases. *Arch. Ind. Hyg. Occup. Med.* 10:134–141.

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

Leibman, K. C. 1965. Metabolism of trichloroethylene in liver microsomes. I. Characteristics of the reaction. *Mol. Pharmacol.* 1(3):239–246.

Lilis, R., Stanescu, D., Muica, N. and Roventa, A. 1969. Chronic effects of trichloroethylene exposure. *Med. Lav.* 60(10):595–601.

Longley, E. O. and Jones, R. 1963. Acute trichloroethylene narcosis. *Arch. Environ. Health* 7(2):249–252.

MacKay, F. J. and Cooper, J. R. 1962. As reported in Byington and Leibman, 1965.

Maloof, C. C. 1949. Burns of the skin produced by trichloroethylene vapors at room temperature. *J. Ind. Hyg. Toxicol.* 31:295–296.

Marshall, E. K., Jr. and Owens, A. H., Jr. 1954. As reported in Byington and Leibman, 1965.

Masoero, V. and Lavarino, A. 1955. Acute toxicosis from trichloroethylene. *Patol. Sper.* 43:124–129.

Mazza, V. and Cascini, F. 1956. Hygiene in defatting with trichloroethylene in a metal mechanical industry. *Folia Med. (Napoli)* 39:979–988.

McConnell, G., Ferguson, D. M. and Pearson, C. R. 1975. Chlorinated hydrocarbons and the environment. *Endeavour* 34:13–18.

McKinney, L. L., Picken, J. C., Jr., Weakley, F. B., Eldridge, A. C., Campbell, R. E., Cowan, J. E. and Beister, H. E. 1959. Possible toxic factor of trichloroethylene extracted soybean oil meal. *J. Am. Chem. Soc.* 81:909–915.

Med. World News. July 28, 1975. Carcinogens, ubiquitous TCE, p. 8.

Migdal, A., Graczyk, E., Obodecka, Z. and Piesiak, K. 1971. Biochemical and neurologic studies in acute oral poisoning with trichloroethylene (Tri). *Wiad. Lek.* 24(17):1669–1673.

Morgan, D. J. and Duxbury, G. 1965. The determination of chlorinated hydrocarbons in the atmosphere by activation analysis. *Ann. Occup. Hyg.* 8(3):253–256.

Mosinger, M. and Fiorentini, H. 1955. Reactions of the liver, kidneys, nervous system, and spleen to experimental trichloroethylene intoxication in the cat. *C.R. Soc. Biol. (Paris)* 149:150–152.

Muller, G., Spassovski, M. and Henschler, D. 1974. Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. *Arch. Toxicol.* 32:283–295.

Muller, G., Spassovski, M. and Henschler, D. 1975. Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. *Arch. Toxicol.* 33:173–189.

Musclow, C. E. and Awen, C. F. 1971. Glue sniffing: Report of a fatal case. *Can. Med. Assoc. J.* 104:315–319.

Nakaaki, K., Onishi, N., Hiroyasu, I., Kimotsuki, K. and Fukabori, S. 1973. Experimental study on the effect of exposure to trichloroethylene in man. *Rodo Kagaku* 49(8):499–563.

National Clearinghouse for Poison Control Centers. 1967. Trichloroethylene congener card. No. 82. DHEW-PHS. Bethesda, Md.

NCI (National Cancer Institute). 1976. *Carcinogenesis bioassay of trichloroethylene,* NCI Carcinogen. Tech. Rep. Ser. No. 2, NCI-CG-TR-2, DHEW Publ. No. (NIH)76-802.

NIOSH (National Institute for Occupational Safety and Health). 1973. *Criteria for a recommended standard: Occupational exposure to trichloroethylene.* Washington, D.C.: Government Printing Office.

Nomura, S. 1962. Health hazards in workers exposed to trichloroethylene vapor. I. Trichloroethylene poisoning in an electroplating plant. *Kumamoto Med. J.* 15:29–37.

Norton, T. R. 1975. Metabolism of toxic substances. In *Toxicology. The basic science of poisons,* eds. L. J. Casarett and J. Doull, pp. 45–132. New York: Macmillan.

Nowill, W. K., Stephen, C. R. and Margolis, G. 1954. The chronic toxicity of trichloroethylene. *Anesthesiology* 15:462–465.

O'Connor, W. A. 1954. A case of trichloroethylene addiction. *Br. Med. J.* 2:451–452.

Osol, A. and Pratt, R., eds. 1973. *United States dispensatory,* 27th ed., pp. 1209–1210. Philadelphia: Lippincott.

Plaa, G. L. and Larson, R. E. 1965. Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. *Toxicol. Appl. Pharmacol.* 7(1):37–44.

Plessner, W. 1915. Trigeminal disease as a result of trichloroethylene poisoning. *Neurol. Zentralbl.* 34:916–917.

Powell, J. F. 1945. Trichloroethylene: absorption, elimination, and metabolism. *Br. J. Ind. Med.* 2:142–145.

Powell, J. F. 1947. The solubility or distribution coefficient of trichloroethylene in water, whole blood, and plasma. *Br. J. Ind. Med.* 4:233–236.

Prendergast, J. A., Jones, R. A., Jenkins, L. J., Jr. and Siegel, J. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. *Toxicol. Appl. Pharmacol.* 10(2):270–289.

Pritchard, W. R., Davis, O. S., Taylor, D. B., Doyle, L. P. 1956. Aplastic anemia in chickens fed trichloroethylene extracted soybean meal and failure of this dietary meal to suppress the development of experimental lymphomatosis. *Am. J. Vet. Res.* 17:771–777.

Prodan, L., Suciu, I., Pislaru, V., Ilea, E. and Pascu, L. 1975. Experimental acute toxicity of vinyl chloride (monochloroethene). *Ann. N.Y. Acad. Sci.* 246:154–158.

Rickles, N. K. 1945. Cerebral intoxication the result of trichloroethylene. *Northwest Med.* 44(9):286–287.

Roche, M. L. 1953. Respiratory poisoning from phosgene formed from trichloroethylene. *Arch. Mal. Prof.* 14:66–67.

Rudali, G. 1967. Potential carcinogenic hazards from drugs. Evaluation of risks. *UICC Monog. Ser.* 7:138–143.

Rundles, W. 1958. Toxic protein derivatives causing aplastic anemia. A review. *Blood* 13(9):899–903.

Sagawa, K., Nishitani, H., Kawai, H., Kuge, Y. and Ikeda, M. 1973. Transverse lesion of spinal cord after accidental exposure to trichloroethylene. *Int. Arch. Arbeitsmed.* 31(4):257–264.

Salvini, M., Binaschi, S. and Riva, M. 1971. Evaluation of the psychophysiological functions in humans exposed to trichloroethylene. *Br. J. Ind. Med.* 28(3):293–295.

Scansetti, G., Rubino, G. F. and Trompeo, G. 1959. As reported in Byington and Leibman, 1965.

Schiøtz, E. H. 1938. Trichloroethylene poisoning with particular reference to chemical cleaning. *Nord. Med. Tidskr.* 15:808–813.

Schirren, J. M. 1971. Skin lesions caused by trichloroethylene in a metal working plant. *Berufsdermatosen* 19(5):240–254.

Seifter, J. 1944. Liver injury in dogs exposed to trichloroethylene. *J. Ind. Hyg. Toxicol.* 26:250–253.

Siegel, J., Jones, R. A., Coon, R. A. and Lyon, J. P. 1971. Effects on experimental animals of acute, repeated, and continuous inhalation exposure to dichloroacetylene mixtures. *Toxicol. Appl. Pharmacol.* 18:168–174.

Smith, G. F. 1966. Trichloroethylene. A review. *Br. J. Ind. Med.* 23(4):249–262.

Soucek, B. and Vlachova, D. 1960. Excretion of trichloroethylene metabolites in human urine. *Br. J. Ind. Med.* 17:60–64.

Spector, W. S., ed. 1956. *Handbook of toxicology*, vol. 1. Philadelphia: Saunders.

Stack, V. T., Jr., Forrest, D. E. and Wahl, K. K. 1961. Determination of trichloroethylene in air. *Am. Ind. Hyg. Assoc. J.* 22:184–186.

Stecher, P. G., ed. 1968. *The Merck index*, 8th ed., p. 1069. Rahway, N.J.: Merck.

Stewart, R. D. and Dodd, H. C. 1964. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. *Am. Ind. Hyg. Assoc. J.* 25(5):439–446.

Stewart, R. D., Dodd, H. C., Gay, H. H. and Erley, D. S. 1970. Experimental human exposure to trichloroethylene. *Arch. Environ. Health* 20(1):64–71.

Stewart, R. D., Hake, C. L. and Peterson, J. E. 1974a. Use of breath analysis to monitor trichloroethylene exposures. *Arch. Environ. Health* 29(1):6–13.

Stewart, R. D., Hake, C. L. and Peterson, J. E. 1974b. "Degreasers' flush": Dermal response to trichloroethylene and ethanol. *Arch. Environ. Health* 29:1–5.

Swinyard, E. A. 1975. *Remington's pharmaceutical sciences*, 15th ed., p. 979. Easton, Pa.: Mack.

Szulc-Kuberska, J. 1972. Chronic industrial trichloroethylene poisoning. *Folia Med. Lodz.* 16:67–90.

Takamatso, M. 1962. Health hazards in workers exposed to trichloroethylene vapor. II. Exposure to trichloroethylene during degreasing operation in a machine factory. *Kumamoto Med. J.* 15:43–54.

Teare, D. 1948. A case of poisoning by ethylene trichloride. *Br. Med. J.* 116(76):559.

Vallee, C. and Leclercq, J. 1935. Intoxication by trichloroethylene. *Ann. Med. Leg. Criminol.* 15:10–12.

Van Duuren, B. L. 1975. Possible mechanism of carcinogenic action of vinyl chloride. *Ann. N.Y. Acad. Sci.* 246:258–267.

Verne, J., Ceccaldi, P. F., Hebert, S. and Roux, J. M. 1959. Hepatic steatosis during intoxication by volatile organic compounds. IV. Biochemistry and histochemistry of fatty livers produced by trichloroethylene poisoning. *Pathol. Biol. Semaine Hop.* 7:2311–2316.

Vignoli, L., Jouglard, J., Vignoli, P. and Terrasson de Fougeres, P. 1970. Acute intoxication by trichloroethylene ingestion. Metabolism of this poison. *Med. Leg. Assicur.* 18(3-4):789–798.

Vyskocil, J. 1953. Effect of trichloroethylene on the central nervous system. *Lek. Listy* 8:269–273.

Vyskocil, J. and Polak, B. 1963. Acute trichloroethylene poisoning. *Vnitr. Lek.* 9(9):860–863.

Waters, E. M. and Black, S. A. 1976. *Trichloroethylene: II. An abstracted literature collection, 1907–1976.* Report ORNL/TIRC-76/2. Springfield, Va.: National Technical Information Service.

Wiecko, W. 1966. Oral poisoning with trichloroethylene. *Wiad. Lek.* 19:1117–1118.

Wirtschafter, Z. T. and Cronyn, M. W. 1964. Relative hepatotoxicity. Pentane, trichloroethylene, benzene, carbon tetrachloride. *Arch. Environ. Health* 9(2):180–185.

Whitteridge, D. and Bulbring, E. 1944. Changes in activity of pulmonary receptors in anesthesia and their influence on respiratory behavior. *J. Pharmacol.* 81:340–351.

Yamaga, S. and Saruta, K. 1953. A case of trichloroethylene poisoning. *J. Sci. Labour* 29:395–399.

Received June 1, 1976
Accepted September 21, 1976