III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Tetrachloroethylene (CCl 2 = CCl 2), also known as perchloroethylene, is a colorless, clear, heavy liquid with an ethereal odor. [1] May determined an odor threshold of 50 ppm with a definite odor at 70 ppm. [2] However, some people may be able to smell it at lower concentrations. Leonardos et al [3] reported an odor threshold for their group of subjects of about 5 ppm. Methodological difficulties in odor detection may account for the discrepancies in these results. Some of the physical properties of tetrachloroethylene are tabulated in Table XII-1. [1,4-6]

Tetrachloroethylene is manufactured by at least eight companies in the United States. [7-9] Several manufacturing processes are utilized. [1,9] Its production in the US began in 1925. [1] In 1955, US production amounted to 178 million pounds, [10] and production increased steadily to 734 million pounds in 1972. [7,8,10-25]

The major uses of tetrachloroethylene are for commercial drycleaning and metal degreasing. Most workers in drycleaning establishments are exposed to it. [9]

Workers in at least 17 companies in the US are subject to tetrachloroethylene exposure in the formulation of a variety of products for home use and into veterinary anthelmintics. [26] Tetrachloroethylene is also prepared for grain fumigation by at least one company and some workers involved in grain fumigation are subject to exposure. [27]

NIOSH estimates 275,000 people are exposed to tetrachloroethylene in their work environment in the US.

Historical Reports

Tetrachloroethylene was studied as an anthelmintic by Hall and Shillinger, [28,29] who reported in 1925 the results of oral doses ranging from 0.05 to 15 ml/kg administered to 58 dogs. No deaths were observed in any healthy dogs that received the tetrachloroethylene, but dogs with clinical cases of distemper usually died 1-3 days after administration. Changes in the liver were reported for three healthy dogs receiving 0.2 ml/kg tetrachloroethylene and in one dog receiving 0.3 ml/kg. Degeneration of the parenchymatous cells, lobular hemorrhage and atrophy, and congestion of the central veins were observed.

Schlingman and Gruhzit [30] reported in 1927 that tetrachloroethylene produced different effects in various animal species. Chickens were notably resistant to single oral doses of 0.83 ml/kg or less. Cats, foxes, sheep, cattle, and horses, in that order, showed increasing susceptibility to tetrachloroethylene indicated by increased frequency of degeneration and necrosis of liver cells. Swelling and clouding of tubular epithelium of the kidneys was also observed.

In 1929, Lamson et al, [31] using thermal conductivity for analysis of gas samples, determined that a tetrachloroethylene concentration of 9,000 ppm was necessary to produce anesthesia in dogs. This concentration also caused secretion of 300 ml of saliva in 5 hours. The usual stages of anesthesia were reproduced, but it was almost impossible to obtain muscular

relaxation except with nearly lethal concentrations.

The investigators [31] reported a series of animal experiments in which 116 animals, including dogs (adults and puppies), cats (adults and kittens), rabbits, and mice, were examined for pathologic changes in liver and kidneys 48 hours after administration of oral doses up to 25 ml/kg or after 5-6 hours of inhalation sufficient to maintain surgical anesthesia. In a few animals, principally puppies and kittens, there was a mild degree of fatty infiltration of the liver, but necrosis was absent in all instances. The fatty infiltration was found to be no more than in control animals on the same diet. In 10 dogs (5 by oral dosage, 5 by inhalation anesthesia) retention of phenoltetrachlorophthalein dye by the liver was essentially normal. In exposures of 35 dogs and 8 cats (oral and inhalation) tetrachloroethylene caused no change in the icteric index. A variety of a 185 animals were killed by lethal oral dose, and in every instance death was due to irreversible narcosis and not to any demonstrable pathologic change in internal organs. [31]

Lambert [32] in 1933 reported 46,000 administrations of tetrachloroethylene as a hookworm anthelmintic for humans on islands of the South Pacific. Dosages varied, but were usually between 2.8 and 4 ml. No deaths were reported but narcotic effects, exhilaration, and inebriation were observed.

The toxicity of anthelmintic doses of tetrachloroethylene was studied by Fernando et al [33] among 111 persons treated for hookworms. Liver functions were studied by sulfobromophthalein retention, icteric index, Van Den Bergh test, levulose tolerance test, and urobilin determinations in at least 40 individuals receiving from 1 to 8 ml of tetrachloroethylene. No

significant variation was found between the liver function tests taken before the treatment and those taken after treatment. Cardiovascular, renal, and respiratory systems showed no toxic effects.

Narcotic properties of tetrachloroethylene were reported in 1911 by Lehmann [34] and again in 1936 by Lehmann and Schmidt-Kehl. [35] Cats were exposed to tetrachloroethylene concentrations ranging from 2,200 ppm (15 mg/l) to 16,500 ppm (112 mg/l). A cat exposed at 16,500 ppm began to salivate after 2 minutes, showed signs of equilibrium disturbance after 5 minutes, lay on its side after 10 minutes, and developed light narcosis after 85 minutes and deep narcosis after 145 minutes. These reactions were also seen at lesser concentrations but took longer to occur. Narcosis was not observed after 6 hours exposure at 2,200 ppm. [34]

Tetrachloroethylene was evaluated for anesthetic uses by Foot et al in 1943. [36] Fourteen patients were administered tetrachloroethylene sufficient to maintain surgical anesthesia. Only patients whose planned surgical procedure required a depth of anesthesia no greater than loss of consciousness were chosen. No patient was carried deeper than the second plane of the third stage of anesthesia. No systemic reactions were observed after administration, but several superficial burns to the face occurred, and there was irritation of the respiratory mucous membranes and the eyes. Tetrachloroethylene was not considered by the authors to be an effective anesthetic. [36]

Effects on Humans

(a) Neurologic Effects

In 1937 Carpenter and three of his colleagues subjected themselves to

exposure to tetrachloroethylene vapor in concentrations of 500, 1,000, 2,000, and 5,000 ppm. [37] Vapor concentrations were measured by means of an interferometer to compare to refractive indices of known concentrations. The odor of tetrachloroethylene was detectable at 50 ppm. In a preliminary experiment, the subjects were able to detect the odor at 50 ppm whether they could detect the odor at lower concentrations was not tested. All subjects exposed at 500 ppm (475-680 ppm) for 30 minutes experienced increased salivation, metallic taste, slight eye irritation, increased perspiration of the hands, and tightness of the frontal sinuses. After eating a full course dinner, the subjects exposed themselves at 1,000 ppm (934-1,140) for 95 minutes and observed lassitude, a stinging sensation in the eyes, tightness of the frontal sinuses, and definite exhilaration after 45 minutes. Light narcosis was produced in all subjects after 7.5 minutes exposure at 2,000 ppm and for this reason they left the exposure chamber. No aftereffects were reported.

More recently, Rowe et al [38] exposed human volunteers at concentrations of tetrachloroethylene up to 1,185 ppm. Continuous analysis of vapor concentrations was made by a micro gas analyzer. Tetrachloroethylene vapor concentrations between 930 and 1,185 ppm were found to be markedly irritating to the eyes and upper respiratory tract in four subjects exposed 1-2 minutes. Two subjects experienced similar effects after a 10-minute exposure at 513-690 ppm. Dizziness, tightness and numbness around the mouth, and some loss of inhibition were experienced. Concentrated mental effort was necessary for motor effect to be comparable with nonexposure conditions.

Exposure at 280 ppm tetrachloroethylene for 2 hours resulted in lightheadedness, burning in the eyes, congestion of the frontal sinus, thickness of the tongue, and, in four subjects, motor coordination required additional mental effort.

Less severe but similar effects were experienced by four persons exposed for up to 2 hours at 216 ppm. Slight eye irritation was the only result of a 4-hour exposure of six individuals at 106 ppm (83-130 ppm). [38]

Stewart et al [39] in 1961 exposed six subjects, some more than once, to tetrachloroethylene. Exposures were separated by 4-week periods. Exposure concentrations ranged between 59 and 224 ppm with no exposure lasting longer than 187 minutes. A 1-4 minute exposure at 75-80 ppm caused a mild burning sensation of the eyes. Exposure at 100-120 ppm for 4-6 minutes resulted in dryness and irritation of the soft palate. Slight lightheadedness was noted after a 30-minute exposure at 210-244 ppm. Increased effort was necessary to maintain a normal Romberg test at this concentration. The authors reported that no other effects were found in the clinical or laboratory tests they performed. [39]

In 1970, Stewart et al [40] reported two experimental exposures of subjects to tetrachloroethylene. The subjects were healthy men ranging in age from 24 to 64 years. All were given a full medical examination prior to exposure. No control group was utilized. Two types of exposures were performed, a single 7-hour exposure of 15 subjects at a mean concentration of 101 ppm, and repeated 7-hour exposures of 5 subjects for 5 days, also at a mean concentration of 101 ppm tetrachloroethylene.

All subjects reported the odor of tetrachloroethylene to be moderately strong after 5 minutes of exposure and to be faint after 1 hour. The ability to perceive the odor progressively diminished in the group exposed over 5 days.

During the single 7-hour exposure, 25% of the subjects reported that they developed a mild frontal headache, 60% complained of mild eye, nose and throat irritation developing within the first 2 hours of exposure and usually subsiding before the 7 hours had elapsed. Twenty-five percent of the subjects complained of a sensation of blushing accompanied by slight lightheadedness. Forty percent of the subjects commented that they felt slightly sleepy and 25% reported some difficulty speaking. [40]

In the group that was repeatedly exposed, subjects had fewer subjective complaints. One subject, who had low-grade chronic sinusitis, developed a mild frontal headache throughout the exposures and two of the five subjects consistently reported mild eye and throat irritation. An abnormal response to the modified Romberg test was found with three of the subjects within the first 3 hours of exposure. With greater mental effort, however, the three subjects were able to perform a normal test when given a second chance. No other effects were found in other clinical, neurologic and behavioral tests. [40]

Stewart et al [41] in 1974 exposed 10 men and 11 women to tetrachloroethylene concentrations ranging from 20 to 150 ppm for specified periods 5 days/week for up to 5 weeks. To maintain the concentrations, the chamber was monitored with an infrared spectrometer, and a gas chromatograph equipped with an automatic sampling device. Test subjects were given, medical examinations before and after exposure and tests that

included clinical chemistry, electrocardiograms (ECG), electroencephalograms (EEG), neurologic and behavior studies, and cardiopulmonary function. Blood, urine, and breath were sampled on a regular basis. No controls were used.

Subjective responses of 19 subjects exposed at several concentrations of tetrachloroethylene up to 150 ppm showed no relationship to dose level. Headaches were the most common response. The number of subjective responses reported under exposure did not show significant variations from each subject's preexposure state. [41]

Only preliminary qualitative analyses of EEG tracings of the experiment subjects were reported. The exposure to tetrachloroethylene resulted in a change in the EEG, characterized by a reduced overall wave amplitude and frequency. The change was most strikingly evident in occipital leads in which alpha wave acitvity (8-10 hertz, 10-50 μv amplitude) was generally replaced by delta or theta wave activity (3-5 Hz, 10-100 μv amplitude). [41]

The altered EEG patterns, similar to those of drowsiness or the first stages of anesthesia, were present in most subjects (three of four men and four of five women) exposed at 100 ppm tetrachloroethylene for 7.5 hours/day. Behavioral testing revealed that subjects exposed at 150 ppm showed impaired coordination after 7.5 hours of exposure. [41]

Central nervous system disturbances have been the most frequently reported result of occupational exposures to tetrachloroethylene. [42-49]

A sailor who used a tetrachloroethylene and water in solution (sic) for 1 month to clean gun parts experienced fatigue, vertigo, nausea, and vomiting. [42] He complained of a drunken feeling after working with the

solution all day. Clinical and laboratory tests revealed no further abnormalities. Coworkers were not affected.

In 1957 Lob [43] reported 10 cases of tetrachloroethylene intoxication. One exposure resulted in a fatality. The death occurred when a worker was exposed for 3 weeks in an electrical plant where tetrachloroethylene was used as a solvent. The ventilation system was not in operation at the time. After 1 day of work, the man showed signs of nausea and inebriation, and vomited the following evening. The next day his symptoms became more severe and he became unconscious on the job. After an injection with a vasoconstrictor, he died suddenly during transport to his home. It is not clear whether these changes were the result of tetrachloroethylene alone or the administration of the vasoconstrictor. Post mortem examination revealed generalized edema of the lungs, bronchi, liver, spleen, kidneys, and cerebrum with multiple hemorrhages. The cause of death was diagnosed as asphyxia due to acute pulmonary edema. [43]

The nine cases of intoxication due to chronic exposure to tetrachloroethylene all showed similar symptoms. These included vertigo, headache, nausea, vomiting, anorexia, insomnia, and eye and throat irritation. In two of the cases involving 2-4 years of employment in an environment where tetrachloroethylene was used, severe neurologic disorders were observed. In one of these two cases, loss of memory, blindness in the left eye, pronounced dermographism and vestibular dysfunction were observed upon examination and persisted even after the man was given a new position. [43]

Headaches and vertigo occurred in another man 2 months after he began using tetrachloroethylene in his work. [43] Six months prior to his work with tetrachloroethylene, he had degreased metal parts with trichloroethylene. He worked with tetrachloroethylene for 9 months, enduring the situation until numbness of the fingers, difficulty in walking, trembling, exaggerated dermographism, and general weakness developed. There were mildly positive reactions for urobilin, urobilinogen and bilirubin in the urine.

Eberhardt and Freundt [44] reported two cases of poisoning due to tetrachloroethylene where there was neurologic involvement. In the first case, a 49-year-old man working for 2 months with tetrachloroethylene in a defatting operation experienced confusion, redness of the face, eye lids, and conjunctiva, and finally became unconscious on the job. The odor of solvent was noticeable on his breath.

The second case involved a 65-year-old woman who used tetrachloroethylene to clean metal parts in a watch factory. [44] After a 2-month exposure, she suffered from confusion and anorexia. She was hospitalized when feelings of confusion and dizziness became so strong that she could hardly walk. She recovered after 8 days. [44]

Peripheral neuropathy was the diagnosis in two cases where people had been working with tetrachloroethylene. These cases were found in the records of the California Department of Health for 1963-73 (E Baginsky, written communication, March 1975).

In one case, a 48-year-old female presser in a drycleaning operation became nauseated, cyanotic, and experienced coughing and tremors. A diagnosis of toxic peripheral neuritis was made by a neurologist. The

duration and extent of exposure were not reported.

In the second case, a service man was splashed on the right side of his face with tetrachloroethylene while moving a drycleaning apparatus. On the following night, the man experienced numbness and inability to close the right eyelid fully. The diagnosis was toxic neuritis of the right facial nerve.

Neuropathies associated with exposure to chlorinated hydrocarbons were the subject of a report to the AMA Committee on Occupational Toxicology (HP Blejer, written communication, March 1975). Thirteen cases of neuropathy were reviewed. In one case, a 29-year-old woman developed optic atrophy attributed to tetrachloroethylene used as a garment spot remover.

A 1973 report from the USSR [45] indicated that 145 cases of various peripheral neuropathies resulted from a variety of unsaturated chlorinated hydrocarbon exposures that averaged more than 5 years duration.

Gold [46] reported in 1969 the effects of chronic exposure of a man to tetrachloroethylene. The man worked 6 days/week as a clerk and cleaner in a drycleaning plant. On the seventh day each week, the man cleaned vats containing tetrachloroethylene located in a small, poorly ventilated room where temperatures reached 120 F. On completion of the vat cleaning, the man always vomited, staggered, was confused and disoriented. He was employed for 3 years in the drycleaning plant before seeking medical care. He showed symptoms of increasing fatigue, dizziness, muscle cramps, memory difficulties, and increasing agitation and restlessness.

A physical examination revealed dry scaly forearms and hands while neurologic tests showed an absence of olfactory sensitivity on the right

side (conceivably related to a septum deviation to the right) and conjurctivitis in the right eye. The patient performed poorly and had marked confusion in tasks requiring immediate concentration. Most signs and symptoms persisted during the followup year despite lack of further exposure. [46]

Acute pulmonary edema and coma were the result of a 7-hour occupational exposure to tetrachloroethylene. [47] In a laundry where tetrachloroethylene was used as the cleaning agent and reused after distillation, a man who worked alone forgot to turn on the cold water that cooled the last phase of distillation and the system overheated, giving off fumes which caused him to become dizzy. He lay down on a bed and shortly thereafter lost consciousness. He was rescued 7 hours later. Upon admission to the hospital he was in deep coma with acute pulmonary edema. Bubbling rales were heard over the entire lung field. Followup tests of liver and kidney function gave normal results.

Asthma induced by exposure to tetrachloroethylene has also been reported. [48] A 55-year-old woman working in a drycleaning establishment experienced an acute reaction from each of two massive exposures to tetrachloroethylene in a 2-year period. As a result of one exposure, she became unconscious. Both exposures were accompanied by asthmatic coughing attacks. After these incidents, she developed asthmatic attacks whenever she was in the shop. Diagnosis of asthma was supported by two indicators. The rate of exhaled air decreased 39% from 4.6 to 2.8 liter/second, and a positive reaction, indicating asthma, was obtained from an acetylcholine test.

Weiss [49] reported on two workers who became unconscious when high pressure tetrachloroethylene vapor at a temperature of about 200 C streamed out of a recovery apparatus in a drycleaning plant. The men received first and second degree burns on their faces, extremities and torsos and became unconscious after a few breaths. When the firemen arrived, the men were still unconscious. On hospitalization, urinary elimination of tetrachloroethylene was monitored in the patients for 26 and 31 days, respectively, beginning on the fourth day after exposure. Trichloroacetic acid was measured by a modified Fujiwara method once a day. The maximum elimination of trichloracetic acid, approximately 60 mg/l of urine, was recorded in both patients on the fifth day after the exposure. The investigator reported that the difference in the absolute amount of tetrachloroethylene eliminated by the patients probably was due to a difference in intake of tetrachloroethylene. This was supported by clinical evidence. The patient who was unconscious the longest and had the most extensive burns eliminated the highest amount of tetrachloroethylene. The tetrachloroethylene elimination in both patients showed an overall trend but fluctuated greatly from one day to the next. The investigator [49] had no explanation for this.

Tuttle et al [50] performed behavioral and neurological evaluations of workers exposed to tetrachloroethylene. The exposure occurred during the regular workday of 20 workers in five drycleaning plants. A group of 10 unexposed laundry workers was evaluated for comparison.

Neurologic testing and medical examinations were performed at the beginning of the study. Several behavioral tests were administered to workers at the beginning and end of each workday. Breath samples were also

collected at these times and every 2 hours during the day. The time-weighted average concentrations of tetrachloroethylene were also calculated. The environmental and breath analysis data are shown in Table XII-2. The TWA concentration ranged from 1.32 ppm for five counter workers to 37.2 ppm for five machine operators. The comparison group reportedly had no tetrachloroethylene exposure or exposure to other nervous system depressants. The only other apparent differences between the exposed and unexposed workers before testing was their mean age of 43.45 years for exposed workers and 34.44 years for unexposed. Differences in the neurologic examination between the exposed and unexposed workers included the proximal motor latency of the peroneal nerve, electrodiagnostic rating score, neurologic rating score, and total neurologic score. The results of behavioral tests showed no significant differences between performance of the two groups. Correlations significantly different from zero were found for years of tetrachloroethylene exposure and critical flicker frequency (CFF) and CFF-Mean. Correlations were shown between years of exposure and the Digit Symbol test, the Neisser Letter Search test, the Critical Flicker Fusion Frequency, and three Santa Ana finger dexterity scores. [50]

(b) Effects on the Liver

In a small plant where tetrachloroethylene was used as a degreaser, one of seven employees who used the solvent was found to have a definite case of cirrhosis of the liver. [51] This prompted an investigation of the other workers employed there 2-6 years. Medical histories were obtained and liver function tests and physical examinations were performed on all seven workers. Liver dysfunction was found in three of the workers, indicated by significant sulfobromophthalein (BSP) sodium dye retention at

30 minutes. Positive urinary urobilinogen was found in four workers. Only the man with cirrhosis of the liver showed a 3+ reaction to the cephalin-cholesterol flocculation test. Medical histories revealed no extensive alcohol consumption by any worker. The man with liver cirrhosis drank no alcohol whatsoever. Determinations of the environmental concentrations of tetrachloroethylene were made using a Halide meter. One of the degreasing operations, which operated for 8 hours twice weekly, resulted in 232-385 ppm of tetrachloroethylene. [51]

Hughes [52] reported a case of toxic hepatitis in a 25-year-old man who had worked for 11 weeks, 12-16 hours/day, sometimes 7 days a week, refilling drycleaning units with tetrachloroethylene. The work was performed in a hot, humid, poorly ventilated room. No protective clothes were worn and on one occasion the man spilled a pint of tetrachloroethylene on his shirt and trousers. On two or three occasions he became lightheaded when the tetrachloroethylene vapor concentration became high. The odor of tetrachloroethylene became increasingly distasteful to him. [52]

Two weeks before the onset of symptoms, the man suffered from excessive fatigue and difficulty in rising in the morning. He also had nausea, vomiting, jaundice, weakness, anorexia, dark urine, and light brown stools. On admission to the hospital, results of unspecified liver function tests were reported as grossly abnormal. The man had no history of heavy alcohol consumption or predisposing diseases of the liver. Recovery occurred after 4 weeks of hospitalization. Ten months after the illness, the man reported that he had again briefly worked near a tetrachloroethylene system and immediately experienced nausea on perception of the solvent. [52]

Hepatitis with hepatomegaly was reported in a 47-year-old woman employed for 2.5 months in a drycleaning establishment. [53] Two weeks before admission to the hospital, the woman was heavily exposed to tetrachloroethylene during cleaning of the machinery. On that day, she worked 10 hours and complained of dizziness, headache, and malaise, all lasting through the next day. A coworker, not exposed as long, suffered similar but milder symptoms. During the next 10 days, the first woman suffered from general weakness and loss of appetite. Two days before admission, she developed acholic stools, scleral icterus, nausea, vomiting, and generalized pruritus. When hospitalized, she had vague discomfort in the right upper quadrant of the abdomen, where a baseball-sized mass thought to be a distended gall bladder was found. Her liver was palpable 3.5 cm below the right costal margin. Alkaline phosphatase was elevated to 22.8 and 26.4 units repectively on the first and second day of hospitalization, compared to normal values of 2-9 units. Serum glutamic-oxaloacetic transaminase (SGOT) on these days was also elevated to 1,270 and 760 spectrophotometric units/ml respectively, compared to normal values of 8-10 units. Direct and total bilirubin and cephalin flocculation also showed values consistent with liver disease. A liver biopsy performed after 2 weeks of hospitalization showed central portions of the lobules to have obvious degeneration of parenchymal cells with exaggeration of the sinusoids and focal collections of mononuclear cells. Six months later, her liver was still enlarged. The patient had no history of alcohol use or of exposure to other factors predisposing the liver to hepatitis. [53]

Mild chemical hepatitis and marked CNS depression were experienced by a worker wearing a general purpose chemical gas mask while scrubbing the

inside of a tank car with tetrachloroethylene. [54] After 5 minutes in the tank, the solvent odor became so strong inside the mask that he left the tank. Believing the mask to be faulty, he removed it and reentered the tank. He realized his error, left the tank, donned his mask and entered for a third time. Approximately 10 minutes later, he was discovered unconscious at the bottom of the tank. Physical examination revealed most vital signs to be normal. The man was drowsy but oriented. Results from a detailed neurologic test were normal except for the Romberg test. Infrared analysis of the patient's breath 1.5 hours after exposure showed 105 ppm tetrachloroethylene, confirming that the patient had been exposed at very high concentrations. SGOT was slightly increased on the third day after exposure and urinary urobilinogen was significantly elevated on the ninth day after exposure. After 10 days, all liver function tests had reverted to normal. [54]

Liver dysfunction, as evidenced by elevated SGOT, occurred in eight of nine firemen who were exposed for 3 minutes at unknown concentrations of tetrachloroethylene. [55] Immediately after the acute exposure, all nine men were reported to be "woozy" but once outside the drycleaning establishment where the exposure occurred, they felt well. All appeared normal the next day except two men, who showed moderate hypertension. Clinical examinations and laboratory tests were not performed until 12 days after the exposure. At that time the SGOT values were elevated in eight of the nine men. Hepatomegaly and splenomegaly were found in one man, and slight depression of total white blood count was seen in three others. Eventually all signs of illness ceased. [55]

Trense and Zimmerman [56] reported that a 33-year-old man who worked 4 months in a drycleaning establishment had died due to inhalation of tetrachloroethylene. During the middle of his fourth month of employment, he developed loss of appetite. A month later, he was hospitalized with respiratory distress, coughing, vomiting, and profuse sweating. Clinical examination revealed an increased respiratory rate, rales over most of the chest, tachycardia, paleness of the skin, and throat irritation with hyperemic mucous membranes. The liver was somewhat enlarged and slightly sensitive to palpation. Blood pressure was 165/65. Death from cardiac arrest occurred 2 days after admission to the hospital. Autopsy findings included hemorrhagic pneumonia and edema of the lungs, liver cell necrosis, and fatty degeneration of the heart muscle. Decomposition products, unspecified in amount or type, were reported in the cerebrum, but not in the lungs, liver, kidneys, or blood. [56]

The work area where the exposure took place was investigated by the authors. [56] Two reported measurements of tetrachloroethylene in workroom air showed 50 and 250 ppm. Clothes saturated with tetrachloroethylene were hung to dry in a poorly ventilated room. The drycleaning machine had a run-over cycle where warm tetrachloroethylene drained out into a bucket, often spilling on hot pipes and vaporizing. Tetrachloroethylene vapor was also released when the drycleaning machines were filled from 50-liter bottles of the solvent. During this procedure, no mask was worn. [56]

Moeschlin [57] described a case involving liver function impairment and gastrointestinal disturbances after 6 years of exposure to tetrachloroethylene. Symptoms of mild gastrointestinal and central nervous system disturbances were reported several times prior to hospitalization. Medical

examination revealed the man was generally in good condition and good nutritional state. Mild hepatic damage was diagnosed on the basis of laboratory findings of serum bilirubin and iron values and BSP retention of 30% and 22%. After 20 days, he had no signs and symptoms of hepatic dysfunction. [57]

Two cases of hepato-nephritis due to occupational exposure to tetrachloroethylene were reported in the French literature in 1955 and 1964. [58,59] In both cases, the subjects were using tetrachloroethylene for degreasing metal parts. The atmospheric concentrations of the solvent were not measured but contact with the solvent was direct in one case and within a few meters in the other.

Vallud et al [58] reported the post mortem examination of one man after his death but gave no clinical description. Post mortem showed an average size liver, with "localized degenerations" and enlarged, yellowish kidneys with congestion in the pyramidal zone.

Dumortier et al [59] concluded that the case of hepato-nephritis they had diagnosed was due to occupational exposure to tetrachloroethylene. The patient experienced vomiting, jaundice, and anuresis within 1 week after he started using tetrachloroethylene to clean metal. There was no evidence of previous infectious disease or medication that would have been predisposing. However, the 34-year-old man had a history of alconolism. Two years prior to the occupational exposure, hepatomegaly had been diagnosed. On admission to the hospital, the liver was found to be palpable four fingerwidths below the costal margin. Oliguria and arterial hypertension, albuminuria and uremia were also diagnosed. Treatment included blood dialysis with an artificial kidney machine. After a month

of treatment kidney function was improved. [59]

A workman using solvent which consisted of 50% tetrachloroethylene and 50% Stoddard solvent experienced marked eye irritation and lightheadedness shortly after beginning work. [60] The work involved alternately cleaning steps and mixing cement in an area where solvent vapors were present. On three previous occasions, he had become dizzy and lightheaded and left the area 3-5 minutes while his head cleared. The work area was poorly ventilated. An auxiliary air hose was employed to circulate the air and this accounted for 1 air change/hour. However, because the air hose produced an annoying whistle, the workman turned it off. Thirty minutes later, he became unconscious and was carried from the area by fellow employees. The man had worked 3.5 hours and had used 1 gallon of solvent before becoming unconscious. Stewart et al [60] simulated the exposure conditions at the accident site and found that the average concentration of tetrachloroethylene for 3.5 hours was 393 ppm, but when the air hose was turned off, the concentration rose to 1,100 ppm. During the whole process of cleaning steps and mixing cement, the concentrations of tetrachloroethylene ranged from 25 to 1,470 ppm. The concentrations of Stoddard solvent ranged from 70 to 425 ppm.

The workman recovered consciousness the same day and showed no abnormalities on medical examination. The man was observed for 44 days after the episode. During observation, a variety of clinical laboratory studies were performed and tetrachloroethylene was measured in the expired air. Some liver function impairment became evident on the ninth day following exposure. Urinary urobilinogen and total serum bilirubin were elevated. Urinary urobilinogen was 1:320 dilution and total serum

bilirubin was 3.2 mg %. These values returned to normal ranges by the 14th day, when the measurement for alkaline phosphatase showed an elevated value of 6.2 Bodansky units. On the 18th day, serum glutamic pyruvic transaminase (SGPT) was slightly elevated. Concentrations of tetrachloroethylene in the breath on days 1, 2, 3, 9, 10, 14, 16, 18, and 21 were 18, 8, 6, 2, 1.5, 0.7, 4.5, 0.4, and 0.2 ppm, respectively.

(c) Effects on the Skin

Skin burns, blistering, and erythema caused by direct contact with liquid tetrachloroethylene were reported in the case of a man in a drycleaning business who became unconscious and fell to the floor, where the solvent had been spilled as a result of faulty machines. [61] The man had worked in this environment about 5 hours before becoming unconscious. Recovery of consciousness occurred over the next 24 hours and the burns healed over the next 3 weeks.

A similar case was reported by Morgan [62] in which a 68-year-old man spilled a container of tetrachloroethylene on himself, soaking his clothes. He became unconscious and was found 30 minutes later lying on the floor. Clinical examination revealed erythema and blistering over 30% of his body. In 5 days, the erythema subsided and the blistering disappeared. Some dryness and irritation of the skin reportedly occurred thereafter.

Skin effects due to chronic tetrachloroethylene exposure have been reported in other studies. [46,63] Munzer and Heder [63] reported a case of eczema as a direct effect of exposure of a man in a drycleaning plant. Gold [46] reported that a drycleaner had severe neurologic disturbances and had dry, scaly forearms and hands.

Absorption of tetrachloroethylene through the skin of the thumb was studied by Stewart and Dodd. [64] Five subjects each immersed one thumb in tetrachloroethylene for 40 minutes, and the concentration of tetrachloroethylene in the exhaled air of the subjects was determined at 10, 20, and 30 minutes of immersion. The concentration ranges found in the breath of the three subjects were 0.02-0.06, μg/l at 10 minutes, 0.11-0.14 μg/l at 20 minutes and 0.17-0.17 (sic) μg/liter at 30 minutes. Five hours after exposure, tetrachloroethylene was still measurable and ranged from 0.16 to 0.26 μg/liter.

(d) Absorption, Metabolism, Excretion and Elimination

Stewart et al [41] determined tetrachloroethylene and its metabolites in breath, blood and urine of exposed volunteer subjects. Breath samples, taken at various times before and after exposure, were collected in plastic bags using a 30-second breath holding technique. All samples were analyzed for tetrachloroethylene using a gas chromatograph with a hydrogen flame ionization detector. The minimal amount of tetrachloroethylene detectable in breath by this method was 0.05 ppm with a reported accuracy of $\pm$0.1 ppm. [41]

The body burden of exposure to tetrachloroethylene was indicated by the distribution in expired air, blood and urine. Breath analyses showed that tetrachloroethylene is excreted in the breath for long periods after exposure. At 21 hours after a 3-hour exposure at 100 ppm, mean breath concentrations of tetrachloroethylene for days 1 through 5 were 1.00, 2.63, 3.33, 3.07, 3.98 ppm, respectively. Tetrachloroethylene concentrations found in expired breath after exposure at 100 ppm for 7.5 hours/day are presented in Table XII-3.

Physical exercise during exposure increased the concentration of tetrachloroethylene in the expired air and blood considerably. Trichloroacetic acid was found in small amounts in the urine of exposed persons but not in amounts indicative of dose. No trichloroethanol was found. [41]

In 1972, Bolanowska and Golacka [65] exposed three men and two women to tetrachloroethylene at an average of 55 ppm (390 μg/l) for 6 hours with two 30-minute rest periods. Additionally there was a 6-hour exposure with no rest periods. Gas chromatographic determinations were made for tetrachloroethylene in the expired air during the exposure and for 40 hours after exposure. The purity of the tetrachloroethylene was not stated. Fujiwara analysis of the urine for trichloroacetic acid was performed on samples taken during the exposure and again 16 hours thereafter. To account for all the tetrachloroethylene that entered the body, the possibility of excretion through the skin was examined. Aluminum foil-covered polyethylene bags were placed on the hands of subjects at the middle and end of the exposure for 1 hour each time, and the amount of tetrachloroethylene was determined.

The investigators, using the summation method of Piotrowski, [66] determined that 25% of the inhaled tetrachloroethylene was contained in the expired air and the hourly excretion through the skin was only 0.02% of the dose. About 62% of the inhaled tetrachloroethylene was retained in the body, and presumably metabolized by some unknown pathway. [65]

Guberan and Fernandez in 1974 [67] exposed 25 subjects at 50-150 ppm of tetrachloroethylene for up to 8 hours. Concentrations of tetrachloroethylene were measured in expired air and these data were used

in the development of a mathematical model to predict uptake and distribution of tetrachloroethylene in the body and its elimination in alveolar air. The tissues of the body were classified into four groups: the vessel-rich group (VRG) (corresponding to brain, heart, hepatoportal system, kidney, and endocrine glands), the muscle group (MG) (muscle and skin), the fat group (FG) (adipose tissue and yellow marrow), and vessel-poor group (VPG) composed of connective tissue (bone, cartilage, and ligaments). The mean values of the 25 experimental subjects were the physiological "parameters" of a "standard man" used in the model. The investigators thought that the predicted uptake of tetrachloroethylene by tissue groups was related to perfusion rates. Based on the mathematical model, the VRG becomes saturated and the partial pressure equilibrates with that in the arterial blood during the first 60 minutes of exposure. It was expected that a rapid depletion of the VRG would take place, followed more slowly by MG and VPG, and finally the FG, starting 8 hours after the end of exposure. Because tetrachloroethylene has a high fat solubility, it accumulated in adipose tissue with a predicted biologic half-life of 71.5 hours.

The investigators [67] concluded that the ratio of alveolar tetrachloroethylene to inhalation concentrations of tetrachloroethylene was a constant at any given time after exposure.

In another study performed by Fernandez et al [68] 24 volunteers were exposed for 1 to 8 hours in a chamber at concentrations of 100, 150 and 200 ppm. The tetrachloroethylene concentrations in the chamber were continuously monitored by gas chromatography and infrared spectroscopy techniques. The concentrations of tetrachloroethylene were determined in

alveolar air during exposure of some subjects and every 15 minutes for the first 3 hours after exposure of others. Several subjects were also monitored 2 to 4 times daily during an 8-day post exposure period.

The concentration of tetrachloroethylene in the alveolar air at a given time was found to be directly proportional to the constant inspired concentration of tetrachloroethylene. Alveolar concentrations were not found to increase proportionally with the length of exposure.

Ikeda et al [69] surveyed seven workshops using tetrachloroethylene to determine the relationship between exposure and metabolites in the urine. The surveys were conducted during the latter half of the week. Urine samples were collected from 34 male workers and Fujiwara determinations were made for total trichloro-compounds (TTC), trichloroethanol (TCE), trichloroacetic acid (TCA) and creatinine. The workers were exposed to tetrachloroethylene for 8 hours/day, 6 days/week while supervising automatic dip-washing machines (connected with ovens for drying off the solvent) used in the removal of synthetic glue from Kimono silk. Concentrations of tetrachloroethylene ranging from 10 to 400 ppm were measured, using Kitagawa detection tubes. TCA and TCE concentrations increased in proportion to environmental concentrations up to 50 ppm. At that point, TTC, TCA or TCE no longer were proportional to exposure. [69]

Ikeda and Ohtsuji [70] used a modified Fujiwara reaction for analysis of the urine of 70 workers exposed to tetrachloroethylene. There were two groups of workers; one group of four workers was exposed at 20-70 ppm and another group of 66 workers was exposed at 200-400 ppm. The exposures were daily and intermittent. Vapor concentrations were determined using Kitagawa detection tubes. The group of four workers had 8-56 mg/liter

total trichloro-compounds in the urine, 4-20 mg/liter trichloroethanol and 4-35 mg/liter trichloroacetic acid in the urine while the group of 66 workers had metabolites of 45-195, 21-100, and 32-97 mg/liter, respectively. [66]

Ogata et al [71] analyzed the urine of four volunteers exposed 3 hours at 87 ppm tetrachloroethylene for metabolites by a chromium oxidation method. Vapor concentrations were determined every half-hour by gas chromatography with flame ionization detection. During the last 2 hours of exposure, analysis of the expired air of the subjects was performed. Urine was collected for 67 hours after exposure. The two metabolites of tetrachloroethylene observed were trichloroacetic acid and an unidentified compound which formed trichloroacetic acid by oxidation with chromium oxide. [71] The excretion of trichloroacetic acid increased until 3 hours from the end of the exposure and nearly returned to normal 64 hours later. The excretion for the unknown chlorinated hydrocarbon followed a similar course. Only the equivalent of 2.8% of the tetrachloroethylene inhaled was recovered in the urine over 67 hours. [71]

Epidemiologic Studies

In 1969, Franke and Eggeling [72] reported the subjective complaints and results of medical examination and liver function tests of 113 workers in 46 drycleaning plants in Germany. The most frequent subjective complaints were headaches, insomnia, dizziness, and heart complaints reported in 35, 34, 29, and 20%, respectively, of the workers surveyed. Medical examination revealed hyperhidrosis, dermographism, and tremors in 40% of the workers and mucous membrane irritation in 33%. Environmental

concentrations of tetrachloroethylene directly associated with these complaints were not given. The concentrations of tetrachloroethylene in the air of the workplaces were reported as the result of 326 discrete measurements in 46 plants. Of these measurements, 75% were less than 100 ppm. To determine fluctuations in air concentrations, measurements were also taken every 15 minutes for several hours in two plants. In one plant, measurements taken at various locations every 15 minutes during a 2-hour drying process showed that air concentrations of tetrachloroethylene never exceeded 80 ppm. In another plant, measurements taken during a spot removal operation revealed tetrachloroethylene concentrations of 175, 220, 100, 280, and 100 ppm. Determination of concentrations of tetrachloroethylene in the air were conducted by colorimetric analysis. [72]

Statistical analysis of data gathered from laboratory studies of the 113 workers and 43 controls revealed that only the thymol turbidity and bilirubin determinations were significantly affected by exposure to tetrachloroethylene. [72]

Munzer and Heder in 1972 [63] used a modified Fujiwara method to analyze the urine of 200 employees working in 55 drycleaning plants where tetrachloroethylene was used. Trichloroacetic acid was found in the urine of 124 employees. The employees were classified in groups of 1-10, 11-20, 21-30, 31-40 and over 40 mg/l of trichloroacetic acid in the urine; the number of workers in each group was 53, 54, 11, 4, and 2, respectively. The investigators considered values of trichloroacetic acid up to 10 mg/l tolerable but did not explain the basis for this. Laboratory tests, and examinations were performed and medical histories were recorded on 40 of

the 71 people with more than 10 mg/l of trichloroacetic acid in their urine. Of the group of 40 workers, 23 were men and 17 were women. Hyperactivity of the autonomic nervous system as indicated by hyperhidrosis, dermographism, and tremors of the fingers and eyelids was found in 12 of the 23 men and 10 of the 17 women. Laboratory tests including erythrocyte sedimentation rate, SGOT, SGPT, and thymol turbidity determinations showed no differences between the exposed group and an unexposed control group. [63]

Tetrachloroethylene was measured at various positions in drycleaning plants and during different processes. The methods of sampling and measuring were not reported. During an operation where tetrachloroethylene was brushed on fabrics, 150-300 ppm tetrachloroethylene were found in the workroom air. Measurements taken behind drycleaning machines ranged from 100 to 400 ppm. The general room air contained 200-300 ppm. When windows were open and cool air streamed in, vapor concentrations of tetrachloroethylene were 25 ppm at 30 cm above the floor, 150-200 ppm at head height, and 400 ppm at ceiling height. When a floor suction apparatus was in operation, 50 ppm were found at shop tables and 150 ppm in the rooms with machines; when suction was turned off, these concentrations increased to 100 and 300 ppm, respectively. [63]

An association between workroom air concentrations and trichloroacetic acid levels was not made. It was reported that generally women were most involved in the brushing operations while the men worked directly with the machines. [63]

Animal Toxicity

(a) Effects on the Nervous System

The neurophysiological effects of single and chronic exposures to tetrachloroethylene were reported by Dmitrieva. [73] Rats were exposed at concentration levels between 15 and 1,500 ppm (0.1 and 10 mg/l) tetrachloroethylene, 4 hours daily, for 15-30 days. After 20 minutes of exposure at 1,500 ppm, rats exhibited an intensified motor reaction which subsequently weakened. No description was given of how motor reaction was measured. There were also distinct alterations of the EEG such as increased frequency of rapid (up to 30-45/minute) and slow (up to 10-15/minute) graphic spikes, and an increase in the amplitude of the slow spike to 220 (u)v. The impedance of cerebral tissue increased 10-15% after 20 minutes and 30-40% after 4 hours. Biopotentials, as indicated by an electromyogram, were decreased as was EEG voltage. An unspecified decrease in activity of blood acetycholinesterase was reported. It was not specified whether this was serum or erythrocyte acetylcholinesterase but serum seems more likely because of its relationship to nervous function. Similar effects were also reported after 4-hour exposures at 600 and 300 ppm (4 and 2 mg/liter) and also after 2 and 4 weeks of repeated 4-hour daily exposures at 140 and 70 ppm. As a result of the repeated exposures, the delta-index of EEG increased to 80-90%, and the animals lost the capacity for assimilation of a preset rhythm. Electrical impedance of cerebral tissue increased 5-8%.

Exposures of 46 rats at 15 and 1.5 ppm for 5 hours daily for 5 months were performed by Dmitrieva and Kuleshov. [74] Concentrations were maintained "spectrophotometrically." Behavior and body weights did not

differ from controls during or after the experiments. Effects on the EEG were observed after 2 weeks' exposure at 15 ppm. The frequency of rapid oscillations was up to 50 cycles/second higher in the experimental rats and the amplitude increased 30-50%. The pattern of EEG waves subsequently changed as slow delta-waves with a frequency of 1-4 cycles/second and amplitude of 100-150 μv appeared. Electrical conductivity and impedance of cerebral tissue were also effected by exposure. Conductivity decreased 10-15% after 1 month of exposure with corresponding increased impedance. The EEG of the exposed animals displayed uniform differences from those of the control animals.

Histologic examination of rats exposed at 15 ppm tetrachloroethylene revealed swelling of the protoplasm of some cerebral cortical cells in addition to the presence of isolated cells with vacuoles in the protoplasm and isolated cells with signs of karyolysis. Fatty infiltration of isolated cells of the liver was also observed. The activity of serum acetylcholinesterase decreased from 3.8 μM of acetic acid/ml of blood to 1.2 μmoles after 5 months of exposure. One month after the exposures were completed, only the EEG pattern was different. [74]

The exposure of rats at 1.5 ppm of tetrachloroethylene resulted in a slight decrease in acetylcholinesterase activity as well as unspecified changes in impedance of the cerebral tissue. [73]

Dmitrieva and Kuleshov [74] also studied the effect of tetrachloroethylene on 29 male rats. A comparison group of 24 rats was also studied. The exposures occurred 5 hours/day, 6 days/week for 5 months at concentrations of 15 and 1.5 ppm (0.1 and 0.01 mg/l). The number of animals exposed at each concentration was not reported.

Electroencephalographs of the rats were taken before exposure and once monthly during the exposure period with the aid of implanted silver and platinum electrodes. Assimilation of rhythmic photic stimulus of constant intensity and pulse duration was the criteria for evaluation. The electrical conductivity of the cerebral tissue was determined by use of the same electrodes used in the EEG tests attached to a conductivity meter. [74]

Distinct changes of the EEG waves developed after 5 months of exposure at 15 ppm. These included inhibition of electric activity evidenced by the appearance of the slow delta-rhythm (1-3 cps) that became dominant. The capacity for assimilation of an imposed rhythm was lacking. There also was a reduction of electrical conductivity by 24-40% after 5 months of exposure.

Microscopic investigation revealed swollen and vacuolized protoplasm in some cells, but these occurred only sporadically, most cells being normal. One to two months after exposure, the EEG and electric conductivity were only slightly or not at all different from controls. The 5-month exposure at 1.5 ppm resulted only in a slightly higher impedance of the cerebral tissue than was found with the controls. [74]

(b) Effects on Liver and Kidneys

Carpenter [37] attempted to discover the highest concentration of tetrachloroethylene vapors that would not anesthetize rats exposed for 8 hours. Rats exposed at 31,000 ppm (3.1%) died after a few minutes of exposure and after 30 to 60 minutes when exposure was 19,000 ppm (1.9%). Some rats survived exposure at 19,000 ppm but their livers showed congestion and granular swelling. Similar liver effects were found after

exposure at 9,000 ppm. In addition, there was marked granular swelling of the kidneys. No deaths were reported after a single exposure at 9,000, 4,500, or 2,750 ppm (0.7, 0.45, 0.275%). Post mortem examinations of rats exposed to those concentrations showed a slight increase in the prominence of liver and kidney markings.

Carpenter [37] performed experiments involving chronic exposure of rats to tetrachloroethylene. Three groups of albino rats were exposed at vapor concentrations which averaged 70, 230 and 470 ppm for 8 hours/day, 5 days/week for up to 7 months. A group of 18 unexposed animals served as controls.

Exposures of 150 days at 470 ppm followed by a 46-day rest period resulted in cloudy and congested livers with swelling but no evidence of fatty degeneration or necrosis; increased secretion, cloudy swelling and desquamation of kidneys; and congested spleens with increased pigment. Pathologic changes were similar but less severe in the rats exposed at 230 ppm. However, in most of the rats, no pathologic effects were found. In some instances, there was congestion and light granular swelling of the kidneys after 21 exposures. After 150 exposures at 130 ppm and a 20-day rest, congestion was found in kidneys and the spleens. The livers showed reduced glycogen storage. No microscopic evidence of damage was discerned in rats exposed at 70 ppm for 150 exposures totaling 1,200 hours. No effects were noted after microscopic examination of heart, brain, eye or nerve tissue in any of the chronic exposures. [37]

Laboratory tests including icteric index, van den Bergh test for bilirubin, and blood and urine analyses, showed no abnormalities as a result of the exposures. Fertility of female rats was increased slightly

after repeated exposures at 230 and at 470 ppm. [37]

Rowe et al [38] exposed four animal species to tetrachloroethylene vapor for 7 hours, 5 days/week for up to 6 months. The exposure concentrations varied from 100 to 2,500 ppm. Rabbits, monkeys and rats showed no effects of repeated exposures at concentrations up to 400 ppm; no effects on growth, liver weight or lipid content, gross or microscopic anatomy were observed in any animal. Guinea pigs however showed marked susceptibility to exposure to tetrachloroethylene, the authors reported. After 132 7-hour exposures at 100 ppm, the liver weights of female guinea pigs significantly increased. At 200 ppm, there was a slight depression of growth in female guinea pigs and increased liver weights in both males and females. Slight to moderate fatty degeneration of the liver was also observed. These effects were more pronounced in guinea pigs that received 169 7-hour exposures at 400 ppm. At this concentration, there also were increased amounts of neutral fat and esterfied cholesterol in livers. Gross and microscopic examination of the tissues revealed slight to moderate fatty degeneration in the liver with slight cirrhosis. [38]

Kylin et al [75] in 1963 studied the hepatotoxic effect of a single inhalation exposure of mice to tetrachloroethylene for 4 hours. The experiments were performed in female albino mice of a single strain with a mean weight of 23 g. The mice were exposed to tetrachloroethylene concentrations of 200, 400, 800 and 1,600 ppm for 4 hours and killed 1 or 3 days after exposure and the tissues were studied microscopically. Evaluation was limited to assessing the extent of necrosis and the degree of fat infiltration of the liver. Mice exposed at 200 ppm for 4 hours and killed 1 day later showed moderate infiltration of fat in the liver but there was

no evident increase in mice killed 3 days after the same exposure. Moderate to massive infiltration was observed in mice killed 1 or 3 days after exposure at 400 ppm or more, but no cell necrosis was observed even after 4 hours exposure at up to 1,600 ppm tetrachloroethylene.

Kylin et al [76] in 1965 exposed four groups of 20 albino mice at 200 ppm. Each group was exposed for 4 hours/day, 6 days/week, for 1, 2, 4, or 8 weeks. Microscopic examinations were performed on livers and kidneys of the exposed mice and controls. Fatty degeneration of the liver was graded in accordance with the following criteria:

(1) Fatty degeneration involving a thin cell layer, up to two to three cells in width, usually at the periphery of the lobules;

(2) Same as in (1), but involving a layer of three to five cells in width;

(3) Pronounced infiltration of fat, either peripheral or central, involving about one-third of the lobules;

(4) Massive infiltration of fat, usually central, involving at least half of the lobules.

Fatty degeneration was particularly marked and tended to be more severe with longer exposure to tetrachloroethylene. [76]

In addition to histologic examination, chemical determination of the liver fat content was also performed. Correlation between the histological and the concentration of fat extraction was ± 0.74. The fat content of livers of the exposed animals was between 4 and 5 mg/g body weight compared to 2-2.5 mg/g for controls. The actual fat content of the livers did not increase with duration of exposure as did the extent of the fatty infiltration. No liver cell necrosis was observed nor were there reported

effects on the kidneys. [76]

Mazza [77] exposed 15 male rabbits, 4 hours/day, 5 days/week for 45 days at 2,790 ppm tetrachloroethylene, to determine the specific location of initial liver injury and to obtain serum enzymes associated with tetrachloroethylene intoxication. This was accomplished using the Schmidt Index, which is the sum of serum glutamic-oxaloacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) divided by the serum glutamate dehydrogenase (GDH). The Schmidt Index was used by the investigators as an indication of hepatic disorders. Enzymatic determinations were made before the exposure and 15, 30, and 45 days after the exposure. Activities of all three serum enzymes under study showed an increase but the GDH increased the most, reducing the Schmidt Index from 6.70 to 1.79. The investigators concluded that this reduction shows the prevalence of mitochondrial injury over cytoplasmic injury in the liver.

Mazza and Brancaccio [78] exposed 10 rabbits for 4 hours/day, 5 days/week for 45 days at 2,790 ppm of tetrachloroethylene. The effects of these exposures on the suprarenal tissues were determined by measuring urinary and plasmatic concentrations of hormones of the cortex and suprarenal medulla and mandelic acid before and after exposure at various intervals. The investigators found a moderate but not statistically significant increase of cortical and medullar hormones as well as an increase in the elimination of 3-methoxy-4-hydroxymandelic acid.

Klaassen and Plaa [79,80] estimated the ED50 for liver and kidney damage in dogs and mice. The ED50 values for organ dysfunction were measured by BSP, SGPT, glucose, protein and phenolsulfonephthalein (PSP). They also determined the potency ratio, which they defined as the ratio of

the LD50 to the ED50. All effects were observed after single intraperitoneal doses. After administration, effects on the liver and kidneys were determined by microscopic examination and by determination of SGPT elevation for the liver and PSP excretion for the kidneys.

The acute lethality and effective liver and kidney doses for dogs and mice are shown in Table XII-4.

(c) Effects on the Heart

Christensen and Lynch [81] observed depression of the heart and respiration in five dogs each given a single oral dose ranging from 4 to 5.3 cc/kg tetrachloroethylene. Autopsy showed fatty infiltration of both heart and liver tissue. In every case the small intestine was extremely shriveled and showed marked inflammation.

Barsoum and Saad [82] determined the greatest dilution of tetrachloroethylene that would have a depressant effect on an isolated toad's and rabbit's hearts were 1:3,000 and 1:4,000, respectively.

Reinhardt et al [83] studied the effect of tetrachloroethylene inhalation for 10 minutes on heart responses of 17 dogs injected with epinephrine. Tetrachloroethylene concentrations of 5,000 and 10,000 ppm were used. Tetrachloroethylene did not sensitize the hearts of any of the dogs to epinephrine. In the same study, sensitization occurred with 1,1,1-trichloroethane, trichloroethylene and trichlorotrifluoroethane. However, the investigator noted the possibility that tetrachloroethylene has the potential for cardiac sensitization but to a lesser degree than other chlorinated hydrocarbons. [83]

(d) Carcinogenicity, Mutagenicity, Teratogenicity

Schwetz et al [84] exposed 17 rats and 17 mice 7 hours daily at 300 ppm tetrachloroethylene on days 6 through 15 of gestation. The exposure was associated with a decrease in the maternal weight gain among rats, and an increase in the maternal relative weight of the liver in mice. There was an increase in the incidence of fetal resorptions in rats, and in fetal mice there were decreased body weights and increased incidences of subcutaneous edema, delayed ossification of skull bones, and split sternebrae.

Leong et al [85] gave an interim report in 1975 on the results of chronic inhalation in rats of tetrachloroethylene after 24 months. A tetrachloroethylene formulation was analyzed for composition by gas chromatography and introduced into a 3.7 cu m stainless steel chamber. The vapor concentration of tetrachloroethylene in the chamber was calculated from the ratio of material delivery rate to the total chamber air flow rate. The concentration was verified at regular intervals by infrared spectrophotometry. Two groups of rats, each consisting of 96 males and 96 females, were exposed at 300 or 600 ppm of tetrachloroethylene for 6 hrs/day, 5 days/week for 52 weeks. Food and water were witheld during exposure. A control group of 192 male and 192 female rats was not subjected to solvent exposure but was deprived of food and water on the same schedule as the experimental group. The investigators measured body weight, RBC count, HB concentration, packed cell volume, differential white count, and urinalysis for pH, specific gravity, sugar and albumic concentrations, presence of ketone bodies, and bilirubin. All animals were observed until moribund or dead. Representative specimens of all major

organs and glands were microscopically examined. Behavioral signs indicative of CNS depression, such as hypoactivity, were sought. The investigators reported that, starting from the fifth month of exposure, the mortality of male rats exposed at 600 ppm was significantly higher than that of control. The cause of death was not stated. There was no difference in mortality rates in male rats exposed at 300 ppm or female rats exposed at 300 or 600 ppm. The investigators reported that spontaneous tumors appeared with comparable frequency in both exposed and nonexposed animals after 29 months.

The National Cancer Institute is currently conducting a study of the carcinogenic potential of tetrachloroethylene. The results of this study will be evaluated when they become available.

(e) Absorption, Metabolism, Excretion and Elimination

Curves depicting the concentrations of tetrachloroethylene in expired air were developed by Boettner and Muranko [86] who exposed Sprague-Dawley rats at various concentrations of tetrachloroethylene ranging from 50 to 500 ppm for up to 40 hours. Samples of the expired air of the rats were taken at various intervals after exposure using plastic bags. The series of curves was constructed to indicate the concentration of tetrachloroethylene in the expired air when duration of exposure and concentration of solvent were varied. The curves showed that the amount of tetrachloroethylene in the breath with constant exposure time (3 hours) was proportional to the exposure concentration.

Yllner [87] determined the urinary metabolites of C 14-labeled tetrachloroethylene in five female mice exposed for 2 hours to vapor in doses of 1.3 mg/g bodyweight. In 4 days, 90% of the absorbed tetrachloroethylene was excreted or metabolized, 70% in expired air, 20% in urine, and less

than 0.5% in feces. Using chromatographic, radiographic, isotope dilution methods and, in part, Jondorf's method, the following metabolites were identified in the urine according to the percentage of total urinary activity: trichloroacetic acid, 52%; oxalic acid, 11%; and traces of dichloroacetic acid.

Daniel [88] studied the partition of Cl 36-labeled tetrachloroethylene in urine, feces and expired air of rats. Wistar rats were administered 1.75 μci or 13 μci of the labeled tetrachloroethylene by stomach tube. The half-life of expiration of tetrachloroethylene was found to be 8 hours, and 97.9% of the radioactivity was found in the expired air 48 hours after administration of the labeled tetrachloroethylene. After 18 days, 1.6-2.1% of the radioactivity was found in the urine. No radioactivity was found in the feces. Trichloroacetic acid and inorganic chloride were the only metabolites detected in the urine. On the addition of silver nitrate to the urine, 25% of the total urinary chlorine was precipitated as chloride. The remaining urinary radioactivity was accounted for by trichloroacetic acid. Oxalic acid was not found. [88]

The toxicity of trichloroacetic acid, a metabolite of tetrachloroethylene, has been the subject of some reports in the literature. [89,90] Woodard et al [89] reported the LD50 to be 3.32 g/kg for rats and 4.97 g/kg for mice. The consequences of chronic excretion of trichloroacetic acid were considered by Frant and Westendorp. [90] Trichloroacetic acid is a strong organic acid which may be neutralized in the body by sodium or potassium. Whether this constant elimination of fixed alkali will result in acidosis or diminution of the carbon dioxide-combining power of the blood has not been studied.

Dmitrieva [91] performed a number of experiments to identify the metabolites of tetrachloroethylene. In two series of chronic exposures, 24 rats were exposed 5 hours/day for 5 months at 15 and 1.5 ppm (0.1 and 0.01 mg/1) tetrachloroethylene. Concentrations were maintained by spectrophotometric monitoring. Trichloroacetic acid and ethylene glycol were found in the urine of the exposed rats but nzt in a group of eight controls. Oxalic acid was found in both exposed and not exposed animals.

Daniel [88] also exposed seven male and seven female rats at 1,000 ppm tetrachloroethylene to determine the effect on liver lipid content. The exposures were for three successive periods of 6 hours each. In the exposed female rats, 8.0 $\pm$ 1.5 mg lipid/100 mg dry liver weight was found compared to 10.7 $\pm$ 2.2 in controls, but this was not considered significant. In the exposed males, 11.3 mg lipid/100 mg dry liver weight was found compared with 11.2 for the controls.

Van Dyke and Wineman [92] found that little chloride was liberated from tetrachloroethylene in vitro by their dechlorinating enzyme system. The enzyme system was located in hepatic microsomes and required NADPH, oxygen, and a factor present in the 105,000 G supernatant. It was inducible by phenobarbital or benzpyrene, but not by methylcholanthrene.

Cornish and Adefuin [93] studied the effect of administering ethanol to rats 16-18 hours before exposing them to different chlorinated hydrocarbons. Two groups of rats, 6 each, were treated with chlorinated hydrocarbons and one of these groups was also pretreated with alcohol. Tetrachloroethylene exposure concentrations of 4,000 ppm for 6 hours, 5,000 ppm for 4 hours, 10,000 ppm for 2 hours, and 15,000 ppm for 2 hours were studied. Alcohol ingestion did not potentiate the toxicity of

tetrachloroethylene under any of these conditions. Serum enzyme levels (SGOT, SGPT and serum isocitric dehydrogenase), lipid stains of liver sections, and other histologic findings in liver, kidney, lung, adrenal gland and spleen were similar to controls in all cases. In this study, ingestion of ethanol enhanced the toxicity of carbon tetrachloride and trichloroethylene.

Cornish et al [94] studied the potentiating effects in rats of 50 mg/kg phenobarbital injected ip 2 days and 1 day before ip administration of different chlorinated hydrocarbons. Four animals were used in each group. Marked potentiation of carbon tetrachloride and chloroform toxicity were found. However there was no potentiation of the toxicity of the other chlorinated hydrocarbons studied including tetrachloroethylene.

Plaa and Larson [95] injected 10 mice ip with tetrachloroethylene at 2.5 ml/kg and 10 others at 5.0 ml/kg and found 100 mg% or more of protein in the urine of 1 of 6 surviving mice injected with the lower dose and in 2 of 4 survivors of the higher dose. The investigators found less than 150 mg% of glucose in the urine of all 10 mice. The urine was sampled 24 hours after the injection of tetrachloroethylene. The kidneys of the mice given the lower dose were examined microscopically. The proximal convoluted tubules were swollen in all animals and necrotic in one.

The metabolism of hexachlorethane, widely used as an anthelmintic in cattle and sheep, was studied by Fowler. [96] He found that pentachloroethane and tetrachloroethylene were major metabolites of hexachloroethane. He also administered tetrachloroethylene orally in doses of 0.3 ml/kg to two sheep. No adverse clinical response of the sheep to the administered tetrachloroethylene was observed, but there were some plasma

enzyme changes. Ornithine carbamoyl transferase did not change, glutamate dehydrogenase increased eight-fold in one animal and three-fold in the other, and sorbitol dehydrogenase was doubled.

Correlation of Exposure and Effect

Occupational exposure to tetrachlorethylene has caused signs and symptoms of acute effects on the central nervous system including loss of consciousness, dizziness, lightheadedness, inebriation, and difficulty in walking. [43,49,60] With prolonged exposures, signs and symptoms of chronic effects on the central, autonomic and peripheral nervous systems have been reported. These signs and symptoms included confusion, impaired memory, numbness of extremities and peripheral neuropathy including impaired vision. [43,46,51,63,72,85] Involvement of the liver in occupational tetrachloroethylene poisoning has been indicated by jaundice and enlarged livers, by clinical findings of impaired liver function and elevated serum enzymes, and by microscopic evidence of tissue changes. [51,53,55-57,59,72] In addition to these effects of absorbing tetrachlorethylene into the body, workers have experienced eye, nose and throat irritation and have developed lesions of the skin. [43,44,46,49,63]

In many of the reports of occupational exposure, environmental concentrations were not reported. [43,44,47,49] However, the conditions of work usually were described and from these descriptions it is possible to identify some of the conditions under which the effects occurred.

(a) Nervous System Effects

The only concentration measurements of tetrachloroethylene associated with unconsciousness in a work situation were reported in a study by

Stewart et al. [60] They reported a situation in which a workman was rendered unconscious while alternately cleaning steps with a solvent mixture (50% tetrachlorothylene and 50% Stoddard solvent) and mixing cement in an area where very high concentrations of the solvent vapor were present. In an attempt to determine the concentration at which the man was exposed, Stewart et al re-enacted the 3.5-hour exposure at the work site under the same conditions. They found 25 to 1,470 ppm tetrachloroethylene (average 393 ppm) and 70 to 425 ppm of Stoddard solvent.

Carpenter et al [37] reported that exposure at 2000 ppm would cause light nacrosis after 7.5 minutes and unconsciousness soon after. The lowest concentration that will produce unconsciousness has not been determined. At 1000 ppm, four subjects experienced tightness of the frontal sinuses, stinging sensation of the eyes, lassitude, slight mental fogginess, increased salivation. Similar but less severe signs and symptoms were reported by subjects in two different studies where exposures were 400-600 ppm. [37,38]

In a study of drycleaning plants where concentrations of tetrachloroethylene ranged from 25-400 ppm, Munzer and Heder found some type of hyperactivity of the autonomic nervous system in 20 of 40 workers examined. This was indicated by hyperhidrosis, dermographism and tremor of the fingers and eyelids. [63]

Lob [43] reported on a man using tetrachlorothylene as a solvent in an electrical plant where the exhaust system had not worked for 3 weeks. After work one day, he experienced nausea, inebriation and vomiting. The next day these effects were more severe and the man finally became

unconscious. In another reported case, [44] a 49-year-old man was exposed to tetrachloroethylene for 2 months while working in a degreasing operation. During this time he experienced redness of the face, irritation of the conjunctiva and eyelids, confusion and finally became unconscious on the job. In another case, [47] a 7-hour exposure in a laundry resulted in unconsciousness of a worker who forgot to turn on the cooling unit of a distillation system for recycling the tetrachloroethylene. The system overheated, causing the man to become dizzy and eventually unconscious. Two similar cases were reported by Weiss. [49] Two workers in a drycleaning plant were overcome when tetrachlorothylene heated to 200 C streamed out of a recovery apparatus. The men were burned on the face and extremities and became unconscious after a few breaths of the vapor.

Neurologic involvement has been a frequent result of occupational exposures to tetrachloroethylene where concentrations were not reported but where unconsciousness did not occur. [43,44-46,85] Lob [43] reported that, in nine cases of chronic exposure to tetrachloroethylene, all workers showed similar symptoms of vertigo, headache, nausea, vomiting, and eye and throat irritation. In two of these cases involving 2-4 years employment, more severe neurologic disorders were observed. In one worker, these included loss of memory, blindness in the left eye, and vestibular dysfunction. The other worker experienced numbness of the fingers, difficulty in walking and trembling of the extremities.

Signs of neurologic response were reported in workers in a degreasing operation where tetrachloroethylene concentrations ranging from 230 to 385 ppm occurred 2 days a week for 2.5 to 6 years. [51] All of 7 workers exhibited lightheadedness, memory impairment, headache, staggering gait,

and an inebriation-like state. Effects on the liver were also observed: these are discussed later.

In a survey of 46 drycleaning plants in Germany, Franke and Eggeling [72] found that 40% of 113 workers had either hyperhidrosis, dermographism, or tremors and 33% had mucous membrane irritation. Subjective complaints such as headaches, insomnia, dizziness, and heart complaints (otherwise undescribed), were made by 35, 34, 29, and 20% of the workers, respectively. Tetrachloroethylene concentrations in the air of these work places were reported as the result of 326 measurements; 75% were less than 100 ppm. In one of two additional plants, measurements taken every 15 minutes for several hours never exceeded 80 ppm.

Most of the reports of the effects of tetrachloroethylene at known low concentrations were experimental studies. They were performed at concentrations usually between 100 and 200 ppm. Preliminary signs of narcosis, as indicated by the overall reduction of the amplitude and frequency of EEG waves, were found in three of four men and four of five women exposed at 100 ppm of tetrachloroethylene for 7.5 hours/day. [41] Behavioral tests revealed that subjects exposed at 150 ppm showed impaired coordination after 7.5 hours of exposure.

In an earlier experiment, Stewart et al [40] found that, in a group of 15 male subjects exposed for one 7-hour period at a mean concentration of 101 ppm, 60% complained of mild eye, nose and throat irritation during the first 2 hours which subsided by the end of the experiment; 40% of the subjects felt slightly sleeply and 25% felt lightheadedness, developed mild frontal headaches or had some difficulty speaking.

Similar symptoms were found in a group of five of these subjects exposed at 101 ppm 7 hours/day for 5 days. Mild eye and throat irritation were consistently reported by two of the five subjects, and three of the five had an abnormal Romberg test on the first attempt. No control group was utilized. [40]

(b) Effects on the Liver

Tetrachloroethylene has been reported to produce effects on the liver, but the concentration at which such effects occur has not been determined.

Liver dysfunction, indicated by increased sulfobromophthalein sodium dye retention and positive urobilinogen, was found in three and four workers, respectively, out of a total of seven workers using tetrachloroethylene as a degreaser. [51] Liver cirrhosis was found in one worker. All men had been employed for at least 2 years. Concentrations of tetrachloroethylene in the workplace ranged from 220 to 385 ppm.

Out of 10 cases of tetrachloroethylene intoxication reported by Lob [43] in 1957, there was one case of liver involvement.

Liver cell necrosis was part of the pathologic diagnosis from an autopsy of a 33-year-old man who died from exposure to tetrachloroethylene. [56] The man had been working in a drycleaning establishment for 4 months. The investigators made two measurements of tetrachloroethylene and reported the concentrations of 50 and 250 ppm. The acute exposures occurred when tetrachloroethylene periodically spilled out of the drycleaning machine and fell on hot pipes, when it vaporized. Exposure also occurred when machines were being filled with tetrachloroethylene.

Bilirubin and thymol turbidity determinations were significantly affected in the 113 exposed workers studied by Franke and Eggeling [72] when compared with 43 unexposed workers.

Elevated SGOT was found in eight of nine firemen 12 days after a 3-minute exposure at an unknown concentration of tetrachloroethylene. [55] An enlarged liver and spleen were found in one man upon examination. At the time of exposure, all nine men became "woozy" for a few minutes. Results of examination of the livers of animals exposed to tetrachloroethylene at various concentrations have been reported in a number of studies. [31,37,38,75] Studying the toxicity of anthelmintic doses of tetrachloroethylene, Lamson et al [31] found no necrosis in a series of 400 animals administered doses up to 25 ml/kg or after 5-6 hours of inhalation of anesthetic concentrations.

Kylin et al [75] exposed mice at concentrations of 200, 400, 800 and 1,600 ppm for 4 hours. No liver cell necrosis was observed. However, fatty infiltration of the liver was evident at all concentrations and its extent was associated with the concentration of tetrachloroethylene.

Four groups of 20 mice were exposed by Kylin et al [76] at 200 ppm for 1,2,4 or 8 weeks. Microscopic examination revealed that fatty degeneration was particularly marked and tended to be more severe as the duration of exposure increased.

Carpenter [37] found no liver damage in rats exposed 150 times at 70 ppm tetrachloroethylene. Cloudy and congested livers with swelling were observed after exposures at 470 ppm for 8 hours/day 5 days/week for up to 150 days. Similar but less severe changes were observed after exposure at 230 ppm.

Rowe et al [38] found no effects in the livers of monkeys, rabbits and rats after repeated 7-hour exposures at concentrations up to 400 ppm. However, effects on the liver were evident in guinea pigs. After 132 7-hour exposures at 100 ppm, liver weights of female guinea pigs were increased; slight to moderate fatty infiltration of the liver was noted after exposure at 200 ppm and was more pronounced after exposure at 400 ppm; and slight cirrhosis was observed in guinea pigs exposed 7 hours/day for 169 days at 400 ppm.

(c) Carcinogenicity, Mutagenicity, Teratogenicity

The potential of tetrachloroethylene to produce carcinogenic, mutagenic or teratogenic effects has not been studied conclusively.

The effects of tetrachloroethylene in pregnant animals and their offspring were reported in two studies. [37,84] Carpenter [37] reported that fertility of rats increased slightly after exposure at 230 or 470 ppm for up to 7 months. Schwetz et al [84] found that mice and rats exposed at 300 ppm tetrachloroethylene for 7 hours/day on days 6 through 15 of gestation showed an increase in the relative maternal liver weights of mice, decrease in maternal body weights of rats, and increase in incidence of fetal resorptions in rats. In fetal mice, there were decreased body weights and increased incidences of subcutaneous edema, delayed ossification of skull bones, and split sternebrae.

Most of the effects found in the study by Schwetz et al [84] represent fetal and maternal toxicity. Only the delayed ossification of skull bones and split sternebrae could be considered as possible teratogenic effects. These occurred in mice but not in rats. The number of animals used in this study was too few to establish the significance of

these findings, since the incidences of the abnormalities in large samples of these strains of rats and mice are not known. Whether these effects would occur in other species including humans has not been determined. This is an important requirement of further research.

(d) Metabolism

The metabolic pathways of tetrachloroethylene are still questions for investigation. Trichloroacetic acid and trichloroethanol have been found in the urine of humans and animals. [41,65,69,71] Additionally, oxalic acid, dichloracetic acid and ethylene glycol have been reported in the urine of exposed animals. [74,87,88]

The effects of tetrachloroethylene at various exposure levels are presented in Table XII-5.