III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

NIOSH has estimated that approximately 200,000 workers are exposed to trichloroethylene in the United States. Almost all of the trichloroethylene produced in the United States is used as a liquid or vapor degreasing solvent by metal fabricating industries, such as automotive, aircraft, and aerospace industries. Specific uses of trichloroethylene range in quantity and complexity from small, "bucket" operations in which the solvent is used in small quantities to clean tools or small parts to the large mass production degreasing units provided with sophisticated engineering controls.

According to Kirk and Othmer, [1] trichloroethylene was first prepared in 1864 by Fischer in the course of experiments on the reduction of hexachloroethane with hydrogen. [1] It did not receive much attention as a potential chemical product until the early 1900's at which time methods for the commercial manufacture of the material became available. Trichloroethylene was first synthesized commercially in the United States [1] in 1935 but had been manufactured in Europe [2] since 1910.

Trichloroethylene is used widely in both large and small industries. The compound is available under a variety of common and/or trade names (see Table X-1). [3,4] Because of the great number of abbreviations and common trade names for trichloroethylene and the lack of general agreement on another name or abbreviation, no abbreviation or synonym will be used in this document.

Prior to 1967, 85% of the U.S. production of trichloroethylene was prepared by the chlorination of acetylene to form 1,1,2,2-tetrachloroethane and by the dehydrochlorination of the latter to yield trichloroethylene. [5] Trichloroethylene is now produced mainly (85%) via the chlorination or oxyhydrochlorination of ethylene with the intermediate formation of ethylene dichloride which is then converted with further chlorination to trichloroethylene.

In the United States trichloroethylene is used primarily (approximately 90% of total consumption) as a solvent in vapor degreasing operations. [5] Approximately 5% of the total consumption of trichloroethylene is used as a dry-cleaning solvent for fabrics or as an extractive solvent, particularly in processes which require the selective extraction of medicines and foods. The removal of caffeine from coffee is an example. The remaining 5% finds application in a variety of operations which utilize trichloroethylene either for its solvent properties or as a chemical intermediate. These applications include the production of pesticides, waxes, gums, resins, tars, paints, varnishes, and specific chemicals such as chloroacetic acid.

Trichloroethylene is a clear, colorless, noncorrosive, nonflammable liquid with the "sweet" odor characteristic of the chlorinated hydrocarbons. Its physical properties are listed in Table X-2. [1,3,6-8]

Chemically, trichloroethylene is not dangerously reactive; however, it does slowly decompose when exposed to light and water vapor to form hydrogen chloride gas and, at elevated temperatures,

chlorine. [1,5,6] Trichloroethylene may react with strong alkalis to form dichloroacetylene (very toxic) and explosive mixtures. [9] In addition, trichloroethylene may decompose on contact with certain metals, eg, aluminum, with open flames or with ultraviolet radiation, eg, many welding operations, forming phosgene, and/or hydrogen chloride. [1,6,10] Because of the slight decomposition that is possible with the pure material, commercial grades of trichloroethylene usually contain stabilizers or inhibitors such as triethylamine, triethanolamine, epichlorohydrin or various stearates. [5,11]

Trichloroethylene vapors can easily be controlled in systems which incorporate partial enclosure, temperature control of the vapors, and/or local exhaust ventilation. However, the potential for overexposure of workers to this material exists whenever such controls are not effective and when there is (1) a need for open transfer of the liquid, (2) leakage from process equipment, or (3) maintenance or repair work on equipment or transfer systems containing trichloroethylene.

Early Historical Reports

In the early 1900's limited experimental studies with animals as well as evidence gained from reports of occupational overexposure in Europe had demonstrated the narcotic action of trichloroethylene. [9] Later in the 1930's it was used as a surgical anesthetic [12] and proposed for use as the basis for treatment of various nervous disorders. [13] The first reported evidence of acute overexposure to

trichloroethylene in industrial applications [2] resulted from its use as a grease solvent.

This first report of chronic poisoning from trichloroethylene in industrial situations [2] suggested that the observed effects were more likely due to impurities in the material rather than to trichloroethylene itself. From 1963 to 1967 the common manufacturing process for trichloroethylene [5] produced as an intermediate chemical 1,1,2,2-tetrachloroethane, a substance of very high toxicity. Exposure to trichloroethylene containing relatively small amounts of contaminants, such as 1,1,2,2-tetrachloroethane, could result in the development of adverse effects much different from those resulting from exposure to pure trichloroethylene. Trichloroethylene produced from acetylene accounted for 85% of total production between 1963 and 1967, 65% in 1968, 55% in 1969, and 51% in 1970-1971. In 1972 only 15% of operating capacity was based on acetylene. [5] Presently, 85% of trichloroethylene is produced from ethylene; ethylene dichloride is produced via chlorination or oxyhydrochlorination of ethylene and trichloroethylene is produced by chlorination and dehydrochlorinating the ethylene dichloride. Process control techniques available today allow manufacture of a trichloroethylene product of very high purity. This was not necessarily true of the trichloroethylene products to which early reports of overexposure refer. [9]

The studies of the metabolic formation of chloral hydrate and trichloroethanol, [14] the discovery that trichloroacetic acid was excreted in the urine of persons exposed to trichloroethylene [15] and

the subsequent adaptation of the Fujiwara reaction for the quantitative analysis of biological samples [16] brought about an era of intensive studies to develop a cause-and-effect relationship for exposures to trichloroethylene.

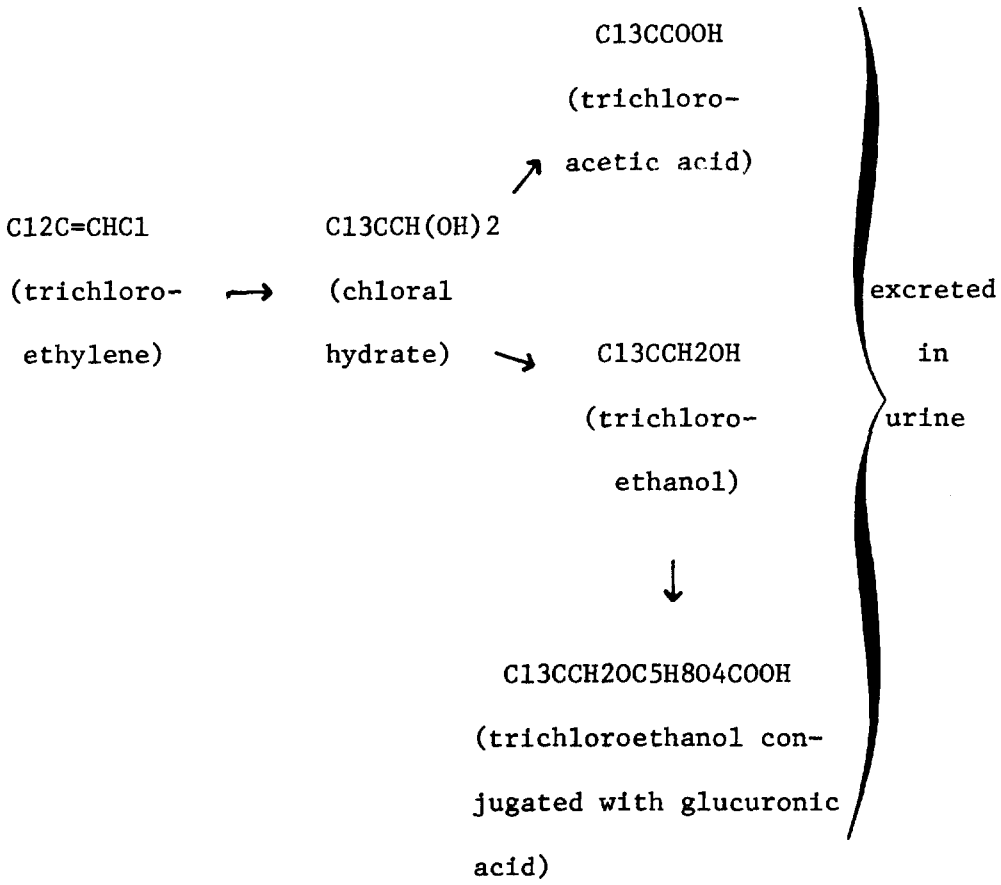
Effects on Humans

(a) Absorption, Metabolism, Distribution, and Elimination

Studies cited below indicate that trichloroethylene is absorbed rapidly by the lungs following inhalation and eliminated to only a small degree by exhalation. Barrett and Johnston [15] reported that the steam distillate of urine from human subjects exposed to trichloroethylene indicated the presence of a metabolite containing three chlorine atoms on a single carbon atom (modified Fujiwara reaction). Further investigation with dogs [16] led to the conclusion that the metabolite was trichloroacetic acid. These studies indicated that the trichloroacetic acid excreted by test animals (dogs) anesthetized with trichloroethylene amounted to 5-8 % of the absorbed trichloroethylene. Powell [17] confirmed the presence of trichloroacetic acid in urine as a metabolite of trichloroethylene in anesthetized humans. Analysis of expired air and blood samples indicated that very little unchanged trichloroethylene was present.

Butler [14] reported finding trichloroethanol, both free and conjugated with glucuronic acid, in large amounts in the urine of dogs exposed by way of inhalation to trichloroethylene. These studies indicated that trichloroethanol was produced in greater amounts than trichloroacetic acid. The author concluded that the metabolism of

trichloroethylene involves initial conversion to chloral hydrate with rapid metabolic conversion to either trichloroethanol or trichloroacetic acid.



The presence of other minor metabolites, including chloroform and monochloroacetic acid, has been reported by Soucek and Vlachova [18].

Attempts have been made by several investigators to correlate the concentrations of the various metabolites of trichloroethylene with either the degree of exposure (environmental concentrations) or the occurrence of symptoms of overexposure. [18-31]

In 1951 Ahlmark and Forssman [19] showed that the amount of trichloroacetic acid excreted in urine of workers exposed to trichloroethylene did not vary significantly with the hour of the day or amount of urine but only with the amount of exposure and the time after exposure.

Soucek and Vlachova [18] in 1960 showed that at concentrations up to 150 ppm exposed persons retained between 58 and 70% (average, 64) of the inhaled vapor. Excretion of monochloroacetic acid began within a few minutes of inhalation and was maximal at the end of exposure decreasing slowly for about 48 to 168 hours (average 112, with a biological half-life of about 15 hours). Monochloroacetic acid accounted for about 4% of the retained trichloroethylene. Excretion of trichloroacetate began shortly after the initial inhalation of trichloroethylene in a slowly rising concentration, maximal at 24 to 48 hours and diminishing thereafter as the sum of 2 exponential rates, the total excretion being equivalent to 10 to 30% (average, 19) of retained vapor. Excretion continued for 312 to 520 hours (average, 387). They noted that the daily excretion of trichloroacetic acid reached a maximum at 1:00 pm daily, irrespective of the quantity of urine excreted. Excretion of trichloroethanol began soon after the initial inhalation and rose rapidly to its maximum a few hours after the end of exposure; the total excreted was equivalent to 32 to 59% (average, 50) of the retained trichloroethylene. Excretion of trichloroethanol also appeared to fall as the sum of two exponential rates, the first phase lasting 3 or 4 days, the second lasting 7 to 9

days. Trichloroethanol excretion did not exhibit fluctuations related to time of day. In these studies, the total amount of metabolites excreted amounted to 43% to 100% (average, 73) of the trichloroethylene absorbed and the three metabolites, monochloroacetic acid, trichloroacetic acid, and trichloroethanol were found in the ratios of 1:5:12, respectively.

Bartonicek, [20] using eight resting volunteers exposed to a concentration of 1 milligram per liter (186 ppm) of trichloroethylene in five-hour periods, found that they excreted an average of 45.4% of the retained trichloroethylene as trichloroethanol and 31.9% as trichloroacetic acid, thus accounting for 77.3% of the retained trichloroethylene. Expired air analyses were performed to estimate retained trichloroethylene. Three days after exposure, the average concentration of trichloroacetic acid was 2.4 milligrams per 100 milliliters of blood plasma and 0.5 milligram per 100 milliliters red blood cells. These studies indicated that a small amount of trichloroacetic acid was excreted in sweat and in feces and, on the third day after exposure, 0.23 milligram per 100 milliliters of saliva was measured. They showed that 58% (a range of 51 to 64) of trichloroethylene inhaled at a concentration of 186 ppm was retained. Trichloroethanol excretion was maximal at the first post-exposure test (within the first 24 hours after exposure) and decreased exponentially while the rate of trichloroacetic acid excretion reached its peak 3 days after exposure and decreased more gradually for 18 days.

Bardodej and Vyskocil [21] reported that they could not correlate the levels of urinary excretion of metabolites to measured concentrations of trichloroethylene in the environment.

Kylin et al [22] showed that after exposure to 1,000 ppm loss of trichloroethylene from the lungs and the blood occurs at approximately the same pace for several hours. Frant and Westendorp [23] calculated that a person subjected to sustained exposure for several days of 100 ppm trichloroethylene in air will excrete 200 milligrams of trichloroacetate per liter of urine. Friberg et al [24] reported that 3 persons exposed for 7 hours daily for 1 week to 100 to 150 ppm trichloroethylene excreted 250 to 300 milligrams trichloroacetic acid per liter of urine during the latter days of the study.

Ogata et al [25] conducted a detailed study of trichloroethylene metabolism by exposing volunteers to trichloroethylene in 2 experiments. In the first experiment, volunteers were exposed to 170 ppm trichloroethylene for 3 hours in the morning and 4 hours in the afternoon following a one-hour break. In the second experiment, volunteers were exposed to 170 ppm trichloroethylene only for 3 hours in the morning. In both experiments the concentration of trichloroethanol in the urine reached a maximum value shortly after exposure ceased and decreased exponentially, although it was still detectable after 100 hours post-exposure. Trichloroacetic acid did not reach maximal values in the volunteers until approximately 48 hours after exposure to trichloroethylene ceased.

Ahlmark and Forssman, [19] in a study of 122 workers, related trichloroacetic acid excretion to a medical survey made independent of the biological excretory levels. Those workers with trichloroacetic acid excretion up to 20 milligrams per liter of urine reported no symptoms of trichloroethylene intoxication. Fifty percent of those excreting between 40 and 75 milligrams trichloroacetic acid per liter reported symptoms of abnormal fatigue, increased need of sleep, diffuse gastric symptoms, irritability, headache, and intolerance of alcohol. Many of the symptoms occurred among those excreting over 100 milligrams per liter and symptoms were observed in all those excreting trichloroacetic acid in excess of 300 milligrams per liter of urine. Absence from work because of illness was frequently reported for those excreting over 200 milligrams per liter of urinary trichloroacetic acid.

Andersson [26] stated in her study that no symptoms occurred in workers excreting less than 20 milligrams trichloroacetic acid per liter but most workers excreting in excess of 75 milligrams trichloroacetic acid per liter of urine exhibited symptoms of trichloroethylene intoxication. In the study reported by Grandjean et al [27] workers appeared to excrete about 8% of inhaled trichloroethylene as trichloroacetic acid in a ratio they stated as 3:1 (milligram per liter trichloroacetic acid in urine to ppm trichloroethylene in air). The ratio of trichloroacetic acid to trichloroethylene was greater (6:1) in younger persons and less (2:1) in older workers.

Ikeda et al [28] reported a deviation of the urinary excretion levels of trichloroacetic acid by 51 male workers from a linear relationship with the atmospheric concentration of trichloroethylene above 50 ppm, measured with detector tubes. Further, the trichloroacetic acid excretion showed a relative decrease with respect to the total trichloro compounds measured in the urine of workers exposed to concentrations above 70 ppm. The authors suggest that this finding may be of toxicological importance as the other metabolite (trichloroethanol) is much more neuro- and cardiotoxic than trichloroethylene.

Stewart et al [29] presented the results of a study in which attempts were made to interpret the significance of trichloroethylene in expired air collected at various times after exposure of volunteers to known concentrations of trichloroethylene. They exposed a group of seven subjects to a time-weighted average concentration of trichloroethylene of 265 ppm (range, 160 to 400 ppm) for 83 minutes. In a second experiment the time-weighted average concentration was 211 ppm (range of 172 to 332 ppm) for 190 minutes. Trichloroethylene was detectable in the expired air for more than 5 hours after exposures ceased. Results of this study, as well as those of a later investigation (1970), [30] indicated that the techniques of analyzing expired air for trichloroethylene show promise for evaluation of trichloroethylene exposures.

Kimmerle and Eben [31] exposed 3 males and 1 female, aged 20 to 30 years, to a trichloroethylene concentration of 48 plus or minus 3

ppm four hours a day on five consecutive days. No difference was found between the male and female volunteers with respect to the trichloroethylene concentration in the blood and its elimination in the expired breath. The authors reported higher concentrations of trichloroethylene in the expired breath two and three hours after exposure on the fifth day of exposure as compared with the values on the first day.

(b) Effects on the Nervous System

The first extensive medical study was that of Stuber [32] who reviewed a total of 284 cases of trichloroethylene poisoning, including 26 fatalities, which had occurred in European industrial operations. Stuber reported that the toxic action of trichloroethylene involved primarily the central nervous system although apparent effects were also observed in the gastrointestinal and circulatory systems. Adverse effects on the kidney were rare and injury to the liver was not observed in any case. The outstanding characteristics of trichloroethylene overexposure included headache, dizziness, vertigo, tremors, nausea and vomiting, sleepiness, fatigue, a feeling and appearance of light-headedness or drunkenness increasing to unconsciousness and, in some cases, to death. In addition to these consistent general symptoms, Plessner [2] noted a specific paralysis of the trigeminal nerve, an observation also reported by Persson [33]. These observations led to the early use of trichloroethylene in the treatment of trigeminal neuralgia (tic douloureux). Krantz et al [34] considered that trichloroethylene was pharmacologically active as a

depressant of all nervous tissue rather than because of a specific action on the trigeminal nerve.

Boulton and Sweet [35] reported that trigeminal palsies occurring in 24 persons after use of trichloroethylene as an anesthetic were considered to have resulted from inhalation of dichloroacetylene or phosgene or both, which the authors concluded could have resulted from the passage of the trichloroethylene through soda lime (designed to eliminate carbon dioxide from the recirculated anesthetic gas) and the subsequent reaction with the alkali to produce dichloroacetylene.

The first report of deaths resulting from acute overexposure to trichloroethylene in the United States summarized five fatal cases among industrial workers. [36] One died of apparent hepatorenal failure after accidental drinking of trichloroethylene. The remaining four workmen had been employed at degreasing operations; all had continued to work in spite of complaints of nausea, drowsiness, dizziness, and vomiting and died suddenly either at work or within a few hours after leaving the plant. The cause of death in these four cases was attributed to ventricular fibrillation. James [37] gave detailed information on a patient who had become addicted to trichloroethylene in the course of his work at an electroplating shop where trichloroethylene was used in a vapor degreaser. In addition to exhibiting symptoms characteristic of central nervous system depressant action, the man lost his sense of smell. He died suddenly some 17 hours after his last known exposure to trichloroethylene. The

cause of death was reported as cardiac arrest attributable to trichloroethylene.

Recently, Tomasini and Sartorelli [38] reported findings on a 54-year old patient following chronic and acute overexposure to trichloroethylene during operation of a dry-cleaning unit. There was a symmetric bilateral VIIIth cranial nerve deafness, slight for lower frequencies, but complete for tones over 1000 cycles per second. There was also evidence of cerebral cortical dysrhythmia and irritation in the electroencephalogram (EEG) as well as gastroduodenal changes. The report did not state whether the hearing improved, only that the individual returned to work.

St. Hill [39] relates the case of a man who died following exposure to trichloroethylene in the course of baling out tanks in a ship's hold. The material being removed from the tanks was condensate from the ship's steam supply, the condenser having been cleaned recently with trichloroethylene. The man worked a total of about twenty hours at this task at the end of which time he complained of headache, dizziness, double vision, and paralysis of the face and neck muscles. The paralysis continued to the point that the man had to be fed intravenously and placed on a mechanical respirator and eventually died several weeks after the incident. Two other men who had worked with the victim experienced similar but less severe symptoms. Weakness and numbness of the face persisted in one of the two men for several months after the exposure. Blurring of vision and diplopia were reported by Maloof [40] in a worker the day after he had been

engaged in retrieving a basket containing metal parts which had dropped into a degreasing tank containing hot trichloroethylene. In addition to symptoms characteristic of effects on the central nervous system and the visual effects, the worker received first and second degree burns to the skin and first degree chemical burns to the eyes which the author ascribed to trichloroethylene vapors from the degreasing tank.

Mitchell and Parsons-Smith [41] reported the case of a man operating a metal degreaser who lost his sense of taste but not smell after one month's exposure to concentrations of trichloroethylene which "occasionally escaped in sufficient quantity to be visible." Two months later he developed trigeminal analgesia and EEG cortical changes which had not cleared up during the two years of the authors' study.

The first published records of chronic occupational overexposures to trichloroethylene in the United States summarized ten individual cases occurring prior to 1944. [42,43] All cases exhibited the general symptoms characteristic of central nervous system disturbances, [43] including one case of total blindness. [42] Duration of exposures ranged from 2.5 hours to 2 years. All workers had been engaged in activities which used trichloroethylene either as a dry-cleaning or degreasing solvent. No quantitative estimations of exposures were provided.

Kunz and Isenschmid [44] cited the case of a worker who removed diamond powder from the rolls of a jewelry mill using

trichloroethylene; an estimated 100 to 300 milliliters of the solvent evaporated directly in front of his face daily. There were increasing changes in vision and color perception leading to blindness within a year after the last known exposure.

McBirney [45] reported that six women working with trichloroethylene to remove small spots of wax remaining on optical lenses reported handling difficulties because of an inability to feel the lenses properly. Subsequent examination indicated a total loss of tactile sense, loss of motion, and inability to grasp objects between the thumb and fingers. Similar findings were reported in the case of a man who operated a degreasing tank which utilized a solvent comprised of 40% trichloroethylene and 60% dichloroethylene. Diplopia was reported in the latter case as well.

With the advent of electroencephalographic (EEG) and psychophysiological testing techniques the question of permanent damage to nerve tissue has been considered more seriously. Fra et al [46] reported a case of chronic poisoning in which electromyographic tests showed peripheral nerves to be intact but some facial muscle changes indicating involvement of the brain stem structures.

Kylin et al [22] measured optokinetic nystagmus to demonstrate the effect of trichloroethylene on the central nervous system. He showed changes in 12 subjects after two hours exposure to 1000 ppm. This test was shown to be a less sensitive indicator of effects of trichloroethylene than of effects of alcohol.

Todd [47] reported the case of a man who had ingested unknown amounts of trichloroethylene. After prolonged unconsciousness and some cyanosis, the result was a temporary paranoid psychosis and a distortion of both vertical and horizontal vision so that persons appeared 12-18 inches high, an effect described as "Lilliputian hallucinations".

(c) Effects on the Cardiovascular System

James [37] reported the case of a man who apparently had become addicted to trichloroethylene vapors in the course of his work at a degreaser. The man's death, which occurred seventeen hours after his last known exposure to trichloroethylene, was due to cardiac arrest attributable to trichloroethylene.

Deaths in four of the five fatal cases of trichloroethylene poisoning reported by Kleinfeld and Tabershaw [36] were attributed to ventricular fibrillation. In all of these cases the men had worked on degreasers and had died suddenly at work or within a few hours after leaving the plant, following complaints of nausea, drowsiness, dizziness, and vomiting.

Bell [48] cited the case of an operator of dry cleaning equipment who died suddenly after mild exertion (starting a motorcycle and riding it a few hundred yards) upon leaving work. The author estimated that the man had been exposed to concentrations of trichloroethylene as high as 4500 ppm prior to his death which was attributed to ventricular fibrillation.

Bardodej and Vyskocil [21], Ogata et al [25], Andersson [26] and others have noted that exposure to trichloroethylene may either speed or slow the heart rate, depending on the degree of exposure. Andersson noted that 77 of 104 workers she studied in thirty different plants in the metal, rubber, and dry-cleaning industries showed abnormal ECG tracings with disturbance of cardiac rhythm, which she suggested might presage permanent heart damage. [26]

Bernstine [49] recorded electrocardiograms of a young marine who sustained cardiac stoppage suddenly after deep inhalation of trichloroethylene in analgesic concentration. Mouth-to-mouth resuscitation, administration of oxygen, intracardiac epinephrine and procaine, transfusion, and direct cardiac massage for 45 minutes was successful in restoring cardiac contraction, but meanwhile ventricular fibrillation was confirmed by ECG. The fibrillation shifted to ventricular tachycardia and more procaine and epinephrine were administered during the massage. One month later the marine was much improved. No follow-up was reported.

Lilis et al [50] recently offered a theory that changes in the level of epinephrine secretion associated with hypersympathicotonia induced by trichloroethylene exposure, particularly when accompanied by physical exertion or stress, might account for the cases of unexplained sudden death reported.

(d) Effects on the Liver and Kidneys

Secchi et al [51] found acute liver disease in three of seven cases of poisoning by accidental ingestion of trichloroethylene. They

determined that the findings could be attributed to contamination with 1,2- dichloropropane and 1,2-dichloroethane. Analysis of samples of the solvents responsible for the poisonings showed that severe liver toxicity occurred only in subjects poisoned by mixtures rich in 1,2-dichloropropane and 1,2-dichloroethane. They had found no liver damage when pure trichloroethylene was ingested.

Ten persons severely exposed to an essentially saturated atmosphere of trichloroethylene in a confined space (the hold of a ship) showed no jaundice, four patients showed hyperglobulinemia, and six hypercalcemia. Cotter [52] stated that no other liver function tests were abnormal and in all but one person the clinical test results returned to normal within two months of exposure. The author concluded that the changes in globulin levels were indicative of some degree of liver damage despite the absence of bilirubin or phosphatase retention or disturbance of the esterification of serum cholesterol.

Lachnit and Brichta [53] reported that of 22 workers (15 females, 7 males) exposed to trichloroethylene primarily in dry-cleaning shops there were three who gave positive reactions to two liver function tests (sulfobromophthalein clearance tests and colloid stability). The authors concluded that much of the clinical evidence of liver injury could be attributed to alcohol abuse and stated that the toxicity of trichloroethylene to the liver was low.

Albahary et al [54] conducted liver function tests (serum glutamic oxalacetic transaminase [SGOT], and serum glutamic pyruvic transaminase [SGPT]) on workers regularly exposed to trichloroethylene

in degreasing operations and reported that there was no evidence of liver disorders.

Guyotjeannin et al [55] studied 18 workers who were not alcoholics but were regularly exposed to trichloroethylene and had no history of preexisting liver disease by electrophoretic separation of various blood constituents. They found some abnormalities of cephalin flocculation, total lipids, and unsaturated fatty acids, and an increase in beta globulins. There was also an increase of gamma globulins. Whether or not these findings were reversible was not evaluated.

Tolot et al [56] reported the results of a comprehensive evaluation of a series of liver function tests conducted on twelve workers who had been exposed to trichloroethylene for at least five years in a degreasing shop. There was no evidence of injury to the liver even though workers were being exposed routinely to trichloroethylene "higher than the tolerance limits: 0.9 to 3 mg of trichloroethylene per liter of air."

Milby [57] noted normal tests for liver and kidney functions (SGOT, SGPT, erythrocyte sedimentation rate) in a paint stripping machine operator. Exposures to trichloroethylene were shown by subsequent sampling to have been 260-280 ppm. The hospitalized patient excreted 780 mg per liter of trichloroacetic acid on the day of the examination, indicating severe overexposure.

Armstrong [58] reported that 27 of 35 normal healthy individuals given trichloroethylene as an anesthetic showed positive evidence of

cephalin cholesterol flocculation, which also is characteristic of patients suffering from catarrhal jaundice (infectious hepatitis) and malaria. All individuals showed a negative reaction two weeks after anesthesia. The author concluded that slight liver impairment caused by trichloroethylene anesthesia is transient and less pronounced than that produced by diethyl ether.

Joron et al [59] reported massive liver necrosis with death more than one month after, last exposure to trichloroethylene estimated to have been several hundred ppm based on evaluation of simulated exposures. James [37] found some fatty degeneration of the liver in a patient whose death resulted from trichloroethylene vapors in a degreasing shop.

Gutch et al [60] described a patient who had been a chronic drinker and also had an inadvertent overexposure to trichloroethylene. The patient had evidence of acute renal failure a week after the last exposure to trichloroethylene. Needle biopsy of the kidney showed acute tubular degenerative changes; biopsy of the liver showed no evidence of cirrhosis or toxic injury. Treatment with peritoneal dialysis for ten days was successful in overcoming oliguria and renal function returned to normal. Electrocardiographic evidence of a toxic myocarditis was believed related to retention of trichloroethylene or its metabolic products. Recovery of the patient was complete without evidence of residual renal or myocardial damage.

Kleinfeld and Tabershaw [36] reported a fatality from hepatorenal failure due to accidental ingestion of trichloroethylene. Autopsy

showed marked lower nephron nephrosis severe centrolobular necrosis, of the liver, and acute pancreatitis. The man reportedly had been a heavy beer drinker.

(e) Other Effects

Friborska [61] showed that leukocyte alkaline phosphatase levels increase in persons repeatedly exposed to trichloroethylene. The acid phosphatase in blood also increased. These increases persisted after two weeks without exposure. The investigator considered that these findings might signify a defense mechanism or an increased capacity to metabolize alcohols, might be a response to changing pH of the blood, or be related to glycogen metabolism in the liver.

Bartonicek and Teisinger [62] exposed four humans for five hours to 1 mg per liter (186 ppm) trichloroethylene and analyzed their urine for metabolites. Later they exposed the same group to the same conditions, having pretreated them with three to three and one-half grams of tetraethyl thiuram disulphide (disulfiram). There was a 40-64% decrease in excretion of trichloroethanol and a 72-87% decrease in excretion of trichloroacetic acid.

Seage and Burns [63] suggested that alcohol was the precipitating factor in the production of severe abdominal pain, retching, vomiting, and pulmonary edema in a cardiac subject. The subject ingested a glass of beer and one of rum subsequent to a three and one-half hour exposure to trichloroethylene vapors arising from a bowl used to dip plastic parts.

Soucek and Vlachova [18] showed that one subject exposed to trichloroethylene after receiving 60 ml of 20% glucose and 15 units of insulin excreted 22% more trichloroethylene metabolites than when untreated. He excreted 2.6 times more trichloroethanol on the first day. Trichloroacetic acid excretion on the first day was unaffected as was the total duration of excretion.

Effects of trichloroethylene on the skin include reddening and dermographism, skin burns on contact, [40] generalized dermatitis resulting from contact with the vapor, [45] and possibly schleroderma. [64] Stewart and Dodd, [65] in a study of controlled skin exposure (thumbs), showed that unless trichloroethylene is trapped against the skin, absorption is too minute to be significant. Absorption varies with age, skin thickness and texture, as well as type of contact.

Epidemiologic Studies

Bardodej and Vyskocil [21] studied 75 exposed workers divided into four groups by years of exposure: less than 1 year, 1-2 years, 2-9 years, and 10+ years. Their findings showed with duration of exposure a statistically significant (P less than 0.05) increase of lacrimation, reddening of skin, and disturbances of sleep, but a decrease of sensitivity of the hands. With duration of exposure, significant increases (P less than 0.01) were found in intolerance to alcohol, tremors, "giddiness", what they termed "severer neurasthenia syndrome with anxiety states," and bradycardia.

Andersson, [26] in a detailed study of 104 persons exposed to trichloroethylene in metal, rubber, and dry-cleaning industries, described the predominant characteristics of trichloroethylene exposure as headache, dizziness, vertigo, tremors, nausea and vomiting, sleepiness, fatigue, a feeling and appearance of light-headedness or "drunkenness," increasing to unconsciousness and in some cases to death. In the Andersson series there was practically no cranial nerve involvement and only an occasional tremor of hands. Detailed correlations by sex, age, place of work, and duration of exposure and some correlations with levels of exposure and excretion of trichloroacetic acid were made. In that study, about two-thirds of workers examined exhibited signs or symptoms of effects on the central nervous system. There was some correlation between the exposure levels and the amount of urinary trichloroacetic acid excreted. Only eight of 104 workers who had been exposed to this chemical for more than three years were without symptoms. Follow-up studies of workers (some severely exposed to trichloroethylene) for three to seven years after exposure showed little residual evidence of trichloroethylene intoxication. The workers reported symptoms had subsided within four or five months after they had stopped working. On the basis of this study and a parallel study of rabbits noted below (see Animal Toxicity), Andersson concluded that 200 to 400 ppm of trichloroethylene constituted too high a standard for an eight-hour daily exposure. "At an average, continuous exposure with trichloroethylene concentrations as low as 1/10 of these ppm values,

symptoms due to trichloroethylene can be expected to appear." However, it should be noted that (1) the levels of exposure in this study were subject to many unmeasurable fluctuations, (2) the author considered that in 35 of the 104 workers studied personal "social" problems had probably affected worker findings, and (3) the trichloroacetic acid studies were not able to be correlated with the exposures sustained but only statistically compared by groups. Some mild EEG changes were evident in a few examinations but none on follow-up.

Lilis et al [50] reported a study of 70 young workers (83% less than 30 years old) exposed up to six years to variable concentrations of trichloroethylene. Environmental levels were high; 40% of 214 analyses showed levels in excess of 50 mg/cu m (about 10 ppm). However, the method of sample collection, types of samples (TWA, etc.), analytical method were not mentioned in the report. The subjects showed symptoms of "asthenia associated with vegetative disturbance." Measurements of stroke volume, cardiac output, cardiac index and cardiac activity indicated sympatheticotonus due to epinephrine. The authors also found vanillylmandelic acid excretion. For the workers studied, the following percentages of complaints were indicated: dizziness, 88%; headache, 74%; nausea, 43%; euphoria, 31%; palpitation, 29%; disturbances of vision, 21%; and sleepiness at the end of the shift, 29%. The study further showed an insidious onset after some months, up to one or two years, of the following complaints: fatigue, 68%; irritability, 56%; disturbed sleep, 46%;

anxiety, 27%; loss of appetite, 50%; alcohol intolerance, 21%. Accompanying findings included excessive sweating in 39%, palpitation in 29%, nausea in 19%, and some parasthesias. While the percentage of workers that indicated complaints are in excess of the percentage of samples at or below 50 mg/cu m (about 10 ppm), a direct relationship can not be established since the sampling protocol is unknown.

Animal Toxicity

(a) Inhalation

Rats exposed to 500, 1000, 2000, and 3000 ppm trichloroethylene for six hours daily, five times per week for six months, revealed no effects below 2000 ppm. At 2000 ppm some narcosis and lessened effort to get food was noted, but at 3000 ppm only 2 of the original 6 rats survived 6 months. [66] Dogs exposed to 2000 ppm trichloroethylene showed no adverse effects. [66] Guinea pigs exposed over 1100 hours to levels of 1200 ppm showed no changes of questionable significance in lungs, spleen, heart, adrenals or brain, and only some very slight degeneration of liver cells. [67] Siefter [68] however found liver damage in dogs exposed repeatedly for three weeks to 750 ppm. Pathological evidence of liver injury was found in the dogs examined in the third week of exposure, but not in the dogs which survived five weeks after the last exposure. Reexposure at 200 ppm did not cause recurrence. Dogs exposed to 500-750 ppm also showed liver changes in the eighth week. [68]

Hunter [69] found that of ten mice exposed to 10000 ppm for one hour in repeated exposures, six died but several about to die could be

revived if subjected to a high oxygen concentration. No liver damage was found and the deaths were considered due to anoxemia from shallow respiration. Andersson [26] found no evidence of liver injury in rabbits exposed to trichloroethylene in a series of five studies: (1) 12 mg/liter (2200 ppm) 5 hours per day for 8 months; (2) 37 mg/liter (6900 ppm) for about 4 hours per day for 8 months; (3) 55 mg/liter (10200 ppm) for approximately one hour per day for 8 months; (4) 80 mg/liter (14900 ppm) for about 30 minutes per day for 12 months; and (5) 190 mg/liter (35300 ppm) for 5-10 minutes per day for 9 months. Kylin et al [70] saw no liver damage in rats after single exposures to 3200 ppm. In addition these investigators studied mice exposed to 1600 ppm, four hours daily, six times a week for periods of one, two, four and eight weeks; twenty mice were exposed in each of the four subgroups. Fatty degeneration of the liver was slight and tended to abate after two weeks of exposure.

Nowill et al [71] exposed one dog, three rats, and three rabbits to concentrations of 500 and 1000 ppm trichloroethylene for about 18 hours daily for 90 days. Liver function tests, blood and routine urine tests, activity, growth rates, and post-mortem tissue studies showed no abnormalities.

Andersson [26] exposed rabbits for a half hour to four hours daily to 37 mg/liter (6900 ppm) for eight months and noted an increasing frequency of anesthesia. It also occurred after shorter periods of daily exposure, and recovery required a significantly longer time after the study had been in progress for a few months.

Reversible heart changes were found by Andersson in rabbits exposed up to 12 months to varying daily concentrations of trichloroethylene. Krantz et al [34] by perfusing hearts of rats, frogs, and dogs demonstrated no effect of trichloroethylene on coronary circulation or heart oxygen consumption.

Adams et al [72] showed that the highest levels of exposure with no effects on rats were: 0.3 hour at 20000, 0.6 hour at 12000, 1.4 hour at 4800, and 5 hours at 3000 ppm. For repeated exposures of 7 hours a day, 5 days per week the no-effect levels were: monkeys 400 ppm, rats and rabbits 200 ppm, and guinea pigs 100 ppm. No-effect levels were also determined by Prendergast et al [73] for rats, guinea pigs, rabbits, dogs, and monkeys at 730 ppm, eight hours daily, five days per week, for 30 exposures (though dogs had less growth than controls) and 90-day continuous (24 hours a day) exposures to 35 ppm. After comparison with control animals, slight liver weight increases were noted but there were no microscopic changes.

In early 1962, Desoille et al [74] showed in tests on 10 rabbits that acute exposure (15-60 minutes at concentrations ranging from 7000 to 14000 ppm) to trichloroethylene gave EEG changes indicative of several degrees of irritation from minor ones up to electroclinical epileptic seizure. The authors also noted that the rabbit is more susceptible to epileptic seizures than other species. Later in the same year, Desoille et al [75] utilized EEG's to study rabbits with chronic alcohol intoxication that were also subjected to trichloroethylene. Graver functional cerebral disturbances of longer

duration were noted in those animals intoxicated with alcohol, even though the trichloroethylene given after alcohol was half the strength used in the single exposures performed earlier. [74]

Studies of effects on blood and bone marrow were performed by Mazza and Brancaccio [76] in 12 rabbits exposed to 15 mg/liter (2790 ppm) of trichloroethylene for four hours per day, six days per week for 45 days. The characteristics of the hemochromocytometric tests and the description of the bone marrow led the authors to the conclusion that chronic intoxication to trichloroethylene has a direct action on the bone marrow and thus causes myelotoxic anemia.

Another factor studied was dehydration before trichloroethylene exposures. Baetjer, [77] in careful hypothalamic self-stimulation performance tests, showed that a three-day dehydration caused rats to make fewer responses than nondehydrated rats. After exposure to trichloroethylene, neither group performed as well as before exposure. The dehydrated rats performed better than the nondehydrated rats, although some tolerance for trichloroethylene developed in both groups. Recovery of nondehydrated rats was prompt after moderate exposures but was not completed in 24 hours, suggesting that either the trichloroethylene concentration in the brain was greater or the dehydrated brains were more resistant to trichloroethylene or both. Ten-day dehydration tests and trichloroethylene exposure resulted in further decrements in performance after the fifth day of exposure, suggesting that high concentration of trichloroethylene combined with dehydration may have produced some residual brain damage.

Behavioral techniques have been devised to study further the effect of trichloroethylene and its metabolites on animals. Grandjean, [78] using food as the stimulant to rats, was unable to show behavioral changes related to trichloroethylene exposures at levels of 200 or 800 ppm. They showed some increased excitability or disinhibition with exposure to trichloroethylene at the levels studied. Battig and Grandjean [79] exposed rats to 400 ppm trichloroethylene for eight hours, five times weekly. This did not affect their general condition but swimming speed after exposure was reduced. However, exploratory behavior seemed increased. In a later work, Grandjean [80] exposed rats for six hours to 400 ppm. Immediately after exposure there were slight decrements in performance of swim tests under load and 800 ppm gave significant decrement and evidence of fatigue compared to unexposed control rats. No difference was present one hour later. At 1600 ppm for six hours rats had a persistent decrement in performance tests and showed fatigue. The rats during their five-hour exposures at the three levels of 400 ppm, 800 ppm, and 1600 ppm showed 81, 65 and 58% of normal activity, respectively. Goldberg and co-workers [81] trained rats in avoidance responses. Four-hour exposures, five days per week for two weeks resulted in appearance of slight imbalance but no difference, in responses to 200, 560, and 1580 ppm; learning appeared to be stimulated by 200 ppm exposures. Decreased avoidance responses were present at 4380 ppm. Exposures to 1568 ppm disturbed growth.

(b) Injection

By using 40-45 mature rats and 30 control (unexposed) rats and sacrificing them at two-hour intervals for 168 hours, Wirtschafter and Cronyn [82] showed that rats injected with 0.004 mole/kg trichloroethylene had changes at 12-16 hours which were reversed at 24 hours. The changes included raised levels of SGOT, indicative of functional hepatic changes, and microscopic evidence of liver cell damage. No subsequent changes were present. Mikiskova and Mikiska [83] studied guinea pigs intraperitoneally injected with trichloroethylene or with trichloroethanol. The animals subsequently given tests of electric stimulation for skin, spinal reflex excitability, excitability of motor cortex, and EEG and ECG recordings showed that trichloroethanol results were similar to those of trichloroethylene but at least three and probably five to six times more effective. The authors advanced the theory that trichloroethylene effects were in part due to trichloroethanol. They further established that trichloroethanol was twice as effective as trichloroethylene in slowing the heart rate. They noted that the conjugation of trichloroethylene with glucuronic acid is reversible, that the trichloroethanol produced deep anesthesia within 5-10 minutes which lasted 3/4 to one hour, whereas trichloroethylene took 15-30 minutes to produce lighter anesthesia but it lasted two to three hours.

Bartonicek and Brun [84] made extensive studies of brain tissue, EEG, acid phosphatase levels, and erythrocyte sedimentation rates in two groups of rabbits. In one group, rabbits were injected with 3 ml

trichloroethylene into the muscle three times per week for 29 days (a total of 53 g per rabbit). The second group was given 2 ml trichloroethylene twice a week for periods lasting from 41 to 247 days, or a total of 18-133 g per rabbit. Controls were also studied. Acid phosphatase was increased after exposure. Brain slices and sections of peripheral nerves were examined histologically and histochemically. The 29-day exposure group, and even more the 41-to-247-day exposure group of rabbits, showed widespread eosinophilic homogenization of cytoplasm, shrinkage of cytoplasm, and nuclear hyperchromasia suggesting anoxic ischemic nerve cell damage. No severe neurological disturbances were noted.

(c) Metabolic Studies

In 1938, Barrett et al [67] had shown that trichloroacetic acid was excreted in urine after inhalation of trichloroethylene. Thereafter many animal studies were undertaken to determine the metabolic pathways involved, especially after Powell [17] developed the Fujiwara reaction with pyridine and alkali as a method of studing the time course of elimination of trichloroethylene and its metabolites. Butler [14] showed that dogs excreted not only trichloroacetic acid but also trichloroethanol conjugated with glucuronic acid as urochloralic acid and postulated the metabolic pathway through chloral to trichloroethanol. He then gave dogs intramuscular injections with 5 g trichloroethanol per kg of body weight. Sixty-five percent of the dose was excreted in the first three hours at a maximum rate of 23 mg per hour in the first hour. Trichloroacetic

acid was also excreted but in much smaller quantity. Friberg et al [24] showed that rats exposed for four hours to 640, 1150 or 2500 ppm excreted trichloroacetic acid increasingly up to 24 hours after exposure then decreasingly for up to six days irrespective of dosage. Studies by Forssman and Holmquist [85] showed that rats exposed for 36-60 minutes to 59-86 mg/liter (11000-16000 ppm) of trichloroethylene exhaled 32-69% of the total inhaled during exposure. Of the retained trichloroethylene at low exposures, 21-28% was excreted as trichloroethanol and 1.2-3.9% as trichloroacetic acid. With higher exposures, 32-69% was exhaled as trichloroethylene and 3.2-7.8% as trichloroacetic acid. Forssman et al [86] further showed that pretreatment with disulfiram (antabuse) in rats did not affect the excretion of injected sodium trichloroacetate, but did stop the excretion of trichloroacetic acid after inhalation of trichloroethylene. They attributed this to an inhibition of the oxidation of chloral to trichloroethanol. Bartonicek and Soucek [87] studied rabbits' metabolism for a year and concluded that their metabolism was qualitatively like humans and only the relative quantities differed. Rabbits excreted 10 times more trichloroethanol than trichloroacetic acid and about 50 times less trichloroacetic acid than man, but equally slowly.

Fabre and Truhaut [88] studied tissue homogenate. They found trichloroethylene in all tissues obtained during exposure, greatest in fat, then in lungs, spleen, liver, and least in brain and kidney. Trichloroacetic acid was present in greatest concentration in fresh

spleen, suprarenal glands, reproductive organs, and urine. In vitro studies of tissue homogenates exposed to trichloroethylene showed the most active conversion of the substance to its metabolites in the spleen, and decreasing activity in the lung, brain, liver, and kidney tissues.

In 1967 Leibman and McAllister [89] reported studies with liver microsomal tissue extracts. They were able to show that there was an increase in the ability to metabolize trichloroethylene to chloral and to trichloroethanol when the animals from which the tissue extracts were obtained had been previously treated with phenobarbital. Rats pretreated with phenobarbital and then exposed to trichloroethylene also excreted more metabolites in the first few hours than the similarly exposed but not pretreated controls. The authors pointed out that drug intake might vitiate conclusions drawn from levels of trichloroacetic acid urinary excretion based on single samples.

Correlation of Exposure and Effects

The most meaningful studies for purposes of establishing a well-defined cause-and-effect relationship are those in which an attempt has been made to relate the environmental exposures with subsequent effects in the exposed population.

Longley and Jones [90] reported that unconsciousness suddenly occurred in a worker who entered a tank in which a paint containing in excess of 75% trichloroethylene had been recently used. An attempt was made to simulate conditions which produced the unconsciousness and air sampling was conducted within the tank after application of some

of the paint. Concentrations of trichloroethylene within the tank varied by location between 1700 and 3300 ppm. The authors estimated that a concentration of 3000 ppm would cause unconsciousness in human subjects after a 10-minute exposure.

Kleinfeld and Tabershaw [36] reported five cases of fatalities resulting from acute overexposure to trichloroethylene in degreasing operations. In only one case was environmental data available (taken subsequent to the incident). In that case, concentrations of trichloroethylene ranging from 200-8000 ppm were measured. The workers in this case had continued to work at his job despite symptoms and complaints of nausea, drowsiness, dizziness, and vomiting, and died suddenly within a few hours after leaving the plant. Death was attributed to ventricular fibrillation.

Kylin et al [22] exposed 12 volunteers to 1000 ppm of trichloroethylene for two hours. Based on the development of optokinetic nystagmus, it was concluded that exposure had had an effect on the central nervous system but much less marked than in similar tests with alcohol.

Vernon and Ferguson [91] reported the results of experimental two-hour exposures of 8 young male volunteers (aged 21-30) to concentrations of 0, 100, 300, and 1000 ppm of trichloroethylene. On the basis of various psychophysiological tests including flicker-fusion, Howard-Dolman depth perception, Purdue Pegboard, Muller-Lyer form perception, a written test of the "code substitution" type, and groove-type steadiness tests, decrements in performance were reported

statistically only at 1000 ppm. One subject exposed at 300 ppm complained of lightheadedness and dizziness.

Stopps and McLaughlin [92] reported the results of psychophysiological testing of one human subject exposed for 2-1/2 hour periods to concentrations of 100, 200, 300, and 500 ppm of trichloroethylene. Tests used were the Crawford small parts dexterity test, Necker cube test, card sorting tests, and a dial display test. Their studies indicated no significant effect on psychomotor performance at the 100 ppm level. There was a slight decline in performance at the 200 ppm level which became progressively more pronounced at the 300 and 500 ppm concentrations.

Stewart et al [29] reported the results of two experiments in which seven human volunteers were exposed to varied concentrations of trichloroethylene. In the first experiment the concentrations ranged between 160 and 400 ppm for a total exposure period (apparently including equilibration time) of 83 minutes. The time-weighted average concentration for this test was 265 ppm. In the second experiment the concentration ranged between 172 and 332 ppm for a total of 190 minutes of exposure. The time-weighted average concentration was 211 ppm. Subjective and psychophysiological responses from the seven subjects used in these experiments were recorded during the exposures. Transient, mild eye irritation was reported by three of the seven subjects only at the lowest concentration (160 ppm). Between 160 and 250 ppm the odor was constantly perceptible but not unpleasant; there were no reports of lightheadedness. Between 350 and

400 ppm two of the seven subjects reported lightheadedness although the results of Romberg and "heel-to-toe" tests were normal in all subjects.

In a later study, Stewart et al [30] conducted a series of experimental 7-hour exposures of five human subjects to a nonfluctuating 200-ppm level of trichloroethylene on five consecutive days. After 30 minutes two subjects complained of throat dryness and one of mild eye irritation. No untoward objective responses were observed during any of the exposures, although on one or more occasions 50% (sic) of the subjects reported that greater effort was required for them to perform normally in a modified Romberg test. The investigators reported that the results of the performance tests, ie, the Crawford manual dexterity tests and the Flanagan coordination and inspection tests, were normal. One consistent response was the complaint of "feeling fatigued" on the fourth and fifth days of the exposure. The authors concluded that the significance of reported fatigue and drowsiness may well be of clinical significance and merit further investigation. Laboratory tests for liver cell damage did not even suggest transient effects.

Salvini et al [93] exposed 6 male university students (between 20 and 22 years of age) to an average concentration of trichloroethylene of 110 ppm (a range of 90 to 130 ppm) in two four-hour sessions separated by 1-1/2 hours. During exposure complex performance tests of perception, memory, and manual dexterity were conducted. Each subject was examined on two different days, one day in the test atmos-

phere containing trichloroethylene and the other in a control atmosphere containing no trichloroethylene. During the trichloroethylene exposure periods, the vapor was circulated periodically into the test room and the air was analyzed at regular intervals by gas chromatography. The investigators concluded that there was a statistically significant (P less than 0.05) decrement in performance, without clinical signs or symptoms, indicating that 100 ppm was very close to the average concentration capable of interfering with psychophysiological efficiency. The entire experiment was repeated using 6 workmen who regularly worked with trichloroethylene. The results of this second test confirmed the conclusions drawn from the results using the university students.

To this point, this discussion of attempts to correlate environmental concentrations and consequent effects has been limited to cases of acute overexposures in industry or voluntary human exposures to controlled environments. Relatively few studies have been conducted in industry in which attempts have been made to document chronic environmental exposure conditions and the resulting health effects in the exposed population. Grandjean et al [27] reported a study in which a total of 73 workers in 24 different workshops were examined. A relatively high frequency of subjective complaints, alterations of the involuntary nervous system and of neurological and psychiatric symptoms were reported. The frequency showed a good relationship with total duration of exposure (months on the job). A total of 96 air samples were collected during the study,

the results of which ranged between 1 and 335 ppm, many of them lying between 20 and 40 ppm. The authors stated that a series of consecutive samples collected during a period of 3 to 4 hours in one workplace showed a great variation in concentrations due to the actual degree of ventilation and utilization of the degreasing apparatus. The authors admitted that air measurements provided insufficient indication of the total exposure. Laboratory tests of hepatic function showed no significant changes. On that basis they stated that they could not conclude that there was any causal relationship between liver troubles and exposure to trichloroethylene.

Bardodej and Vyskocil [21] reported a statistically significant (P less than 0.01) correlation of the following symptoms with length of exposure in dry-cleaning and degreasing occupations in a total of 75 workers studied: intolerance to alcohol, tremors, giddiness, bradycardia, and "severer neurasthenic syndrome with anxiety states." The authors reported that the atmospheric concentrations of trichloroethylene in these plants varied between 0.028 and 3.4 mg per liter (5 to 630 ppm). At high environmental levels there was agreement on reported symptoms with other authors. However, Bardodej and Vyškocil reported some response at low levels. In their study, no controls were used, the number and frequency of environmental samples was not given, the areas sampled were not reported, and the general health of the worker population studied was not given. Although not considered statistically significant, some percentages of reported symptoms were given for ranges of exposure. For a group of 12

drycleaners exposed to 0.16 to 3.4 mg per liter (about 30 to 630 ppm), 75% complained of headache, 92% intolerance to alchol, 83% disturbance of sleep, 92% fatique, 33% bradycardia (below 60 beats per minute), 8% conduction disturbance (ECG), and 8% heart muscle disturbance (ECG). Nineteen degreasers exposed to 0.54 to 0.83 mg per liter (about 100 to 154 ppm) reported the following percentages of symptoms: 26%, headache; 63%, intolerence to alcohol; 26%, disturbance of sleep; 47%, fatigue; 40%, bradycardia; 16%, condition disturbances (ECG); and 5%, heart muscle disturbances. Another group of 36 degreasers were exposed to 0.028 to 0.055 mg per liter (about 5 to 10 ppm) and reported the following: 67%, headache; 22%, intolerence to alcohol; 22%, disturbance of sleep; 61%, fatigue; 16%, bradycardia; 3%, conduction disturbances; and 3%, heart muscle disturbances.

For the most part the results of experimental exposures of animals to trichloroethylene have been consistent with effects in humans exposed to equivalent concentrations. Exposures of rats and mice to concentrations of trichloroethylene in excess of 3000 ppm resulted in immediate narcosis or death after one to six hours exposure. [24,66,69,72,81] Varying degrees of intoxication by inhalation of trichloroethylene have been reported by various investigators and discussed in the previous section.

In published case reports, [36,60] it has been suggested that ingestion of alcohol may potentiate the effects of trichloroethylene intoxication. This is a clinical impression of industrial physicians and has not been adequately demonstrated.