III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Tetrachloroethane ($CHCl_2 - CHCl_2$), also known as acetylene tetrachloride, is a colorless liquid at room temperature having a moderately strong, sweet, chloroformlike odor [1]. Compared to other chlorinated hydrocarbon solvents, tetrachloroethane has a low vapor pressure (5 mmHg at 21 C) and a high boiling point (146 C). Some important physical and chemical properties of tetrachloroethane are listed in Appendix IV [2,3,4].

Tetrachloroethane was the first chlorinated hydrocarbon solvent produced in high tonnage before World War I [3]. Because of its powerful solvent properties, it found industrial use as a solvent for cellulose acetate, fats, waxes, greases, rubber, and sulfur [3,5]. However, because of its toxicity, tetrachloroethane has been largely replaced since World War II by other, less toxic solvents. Its current use is quite limited; in 1975, Hooker Chemicals and Plastics Corporation was the only manufacturer in the United States [6 (p 1)]. The manufacturing process for tetrachloroethane involves the chlorination of acetylene [6 (p 4)]. Most of the tetrachloroethane produced by the one company (production figures not available) is used at the same location as an intermediate in the manufacture of trichloroethylene and tetrachloroethylene. Prior to 1967, tetrachloroethane was the primary starting material for producing these other chlorinated hydrocarbon solvents but, since that time, a process involving chlorination of ethylene has predominated. A small percentage of the tetrachloroethane produced is used as a carrier or reaction solvent in

the manufacturing processes for other chemicals. Tetrachloroethane is used also by a number of textile manufacturers as an analytical reagent in polymer characterization tests [6 (p 1)].

NIOSH estimates that 5,000 workers in the United States are potentially exposed to tetrachloroethane.

Historical Reports

The adverse health effects from exposure to tetrachloroethane first became apparent at the beginning of World War I with reports [7,8] of numerous poisonings of workers in the aircraft industries of several European countries. Tetrachloroethane was the solvent in the varnish or "dope" used to make airplane wing surfaces impervious to moisture and air. The chemical was chosen because of its low cost, limited solubility in water, incombustibility, and its unique ability to tighten the stretched fabric forming the wings [8].

In 1914, Heffter [7] reported that inhalation of tetrachloroethane was responsible for an increasing incidence of poisoning among Germany's aircraft factory workers. Heffter was a member of a commission that investigated the illnesses of 12 of 15 workers who regularly used two varnishes containing 30 and 50% tetrachloroethane by weight; 2 of the 12 afflicted workers had died. Heffter classified the patients by signs and symptoms into two groups: one group showed mainly gastrointestinal disturbances, jaundice, and enlarged livers; the second group had neurologic disturbances such as hand tremors, sensations of deafness, paresthesias in the extremities, reduced patellar reflexes, and headaches, in addition to anorexia and nausea. Animal experiments [7] designed to

verify suspicions that tetrachloroethane was the varnish constituent responsible for the illness showed that tetrachloroethane and the two varnishes produced similar gastrointestinal and hepatic effects in dogs. The neurologic effects seen in the humans were not found in the dogs. The German commission recommended banning the use of all varnishes containing tetrachloroethane. Before the end of World War I, there were numerous poisonings attributed to tetrachloroethane in the aircraft industries of Germany, France, England, and Holland; in England alone, there were 70 reported cases with 12 deaths [9].

A 1917 study by Hamilton [10] of 18 domestic airplane factories revealed no severe overexposures to tetrachloroethane. Noting only complaints of headache, drowsiness, and nausea, Hamilton concluded that the absence of serious hepatic symptoms was due to the limited production and to the short exposure time for workers in the American factories compared with those in European plants.

Effects on Humans

As a result of the numerous occupational poisonings attributed to overexposure to tetrachloroethane, much clinical data have been presented in medical reports [5,8,11-14]. Most of these overexposures occurred before World War II. Although none of the reports contained quantitative exposure data, they consistently indicated primary involvement of the liver and of the nervous and gastrointestinal systems.

Most of the reported poisoning cases had a clinical picture characterized by gastrointestinal and hepatic symptoms. Browning [9] described this form of tetrachloroethane poisoning in four progressive

stages, as follows:

(a) Prejaundice - anorexia, constipation, drowsiness, exhaustion, and nausea.

(b) Jaundice without toxemia - jaundice with pale stools and bile-stained urine, increased exhaustion, albuminuria, and vomiting.

(c) Jaundice with toxemia - increased vomiting and jaundice accompanied by other toxic manifestations such as delirium and convulsions.

(d) Fatal - severe jaundice of the entire body.

Willcox et al [8], in 1915, reported 14 poisonings, 4 of which were fatal, and all were of the gastrohepatic type associated with exposure to tetrachloroethane. The 14 victims, 11 men and 3 women between the ages of 17 and 58, were employed in three separate aircraft factories in Great Britain. The authors stated that there were additional poisonings, but these 14 cases were the only ones detailed in clinical reports. The varnishes used in the three plants all contained about 12% tetrachloroethane by weight; acetone, benzene, methylated spirit, and cellulose acetate were the other constituents. From autopsies of rats subjected to inhalation exposures to the individual constituents of the varnishes, the authors [8] concluded that tetrachloroethane was the primary liver poison in the varnish. The poisoned workers included several "dopers" who applied the varnish and probably had dermal contact in addition to inhalation exposure, as well as several workers who did not handle the varnish but were exposed by inhalation.

The first indications of effects from tetrachloroethane on the workers [8] were complaints of general malaise, drowsiness at work, anorexia, nausea, retching in the morning, unpleasant taste in the throat,

constipation, and headache. Two of the workers complained of these early symptoms immediately or soon after the start of exposure; the other 12 were exposed for 2-4 months before becoming ill. These nonspecific symptoms lasted several days or even weeks before definite jaundice, often accompanied by pale stools, biliuria, and vomiting, developed. According to the authors [8], this was the stage at which most of the affected employees left work. In early stages of the illness, there was often slight liver enlargement but no accompanying abdominal pain; as the illness progressed, the liver diminished in size. Workers who were removed from tetrachloroethane exposure when they showed the early stages of poisoning recovered fairly promptly, although it was usually several weeks before the jaundice was no longer evident. As the disease progressed, the workers became mentally confused, stuporous or delirious, and finally comatose. Purpuric rash, suppression of urine, hematemesis, and convulsions were also noted in the later stages.

Post-mortem examinations were performed on three of the four workers who died [8]. Examination of the first victim revealed pathologic changes predominantly in the liver, although some changes in the heart and kidney tissues also were observed. The heart showed fatty degeneration, as did the kidneys which were enlarged and bile-stained. The liver was reduced in size, soft, wrinkled, and deeply bile-stained throughout. Microscopic examination revealed extreme liver destruction, large portions of liver tissue having been replaced by fibrous tissue. The livers of the other two victims were greatly reduced in size with large areas of necrotic liver cells; however, no fibrous replacement tissue was yet apparent. The authors suggested that death had occurred more quickly in these patients

than it had in the first, before regeneration of the liver had begun.

Symptoms involving the nervous system occurred in a second group of occupational poisoning cases [5,12,13]. These usually started with a sensation of numbness and loss of feeling in the toes and fingers, paresthesias, hand tremors, and plantar pain. Two such examples reported by Leri and Breitel [13] in 1922 involved two young women, a 16-year-old and a 17-year-old, who had been exposed to tetrachloroethane while employed at a plant manufacturing artificial pearls. Both women were assigned to dipping artificial pearls into a varnish composed of an oil made from "ablet" shells that had been dissolved in tetrachloroethane and small amounts of alcohol and cellulose acetate. The onset of poisoning occurred after 2 years of employment for the 17-year-old and after only 3 months for the other; however, the latter had the additional responsibility of stirring the varnish, which she did with her hands. The initial effects consisted of vertigo and a feeling of inebriation for the older woman, while diarrhea, colic, amenorrhea, and the inability to control evacuative functions were reported for the younger woman. In spite of these initial differences, the advanced clinical pictures in the women were similar--difficulty in walking, paresis of the last phalanges of their toes and fingers, severe hypoesthesia of the ends of the toes, tingling sensations in the toes and terminal phalanges of the fingers, and paresis of the soft palate with an absence of pharyngeal reflex. The only reported difference was that the 17-year-old developed paresis of the sphincter muscles of the eyelids and lips, whereas the other did not. The signs and symptoms were quite persistent and were still present, although diminished, 1 year after the women had left the factory.

Similar neurologic disturbances in German aircraft workers during World War I were reported by Grimm et al [12]. In several cases reported by Schultze [11], Zollinger [5], and Fiessinger and Wolf [14], gastrointestinal and hepatic effects, as well as neurologic signs and symptoms, occurred simultaneously during the course of the disease.

There have been several reports of nonoccupational poisonings from tetrachloroethane consumed with suicidal intent. Two similar cases, one described by Hepple [15] in 1927 and another by Elliott [16] in 1933, involved a 21-year-old man and a 43-year-old member of the British Armed Forces, respectively. Shortly after drinking an unknown quantity of silk cleaning fluid containing tetrachloroethane, each subject lost consciousness and, when examined after hospitalization, showed complete absence of corneal reflexes. Elliott [16] reported marked cyanosis in the older man, while Hepple [15] described progressive respiratory difficulty leading to Cheyne-Stokes respiration (periods of hyperpnea alternating with periods of apnea) in the younger man. Neither subject regained consciousness despite efforts at resuscitation; the older man died within 12 hours and the younger man died 20 hours after exposure. Forbes [17] and Lilliman [18] documented the deaths of two other men who had consumed unknown volumes of tetrachloroethane. Signs and symptoms were consistent with those previously described, ie, early loss of consciousness, further CNS depression, and death. Forbes [17] reported that a 33-year-old man died 6 hours after ingesting tetrachloroethane; according to Lilliman's report [18], death occurred after approximately 9 hours. Gross and microscopic post-mortem examinations of the four victims [15-18] revealed no remarkable changes except "tissue congestion" and hyperemia.

A case reported by Lynch [19] in 1967 involved a 67-year-old man who, having ingested an unknown quantity of tetrachloroethane, collapsed in the street and was taken to the hospital already comatose. He did not respond to unspecified stimuli and, although breathing rapidly and regularly, he was cyanotic; his condition rapidly deteriorated until death 8 hours after hospital admission. Histologic examination showed small droplets of fat in the hepatic cells and in the cells lining the proximal and distal renal tubules. Although the victim, an active gardener, had used a tetrachloroethane spray for whiteflies, the likelihood of inhalation effects could not be determined from the information given. Moreover, the recovery of 4 ml of tetrachloroethane from the victim's stomach indicated that death was primarily due to ingestion.

There were two incidents in Africa, where tetrachloroethane was mistaken for tetrachloroethylene and given as a treatment for hookworms. In 1953, Sherman [20] reported that eight adults each received 3 ml tetrachloroethane orally with 1 oz of magnesium sulfate and water. Within 2 hours, the three who were hospital patients became comatose, but were revived with enemas and methedrine injections; the five outpatients were found in various stages of semiconsciousness, but revived without treatment. None of the eight experienced any adverse aftereffects during a 3-month observation period. A similar incident in which a young man, a young woman, and a 12-year-old girl were erroneously given 3, 3, and 2 ml of tetrachloroethane, respectively, was described by Ward [21] in 1955. The man and woman became comatose but they were revived by gastric lavage and iv injections of nikethamide, a stimulant. The girl was induced to

vomit with a strong emetic and did not lose consciousness or suffer other ill effects.

In 1970, Morgan et al [22] reported their use of a radioactive tracer method to study the absorption and excretion rates of inhaled tetrachloroethane. A gas chromatograph with a radioactivity detector was used to isolate and quantitate 38Cl-labeled tetrachloroethane, which was eluted directly into a collection tube. All subsequent monitoring was done by gamma-ray scintillation spectrometry. A volunteer deeply inhaled 2.5 mg of 38Cl-labeled tetrachloroethane vapor from a 150-ml bulb. Measurement of residual radioactivity in the bulb indicated that almost all of the labeled tetrachloroethane was inhaled. After holding the breath for 20 seconds, the subject exhaled through an activated-charcoal trap. He then inhaled room air and exhaled through the trap a second time. The radioactivity of the trapped material was then measured, and it was determined that about 97% of the inhaled tetrachloroethane was retained in the lungs. The subject continued to breathe room air and to exhale for 1 hour through charcoal traps that were changed periodically. Analysis of the radioactive material on these traps indicated that only 3.3% of the initially retained tetrachloroethane was exhaled in 1 hour.

After performing in vitro experiments, Morgan et al [22] reported the partition coefficient, KD (concentration in liquid/concentration in gas), of tetrachloroethane between blood and air to be 72.6 and between serum and air to be 78.2. The KD's for tetrachloroethane were much higher than those for the other chlorinated hydrocarbons tested, eg, the blood-air and serum-air KD's were 9.5 and 5.9, respectively, for trichloroethylene and 44.2 and 37.1, respectively, for trichloroethane. These experiments were performed

at 40 C. Because of tetrachloroethane's high KD values in spite of its poor solubility in water, the authors [22] postulated that its KD's between blood and air and between serum and air actually represented the solubility of tetrachloroethane in blood and serum lipids. A later report by these authors [23], in 1972, supported their earlier findings when they reported the partition coefficient of tetrachloroethane between olive oil and air to be 1,110 as compared to 220 between serum and air (at 25 C). Inhalation and partition-coefficient experiments [22] with several other halogenated hydrocarbons indicated a definite correlation between their absorption and retention and their respective KD values. Of the compounds tested, tetrachloroethane had the highest KD values, one of the highest rates of absorption, and one of the lowest rates of elimination by exhalation. The measured absorption of 94% (total of 6% exhaled in 1 hour) may not be directly applicable to acute occupational exposure because in the experiments there was optimum absorption efficiency (holding the breath for 20 seconds).

Barrett et al [24] reported in 1939 that one of the authors voluntarily for 10 minutes inhaled vapor which was generated from an open vessel of tetrachloroethane heated to 50 C. No specific information on the exposure concentration was given. The subject stated that the sensations produced were less pleasant than the sweetish taste and very slight euphoria that were experienced with trichloroethylene inhalation. No noticeable aftereffects were reported, and direct urinalysis for chlorinated hydrocarbons by the Fujiwara test [25] was negative. Two hours after the exposure, the first 5 cc of steam distillate obtained from 25 cc of urine gave a faintly positive Fujiwara reaction; at 24 hours, analysis

of the distillate for chlorinated hydrocarbons was negative.

The results of this qualitative experiment were consistent with those reported for dogs, rats, guinea pigs, and rabbits in the same study [24], as described in this document in Animal Toxicity. Because no chlorinated hydrocarbon compounds were found in the urine, Barrett et al [24] concluded that, contrary to their speculation, tetrachloroethane was not initially metabolized to trichloroethylene, a compound which does produce chlorinated hydrocarbons (ie, trichloroacetic acid) in the urine.

In 1936, Lehmann and Schmidt-Kehl [26] reported the effects of acute inhalation of tetrachloroethane in two male volunteers. At the beginning of each experiment, a technician sprayed tetrachloroethane into a 10-cu m exposure chamber either with a hand sprayer or an atomizer with oxygen as the propellant. The tetrachloroethane concentration was measured by absorption on calcium oxide, hydrolysis in alcohol, and chloride determination by the Volhard method [27]. The eight reported test concentrations were determined as exposure periods began; however, measurements showed that concentrations decreased only by about 10% during exposure. The two men were exposed simultaneously at concentrations ranging from 0.02 to 2.3 mg/liter (2.9-335 ppm) for exposure periods up to 30 minutes. The men did not complain of any effects during 10-minute periods of exposure to tetrachloroethane at concentrations of 0.02, 0.03, or 0.09 mg/liter (2.9, 4.4, or 13 ppm). A detectable odor was reported, even at the lowest concentration; at 13 ppm, the odor was discernibly stronger. After exposure at 0.8 mg/liter (116 ppm) for 20 minutes, the men experienced dizziness and mild vomiting. Initially, the odor was even stronger than at the previous concentration but was not discernible by the

subjects after 10 minutes. At 0.9 mg/liter (131 ppm), the men experienced dizziness after 10 minutes and the exposure was terminated. The exposure at 1.0 mg/liter (146 ppm) lasted 30 minutes, although the subjects experienced dizziness after 10 minutes, mucosal irritation at 12 minutes, and fatigue after 20 minutes. A 10-minute exposure at 1.8 mg/liter (262 ppm), resulted in dizziness and mucosal irritation of the mouth, eyes, and nose. The odor produced a repulsive bitter-sweet taste which disappeared after 5 minutes. The highest exposure concentration, 2.3 mg/liter (335 ppm), initially produced a stronger odor which was not discernible after 3 minutes. Tetrachloroethane at this concentration produced dizziness in 3 minutes and fatigue and mucosal irritation at 10 minutes at which time the exposure was ended. Although the subjects also experienced weakness in the knees, they said that they did not feel faint. This report [26] of effects on humans experimentally exposed to tetrachloroethane is one of the few found and indicates that although the odor of tetrachloroethane was detected at even the lowest concentration used, 0.02 mg/liter (2.9 ppm), odor is an unreliable indicator of tetrachloroethane exposure because workers may become inured to its presence.

Lehmann and Schmidt-Kehl [26] also measured tetrachloroethane in the expired breath of the two subjects during exposures at five concentrations ranging from 0.8 to 2.3 mg/liter (116-335 ppm). The only detail reported was that the two subjects exhaled into a bottle of air that had been warmed for 3 minutes in a 37 C water bath, probably to deter condensation and thus allow an accurate measurement of the expired tetrachloroethane concentration. These determinations indicated that 45-62% of the inspired tetrachloroethane was not exhaled.

Epidemiologic Studies

In 1957, Jeney et al [28] reported the findings from a 3-year study of the effects of tetrachloroethane on workers in a penicillin factory in Czechoslovakia. Tetrachloroethane was used in this plant as a solvent for extracting the penicillin from the fermentation liquid. The process included two different liquid-liquid extractions; the resulting emulsions were separated with equipment designated as "separators." When the workers routinely dismantled these separators to clean and rinse the parts, much higher concentrations of airborne tetrachloroethane resulted than during normal operation. Workers were required to wear gas masks with filters while dismantling and cleaning the separators; the efficiency of these protective devices was not reported. The workers spent about 90% of their 6- to 8-hour workday in the extraction room, with approximately 60 hours/month spent cleaning the separators. The ventilation system used in the work area was improved twice during the course of the study. In April 1954, two exhaust vents were added to the system after it had been evaluated as inadequate in 1953. The entire extraction system was moved in March 1956 to another building where the concentration of tetrachloroethane in the air was initially higher than it had been in the first plant. Eventually, the new ventilation system was greatly improved. Also, the work shifts were shortened from 8 hours to 6 hours, and the workers started to wear overalls that were periodically changed. The authors [28] did not mention whether or not dermal contact had any importance in the exposure of workers to tetrachloroethane.

During the study [28], from 34 to 75 workers were employed at the factory at any given time. They were between 20 and 50 years of age, were

of average body weight, and had no apparent liver ailment, anemia, gastric disorder, or alcoholism. Because liver disorders appeared in workers soon after production started at the factory in 1952, physical examinations, every other month, were instituted in July 1953. Several blood and urine tests to measure liver function were included with general physical examinations. All prospective employees were also given this screening examination.

The authors [28] reported that area air samples taken at various locations within the plant were collected with bubblers containing amyl alcohol and analyzed for tetrachloroethane by a method utilizing alkaline dechlorination followed by titration of the liberated chloride. The measured concentrations of tetrachloroethane in 170 air samples were from 0.01 to 1.7 mg/liter (1.5 to 247 ppm). The concentration ranges for each of four processes with three different ventilation systems are shown in Table III-1. More specific sampling results were not reported. The decrease in the tetrachloroethane concentration was greatest in the area of sludging, a part of the cleaning process, where the maximum concentrations were reduced from 247 to 36.4 ppm.

During the first year after the screening examinations were initiated, 31% of the workers had adverse signs and symptoms, particularly digestive organ complaints. These were loss of appetite, bad taste in the mouth, epigastric pain, and sensations of pressure in the liver area for 66% of these workers; headaches, general debility, and lack of stamina for 29%; lost body weight for 4%; and painful prurigo for 1%. During the second year, only 13% of the workers had such symptoms, and this percentage

TABLE III-1

CONCENTRATIONS OF TETRACHLOROETHANE (PPM) IN THE AIR DURING PENICILLIN MANUFACTURING

Process	Ventilation System		
	Original 1953 - March 1954	Improved April 1954 - February 1956	New Plant
First separation	2.3- 14.6	1.5- 14.6	1.5-21.8
Second separation	4.4- 58.2	1.5- 46.6	1.5-29.1
Sludging (elutriation)	11.6-247	4.4-124	1.5-36.4
Disk rinsing	10.2- 58.2	7.3- 29.1	1.5-36.4

Adapted from Jeney et al [28]

had decreased to 2% the third year. These results are shown in Table III-2, as are other signs that were detected in the periodic examinations. As a direct consequence of the results of these examinations, 18-21 workers were transferred each year to other work areas where there was considerably less exposure to tetrachloroethane. Palpable livers disappeared within 2 weeks after the workers were transferred if no jaundice had yet developed. No cirrhosis developed as a sequela of enlarged livers. The morbidity data for the factory, which included sick leave records, showed that during the year before the screening examinations were started, 21 workers (50%) were absent some time because of ailments related to the liver. In the next 3 years, this percentage was 5.5%, 20%, and 6.3%, respectively.

TABLE III-2

PERCENT OF PENICILLIN FACTORY WORKERS SHOWING SIGNS AND SYMPTOMS DURING PERIODIC EXAMINATIONS

Signs and Symptoms	First Year	Second Year	Third Year
General digestive organ complaints	31	13	2
Enlarged liver	17.8	20	5
Urobilinogenuria	50	24	12
Increased serum bilirubin	20	18.7	7.6

Adapted from Jeney et al [28]

The thymol coagulation test was used during the 3 years [28] to indicate liver dysfuntion. The correlation coefficient between number of workers showing positive results versus employment duration was +0.381 and was significant at the 0.1% level. Other liver function tests such as the Takata-Ucko, gold salt, and Weltmann reactions showed much weaker correlations. The results of the periodic examinations revealed no neurologic disorders, such as paresthesia or loss of reflexes. There was also no correlation found between the duration of employment at this factory and abnormal variations in RBC, hemoglobin content, WBC, and differential WBC.

Signs and symptoms of adverse effects definitely decreased after screening examinations were instituted in July 1953 [28]. The practice of transferring workers as soon as they showed intial signs of liver dysfunction was probably a major factor in this improvement as well as in

the prevention of more advanced liver disease. It is difficult to determine the degree to which the improved conditions, resulting from the different ventilation systems, affected the occurrence of signs and symptoms. Although there was a decrease in concentrations of airborne tetrachloroethane, the wide ranges make it difficult to estimate worker exposure with each ventilation system. Furthermore, it is not possible to accurately correlate the results of the screening examinations with the different conditions because the periods under each ventilation system did not coincide with the yearly intervals for which the signs and symptoms were reported. Even with the periodic examinations and the improved ventilation at the new plant where the concentrations ranged from 1.5 to 36.4 ppm, workers still showed indications of liver dysfunction. At the new plant, the workers were exposed to tetrachloroethane at 15 ppm for most of each work shift and at higher concentrations (up to 36.4 ppm) during the cleaning operations. The authors [28] stated that tetrachloroethane even at these reduced levels caused liver disease. The health effects described in this study were ascribed to tetrachloroethane exposure by the authors. No contaminants that could have contributed to the observed effects were mentioned.

In 1963, Lobo-Mendonca [29] reported the occurrence of nervous and gastrointestinal disorders among workers exposed to tetrachloroethane in India's bangle-manufacturing industry. This survey included 380 of the 474 workers employed in 23 different factories. The manufacturing process included two steps in which the workers had direct dermal contact with liquid tetrachloroethane as well as inhalation exposure to tetrachloroethane vapor. This included 85 cylinder makers who worked with

a 50:50 mixture of tetrachloroethane and acetone and 107 bangle polishers who used undiluted tetrachloroethane. The exposure of the other 188 workers was alleged to be primarily by inhalation of tetrachloroethane at concentrations that varied from one work area to another within a single factory, as well as between the different factories. Air concentrations were measured by the method of Fahy [30], which includes collection on silica gel, extraction with alcohol, hydrolysis with potassium hydroxide, and titration of the liberated chloride against silver nitrate.

Case histories and physical examinations were used in this study [29] to assess the condition of the workers. The number and percent of workers in each job category who showed general, nervous, and gastric effects and the ranges of tetrachloroethane in air concentrations that were measured at the jobsites in several of the factories are listed in Table III-3. These figures are only general indicators of exposure since there was no systematic sampling system or evaluation of skin absorption.

The most common effect [29], fine hand tremors, occurred in 35% of the workers. However, more than 63% of the cylinder makers, one of the two dermally exposed groups, showed this effect. The effect of acetone, which was used in this step, was not considered by the author. In the other dermally exposed group, the bangle polishers, 36% showed fine hand tremors. The author [29] also compared the number of workers showing tremors at four factories having different tetrachloroethane in air concentrations and found a dose-dependent effect. Breathing zone air samples were taken at only two worksites in each factory, and Lobo-Mendonca (written communication, August 1976) stated that the reported concentrations were averages, but he did not specify the number of determinations made for each

TABLE III-3

EFFECTS ON BANGLE FACTORY WORKERS EXPOSED TO TETRACHLOROETHANE

Job Category	Cylinder Making, Turning	Polishing, Separating	Cylinder Cutting	Heating	Packing	Other	Total
Avg Concentrations (ppm)	17, 98	20, 61	14	11	9	No data	-
No. of Workers	85	107	52	50	42	44	383
Effects	Number (%) of Workers Reporting Symptoms						
Tremors	54 (63)	39 (36)	14 (27)	3 (6)	14 (33)	9 (20)	133 (35)
Anemia	33 (39)	45 (42)	12 (23)	9 (18)	15 (36)	14 (32)	128 (34)
Vertigo	33 (39)	43 (40)	6 (12)	22 (44)	7 (17)	5 (11)	116 (31)
Headache	22 (26)	36 (34)	8 (15)	18 (36)	11 (26)	6 (14)	101 (27)
Abdomen pain	14 (16)	36 (34)	11 (21)	16 (32)	6 (14)	7 (16)	90 (24)
Anorexia	22 (26)	28 (26)	14 (27)	11 (22)	8 (19)	3 (7)	86 (23)
Flatus	17 (20)	11 (10)	7 (13)	1 (2)	4 (10)	5 (11)	45 (12)
Vomiting	9 (11)	13 (12)	2 (4)	7 (14)	2 (5)	2 (5)	35 (9)
Fatigue	13 (15)	10 (11)	4 (8)	1 (2)	2 (5)	3 (7)	33 (9)
Nervousness	6 (7)	14 (13)	0 (0)	8 (16)	0 (0)	1 (2)	29 (8)
Constipation	5 (6)	7 (7)	3 (6)	5 (10)	3 (7)	4 (9)	27 (7)
Nausea	1 (1)	10 (11)	1 (2)	11 (22)	0 (0)	1 (2)	24 (6)
Sweating	0 (0)	13 (12)	0 (0)	7 (14)	0 (0)	1 (2)	21 (6)
Numbness	2 (2)	5 (5)	1 (1)	2 (4)	0 (0)	0 (0)	10 (3)
Weight loss	0 (0)	2 (2)	4 (8)	0 (0)	0 (0)	2 (5)	8 (2)

Derived from Lobo-Mendonca [29]

value. In the factory with the highest average tetrachloroethane concentrations (65 and 98 ppm), 50% of the workers exhibited tremors. In the second and third factories, with average concentrations of 50 and 61 ppm, and 40 and 74 ppm, respectively, 41% and 33% of the workers exhibited this effect. Even in the factory with the lowest average concentrations, 9 and 17 ppm, 14% of the workers showed fine tremors of the hand.

Other neurologic complaints reported in this study [29] were headaches in 26.6% and vertigo in 30.5% of the 380 workers surveyed. Gastric symptoms included anorexia (22.6%), abdominal pain (23.7%), and flatus (11.8%). The urine of several workers was analyzed for urobilinogen, but the results were negative. Lobo-Mendonca [29] stated that a 3-month exposure period ensued before the appearance of the various signs and symptoms, which became more pronounced after 6 months. Examinations indicated that 128 workers were anemic but, without a control group, this finding was considered inconclusive because anemia was a common finding in persons of the socioeconomic group from which these workers were drawn.

It appears from this study [29] that hygienic practices were virtually nonexistent in the bangle-manufacturing industry in India. The study was hampered because the workers were transient, only minimal environmental data were presented, and many of the reported signs and symptoms are often associated with common ailments. Nevertheless, Lobo-Mendonca [29] reported that there was an exposure-effect correlation for the most common disorder observed, hand tremors.

In 1964, Horiguchi et al [31] reported tetrachloroethane concentrations measured at three artificial pearl factories (designated A,

B, and C) where tetrachloroethane was used, and the results of clinical examinations of workers in each of them. During the several steps in the pearl-manufacturing process, workers immersed racks of beads into different tanks containing various organic solvents; the first tank contained ethyl acetate and butyl acetate, amyl acetate was in the next tank, and the third tank contained tetrachloroethane. The racks were then put on shelves to dry. The authors [31] reported that tetrachloroethane concentrations in July 1960, during the first of two surveys, ranged from 75 to 224 ppm at the three factories. No information on the sampling and analytical procedures or on whether the values represented single or mean measurements was reported. According to the authors, none of the factories had ventilation equipment, nor did any of the workers use respirators or other protective equipment. A second survey, conducted 16 months later, showed that factories A and C had stopped using tetrachloroethane altogether, while at factory B, the tetrachloroethane in air concentration had been reduced to 20 ppm, primarily by local ventilation (see Table IV-2).

Clinical examinations [31] were performed on 18 male workers during the first survey and on 20 male workers during the second. Most of these workers were examined during both surveys, but neither the number of workers employed at each factory nor the total number of workers exposed to tetrachloroethane at each factory was reported. No control workers were included in this study. Ten different clinical tests were performed in 1960, and 12 tests were done in 1961; however, only 8 of the tests were common to both surveys. Thus, a direct comparison of all of the test results was not possible. The signs which were tested for in both clinical surveys and the criteria used were: lymphocytosis (over 45% of white blood

cells), low whole blood specific gravity (below 1.054), erythropenia (below 4.49 million/cu mm), low white blood cell count (below 4,999/cu mm), reduced hemoglobin content (below 12.9 g/dl), positive urinary urobilinogen and albumin tests, and enlarged liver. A comparison of the percentages of the examined workers having these signs in the two surveys showed a marked reduction in lymphocytosis for workers at factories A and C, down from 50 and 100% to 14 and 20%, respectively; in factory B, the improvement (from 88 to 50%) was less pronounced. The occurrence of abnormal whole blood specific gravity also decreased in workers at factories A and C, from 75 and 83% in the first to 14 and 0% in the second survey, while those workers affected in factory B decreased from 50 to 25%. The occurrence of erythropenia in workers decreased at factories A and C from 50 and 67% to 14 and 20%, respectively, and at factory B from 25 to 13%. The percentage of workers with abnormal white cell counts and urinary urobilinogen showed no definite reductions with decreased tetrachloroethane exposures; the percentage of workers with an enlarged liver increased from 5 to 10% between surveys. No worker had either abnormal hemoglobin content or urinary albumin. An important observation, reported for the first survey only, was that 39% of the workers had abnormal neurologic indications, including tongue spasm, weakened quadricep reflex, headache, and paresthesia.

By comparing the clinical results at the two factories that had discontinued the use of tetrachloroethane totally by the time of the second survey with those at factory B where the exposure level was still 20 ppm, Horiguchi et al [31] inferred a correlation between the tetrachloroethane concentrations and the adverse clinical findings. The absence of

information in several aspects of this report limits the conclusions that can be derived from the study. The exact times of the changes in industrial processes were not reported. It was also unclear whether there was dermal contact in the dipping process or if exposure was limited to inhalation. In addition, the workers were exposed to several other solvents, including ethyl acetate, butyl acetate, and amyl acetate.

Gobbato and Bobbio [32], in 1968, reported on the cardiovascular status of 75 workers employed in the production of tetrachloroethane, trichloroethylene, and tetrachloroethylene in Italy. Observations were made on workers in four different areas: (A) in the plant where tetrachloroethane was produced via chlorination of acetylene; (B) in the plant where trichloroethylene and tetrachloroethylene were produced from tetrachloroethane; (C) in the storage and loading department; and (D) in the quality control laboratories of the two production plants. According to the authors [32], tetrachloroethane exposure was likely to occur in both production plants, which included many different worksites and types of jobs, and in the laboratories, where there was only one type of job in one work area. All worksites at the production plants except the laboratories were outdoors; staff rooms were inside. The 75 workers were 20- to 59-years-old and had worked an average of 7.7 years at the plants. Of the total, 25 worked or had worked in area A, 29 in area B, 7 in area C, 4 in area D, and 10 on the maintenance crew. The authors did not report the age, sex, or number of workers assigned to specific worksites within each production plant. Neither the percentage of the total factory population represented by this study group of 75 workers, nor the basis for their selection was reported.

Gobbato and Bobbio [32] used Truhaut's modification of the Fujiwara method [33]; this is a nonspecific analytical procedure for chlorinated hydrocarbons. All reported worksite concentrations were related to one or a group of compounds and were not assumed to be totally accurate. In production plant A, the minimum tetrachloroethane concentration (average for six determinations) was 0.37 ppm in the staff room, and the maximum average measured concentration was 1.33 ppm in the product recovery zone. An average concentration of 0.79 ppm was reported for the laboratory. The single maximum tetrachloroethane concentration over the five sampling zones in production plant A was 3.20 ppm, measured in the product recovery zone. During maintenance and unusual circumstances, values between 5 and 15 ppm and, occasionally, as high as 40 ppm were measured in the work zone. These routine maintenance operations lasted less than 30 minutes for each work shift; the workers wore filter masks during these operations. The tetrachloroethane concentrations at production plant B could not be estimated because tetrachloroethylene and trichloroethylene were the predominant compounds present. It was noted that concentrations of tetrachloroethylene and trichloroethylene combined did not exceed 10 ppm in the air of production plant B.

The results of clinical examinations of the 75 workers [32] indicated that pulse rates, cardiac capacities, circulatory responses to postural changes, and ECG's were not significantly different from "normal" values the authors chose from the literature. The authors did not report any attempt at considering ages in these comparisons. Eight workers had arterial blood pressure values which were high compared to "normal" values which took age into account; however, the authors [32] minimized the

importance of these cases by noting that five of the eight workers had shown no elevated arterial pressures in previous periodic examinations and the other three workers had either hereditary sclerotic cardiopathy or hypertension. The results from the other cardiovascular function tests did not receive similar critical examination.

Gobbato and Bobbio [32] concluded that the chronic low-level exposures to tetrachloroethane, as well as to trichloroethylene and tetrachloroethylene, in this factory caused no greater occurrence of cardiovascular lesions than that in the general population. However, the exact extent of exposure to tetrachloroethane is uncertain from the data presented in this study. Production plant A was probably the best location for the effects of exposure to tetrachloroethane alone to be investigated, but the clinical test results for workers there were not distinguished from those of the total working group. Furthermore, the authors [32] were inconsistent in their analysis of the data; ages were not considered for those examinations indicating no significant differences from the chosen "normal" values.

Animal Toxicity

In two animal studies, tetrachloroethane has been shown to be readily absorbed through the lungs [34] and through the skin [36]. In 1910, Lehmann and Hasegawa [34] studied the absorption efficiency of inhaled tetrachloroethane in one rabbit exposed at 9.1 mg/liter (1,300 ppm) for 3 hours. The rabbit was tracheotomized for continuous monitoring of expiration volume as well as tetrachloroethane in the expired breath. Tetrachloroethane was determined by absorption and hydrolysis in alkaline

alcohol, in conjunction with the Mohr method [35] of chloride determination. During the first 15-minute exposure period, the rabbit absorbed 44.5% of the inspired tetrachloroethane. Absorption decreased to 34.0% during the second 15 minutes and 21.2% during the third; it fluctuated near this latter figure for the duration of the exposure. During this 3-hour period, the rabbit inspired a calculated total of 883.3 mg of tetrachloroethane and absorbed a total of 258.3 mg. During the 4-hour period following exposure, the rabbit expired only 19.8% of the absorbed tetrachloroethane.

In a 1936 report, Schwander [36] described the application of tetrachloroethane to the shaved abdomens of two rabbits to investigate its dermal absorption. A semispherical glass vessel was attached to the abdomen and sealed with a bandage and a gelatin sealant. Although the amount of tetrachloroethane applied was not given, a 22 sq cm area of skin was in contact with the liquid. An airtight mask was placed over each rabbit's head and the exhaled air was passed through a trap containing alcohol which dissolved any expired tetrachloroethane. A valved duct allowed the rabbits to inspire fresh air. Periodically, a copper wire was dipped in the alcohol and then placed in a Bunsen burner flame. A green-colored flame would indicate that a halogenated compound was being exhaled by the rabbit.

Tetrachloroethane was applied to rabbit A for 3 hours [36], after which the corneal reflex was almost obliterated and "peculiar" actions (motionless periods followed by spontaneous, excited movements) were observed. The flame test was strongly positive after 40 minutes. At the conclusion of the test period, the exposed area of the abdomen was washed

and the rabbit was recaged. The tetrachloroethane odor in the cage several hours later was attributed to its continuing presence in the rabbit's expired air. After an unspecified time, the rabbit was again exposed for 2 hours in the same manner. At the end of this second exposure, the corneal reflex was present but there was mild paralysis of the extremities. The flame reaction after 40 minutes was again strongly positive. The rabbit died 3 days later.

The second rabbit in this study [36] was completely anesthetized after a 6-hour exposure. The animal was flaccid and unresponsive to strong pinching, and its expired breath had the odor of tetrachloroethane. Pulse and respiration were reported to be normal. The flame test at 20 minutes was weakly positive but at 40 minutes was strongly positive. After an unspecified recovery period, the rabbit was exposed a second time for 7 hours. The rabbit, completely anesthetized, was killed by a sharp blow to the head and autopsied. The thoracic cavity had the odor of tetrachloroethane, and microscopic examination showed fatty degeneration of the liver and kidneys. It was further reported that deep anesthesia could be induced within 10-15 minutes if the exposed abdominal area was large enough.

A number of studies [37-39] have been performed which investigated the acute toxicity of tetrachloroethane. Smyth et al [38] reported, in 1969, that three out of six rats died within 14 days after a single 4-hour inhalation exposure to tetrachloroethane at 1,000 ppm. They also reported an oral LD50 for rats of 0.2 ml/kg (0.3 g/kg) and a dermal LD50 for rabbits of 3.99 ml/kg (6.38 g/kg).

In 1934, Barsoum and Saad [37] reported the fatal doses of tetrachloroethane that was administered by three different routes to dogs and rabbits. The following "minimum lethal doses" for tetrachloroethane were reported: oral, 0.7 g/kg within 24 hours (4 dogs); iv, 60 mg/kg within 30 minutes (7 dogs); subcutaneous, 0.5 g/kg within 24 hours (5 rabbits). The possible influence of ether or sodium barbital which were used to anesthetize the dogs prior to administration of the tetrachloroethane was not mentioned.

As part of a screening study reported by the National Research Council [39], a total of 29 adult mice were given single ip doses of tetrachloroethane dissolved in propylene glycol at doses ranging from 500 µl/kg (800 mg/kg) down to 3.8 µl/kg (6.1 mg/kg) and observed for the ensuing 7 days. Deaths occurred in mice injected with doses of 800, 400, 200, and 48 mg/kg; the animals exhibited ataxia, prostration, and dyspnea. No deaths occurred in any of the mice receiving doses of 24.0, 12.0, or 6.1 mg/kg.

Several early studies [26,40-42] demonstrated the anesthetic effectiveness of tetrachloroethane relative to other chlorinated aliphatic hydrocarbons. Lehmann [40] and Lehmann and Schmidt-Kehl [26] performed similar studies of the effects on cats of acute and chronic inhalation of tetrachloroethane at various concentrations. In 1911, Lehmann [40] reported the results of exposing seven cats in a glass chamber ventilated with air mixed with a stream of air bubbled through tetrachloroethane. One cat was used at each of seven test concentrations that were calculated from the weight loss of the liquid divided by the volume of ventilation air. At the lowest experimental concentration, 5.7 mg/liter (830 ppm), the exposed

cat assumed a prone position within 3 hours, reached light narcosis in 4 hours, and attained deep narcosis in 5 hours. The highest tetrachloroethane concentration, 57 mg/liter (8,300 ppm), produced the prone position in 7 minutes, light narcosis in 25 minutes, and deep narcosis in 40 minutes. (Since the air concentration of tetrachloroethane at saturation (21 C) is about 6,600 ppm, the temperature in the exposure chamber had to have been above room temperature to achieve the experimental concentration.) From the seven experimental concentrations employed, consistent dose-dependent effects were demonstrated. Besides showing general signs of irritation, the cats sneezed vigorously both before the onset of, and on slow awakening from, narcosis. Lehmann [40] conducted similar acute experiments with several other chlorinated aliphatic hydrocarbons; tetrachloroethane was reported to be about 9.1 times more toxic than tetrachloromethane (carbon tetrachloride), the least toxic substance according to the criteria of anesthesia selected for this study.

To investigate the effects of chronic exposure, Lehmann [40] exposed two cats and one rabbit to tetrachloroethane at concentrations ranging from 1.1-2.3 mg/liter (160-335 ppm) for 6-7 hours/day, 18 times during 4 weeks. Intervals between exposures were not given. No adverse effects were observed aside from varying degrees of "numbness" and sleep. Body weights dropped by 260-380 g. No autopsies were performed.

Lehmann and Schmidt-Kehl [26], in 1936, exposed cats to tetrachloroethane by inhalation at concentrations ranging from 4.9 mg/liter (710 ppm) to 42 mg/liter (6,100 ppm). The concentrations were calculated as described by Lehmann [40] but, in addition, quantitative measurements were also performed by absorption on calcium oxide, extraction with

alcohol, hydrolysis with alkali, and chloride determination by the Volhard method [27]. Two cats were exposed at each concentration and the time of onset was recorded for each of the predesignated stages of anesthesia from prostration to deep narcosis. The resulting dose-dependent effects were consistent with those observed previously by Lehmann [40]. In the chronic inhalation experiments, two cats and two rabbits were exposed simultaneously at concentrations of 0.8-1.1 mg/liter (116-160 ppm) for 8-9 hours/day, 6 days/week, for 4 weeks. All four animals showed the designated initial stage of prostration, but body weights, behavior, body temperatures, and blood studies did not show any remarkable changes. These results were also consistent with those observed earlier by Lehmann [40]. The animals were killed 7 weeks after the end of the exposure, at which time, gross and microscopic examinations revealed no pathologic changes.

In 1929, Lazarew [42] reported the minimum concentration of tetrachloroethane vapor causing (1) assumption of a lateral (prone) position, (2) loss of reflexes (responses normally displayed when the chamber was tapped), and (3) death, in mice, but gave little detail on the experimental procedures employed. An unspecified number of albino mice was exposed to tetrachloroethane vapor in hermetically sealed glass bottles (10-liter capacity) for a maximum of 2 hours. In comparison with several other chlorinated hydrocarbons, tetrachloroethane ranked most toxic or nearly so according to all three of the stated criteria. Within 2 hours, mice assumed a lateral position when exposed to tetrachloroethane at 7.5-10 mg/liter (1,091-1,455 ppm), lost their reflexes at 10-15 mg/liter (1,455-2,182 ppm), and died at 40 mg/liter (5,820 ppm). No autopsies were performed.

In 1933, Pantelitsch [41] reported the exposure of mice by inhalation to tetrachloroethane at concentrations ranging from 7 mg/liter (1,020 ppm) to 34 mg/liter (4,900 ppm). Results were presented as the recorded times of onset of disturbed equilibrium, prostration, loss of reflexes (determined by slight pressure applied on the paws), and death. The exposure chamber was a 10-liter glass bottle into which tetrachloroethane was discharged from a buret via a small, suspended cup that was lined with filter paper to facilitate evaporation. The concentrations of tetrachloroethane were calculated as well as actually measured, but by unspecified methods. Groups of three mice were exposed at each concentration. A dose-effect relationship was found that was reported to be consistent with the findings of Lazarew [42]. At a concentration of 7 mg/liter (1,020 ppm), the average times for the three mice to reach the sucessive stages of disturbed equilibrium, prostration, and loss of reflexes were 25, 82, and 131 minutes, respectively. After 152 minutes, the experiment was terminated and by the next morning all three mice appeared completely recovered. At 34 mg/liter (4,900 ppm), the average times of onset for each stage were 2, 7, and 7 minutes, respectively, and all three mice died in 100 to 120 minutes.

Horiuchi et al [43], in 1962, reported the results of inhalation exposures of mice, rats, and a monkey to tetrachloroethane at high concentrations. A "dynamic flow" chamber was used in the experiments, but neither the chamber nor the sampling and analytical procedures used were described. Among one group of 10 mice exposed to tetrachloroethane at

5,900 ppm for 3 hours, three died within 1 week. Another group of 10 mice was exposed at 6,600 ppm for the same duration; four of them died within 1 week. In repeated exposure experiments, nine male mice were exposed at an average concentration of 7,000 ppm tetrachloroethane for one 2-hour period/week. Five mice died after the first exposure, three more after the third, and the remaining mouse died soon after the fifth exposure. Six rats were exposed at 9,000 ppm for 2 hours/day, 2 days a week. One rat died after the second exposure, two more rats died after the fourth exposure, and the remaining three rats died after the 11th exposure. The rats lost consciousness within 1-1.5 hours after the beginning of exposure. Blood examinations were performed on three exposed and two control rats prior to and 14 days after the start of the experiment. Two of the three exposed rats had decreased red blood cell counts and hemoglobin levels, but no significant change was found in white blood cell counts of either the exposed or the control groups. Post-mortem microscopic examinations of exposed mice and rats showed "congestion" of tissues and fatty degeneration of the liver. To achieve the reported air concentrations above 6,600 ppm, the temperature in the exposure chamber had to be elevated above room temperature (21 C).

The adult male cynomolgus monkey weighing 7 kg was exposed to tetrachloroethane vapor 2 hours/day, 6 days/week, for 9 months, for a total of 190 exposures [43]. The concentration of tetrachloroethane ranged from 2,000 to 4,000 ppm during the first 20 exposures, from 1,000 to 2,000 ppm for the next 140 exposures, and from 3,000 to 4,000 ppm for the rest of the experiment. The monkey became noticeably weak after about seven exposures and developed diarrhea and anorexia after the 12th exposure. After

recovering from this condition, and beginning with the 15th exposure, it became nearly unconscious 20-60 minutes after the beginning of each exposure. There was a gradual increase in body weight during the 3d through 5th months of exposure and a gradual decrease thereafter. Red blood cell counts and hemoglobin levels decreased during the 3d and 4th months but then increased gradually to preexposure values. White blood cell counts decreased immediately after exposure began, remained low for about 5 months, then tended to increase; however, the recovery was variable for the remaining exposure periods. Urinary albumin and urobilinogen did not change appreciably. The monkey was exsanguinated at the end of the 9-month experiment. Histologic examination showed no definitive changes in tissues of the heart, lungs, kidneys, pancreas, and testes; however, the central zone of the liver had marked vacuolation of the cytoplasm as noted with hematoxylin-eosin staining.

In this same study [43], a second adult male monkey (4.5 kg) was injected subcutaneously with tetrachloroethane in 50% v/v olive oil solution. The dosage was 5 ml on day 1, 2 ml on day 4, 1 ml on day 19, 2 ml on day 20, and 4 ml on day 29. Thus, a total of 7 ml of tetrachloroethane in five applications was given over a 29-day period. The monkey showed signs of CNS depression after the first administration and thereafter, periods of unconsciousness and recovery occurred after subsequent injections of tetrachloroethane. The monkey was comatose after the last injection and died 2 days later. Its body weight had decreased from 4.5 to 3.3 kg at death. Red blood cell count and hemoglobin level increased slightly during the experiment; there were no remarkable changes in the total white blood cell count, but the differential count showed

lymphopenia and neutrophilocytosis. There were no appreciable changes in urinary albumin and urobilinogen, but urinary coproporphyrin increased toward the end of the experiment. Histologic examination of the heart, lungs, liver, and kidneys showed no remarkable changes apart from "congestion."

The findings reported by Horiuchi et al [43] are of limited value, primarily because of the high doses employed. The indication of fatty degeneration of liver in rats is consistent with reports of other investigators [36,44,45]. Although only two monkeys were studied, the lack of pronounced liver involvement in the 9-month inhalation study and the total absence of liver effects in the injection experiment, both at exposure levels sufficient to maintain profound CNS depression, is noteworthy.

Fiessinger et al [45], in 1922, reported the effects in mice of repeated inhalation exposure to tetrachloroethane. Groups of four mice were placed in a 17-liter chamber with a Petri dish containing 10-20 ml of tetrachloroethane. The mice were left in the chamber for 1-1.5 hours; the evaporation never exceeded 1.5 ml for each exposure. Some of the mice were comatose by the end of an exposure period. They exhibited convulsive movements and staggering of the hindquarters. After the eighth exposure, or a total of 10 hours, the mice had "bristly hair," had lost weight, and were anorexic. There was no mention of the interval between exposures. The urines contained bile pigment and the feces were discolored; autopsies indicated the peritoneum to be slightly yellowish and the liver nutmeg in color. Between the 8th and 28th exposures, hepatic lesions developed, the liver became yellowish, and histologic examination revealed signs of

centrilobular parenchymal degeneration with some fatty infiltration.

In 1931, Bollman and Mann [46] reported that repeated administration of 150 1-ml doses of tetrachloroethane to a dog over a 1-year period produced a condition typical of portal cirrhosis of the liver. Neither the route of administration nor the specifics of the experimental procedures were stated. Early symptoms consisted of gastrointestinal upsets, diarrhea, and intestinal hemorrhage, followed by jaundice and marked ascites with continued administration. The liver which was hypertrophic after 1 year, returned to normal size within 3 months after the exposures were discontinued.

In 1932, Muller [44] detailed the effects of tetrachloroethane administered by various routes to mice, guinea pigs, and one rabbit. An unspecified number of mice was placed in a 0.5-cu m chamber in which tetrachloroethane was evaporated to an initial concentration of 80 mg/liter (11,400 ppm). After 6 hours, the deeply anesthetized mice were removed and they recovered rapidly in fresh air. This procedure was repeated the next day with the same mice. After a second apparent recovery, all the mice had convulsions and died within a few hours. Autopsies showed fatty degeneration of the liver, particularly in the peripheral lobes and also focal fatty degeneration of the renal tubular cells. The stated concentration of tetrachloroethane in the inhalation chamber was only the initial, calculated concentration and there were no indications of what concentrations existed as the exposure progressed.

When tetrachloroethane was injected iv, ip, or subcutaneously into an unspecified number of guinea pigs and mice by the same author [44], no notable species or injection-mode differences were found. The animals died

in convulsions shortly after being injected with doses of 0.2 ml. No other test doses were reported. Autopsies revealed no morphologic changes. In an attempt to simulate chronic poisonings, Muller [44] injected mixtures of tetrachloroethane in olive oil, glycerin, or paraffin subcutaneously into an unspecified number of guinea pigs. The mixtures of tetrachloroethane in olive oil or glycerin (liquids at animal body temperature) produced effects similar to those reported (above) in mice injected with unmixed tetrachloroethane at a dose of 0.2 ml; the guinea pigs died within a few hours in convulsions, and no morphologic changes were apparent at autopsy. Tetrachloroethane mixed with paraffin (semisolid at animal body temperature) increased the lethal dose of tetrachloroethane to 0.7 ml administered in five injections over 14 days. Details on the schedule of individual injections were not given. Other than body weight losses, the guinea pigs showed no clinical symptoms preceding death. Autopsies revealed liver and kidney effects similar to those noted above in Muller's inhalation studies in mice [44].

An iv dose 0.2 g tetrachloroethane was also administered to a rabbit [44]. The animal went into immediate narcosis, apparently recovered after about 15 minutes, but died after 30 hours. Autopsy indicated liver enlargement with pasty, fine yellow fields. Microscopic examination showed severe coarse- and fine-droplet fatty degeneration of the parenchymal cells corresponding to the yellow fields, especially in the periphery of the lobes.

In 1972, Deguchi [47] reported the effect of tetrachloroethane on the activities of serum transaminases in male Wistar Daikoku rats exposed at 10, 100, and 1,000 ppm by inhalation for 6 hours. Six mature (200 g) rats

were exposed at each concentration and 20 rats served as controls. A stream of air was passed over saturated wicks immersed in flasks of tetrachloroethane and directed into a 66-liter exposure chamber. The measured tetrachloroethane concentration fluctuated by ± 20% of the nominal concentration. The techniques used for air analysis were not reported. The rats were killed prior to serum transaminase determinations. At 24 hours after the single inhalation exposures at 10 and 100 ppm, the average serum glutamic oxaloacetic transaminase (SGOT) values were 144 and 206 units, respectively, while the control rats showed an average value of 110 units. The corresponding average serum glutamic pyruvic transaminase (SGPT) values were 51 and 53 units, respectively, for the exposed groups and 41 units for the control group. Four of the six rats exposed at 1,000 ppm for 6 hours died within 24 hours after the start of the exposure. Serum transaminase values for the two surviving rats were lower than control levels. Transaminase activities for rats exposed at 10 ppm were monitored further at 48, 72, 96, and 120 hours after exposure; three values were reported for each period. The mean SGOT values of 214, 245, 160, and 140 units, respectively, increased gradually up to 72 hours and then decreased. The respective mean SGPT values of 45, 55, 46, and 48 units showed no significant trends over the observation period. Histologic examinations performed at necropsy after 24 and 120 hours of recovery by the 10-, 100-, and 1,000-ppm groups showed no definite changes in the liver, heart, kidney, spleen, brain, or bone marrow.

In 1969, Tomokuni [48] reported the development of fatty livers in 18 female Cb mice exposed to tetrachloroethane at 600 ppm for 3 hours. The exposure chamber was supplied with a constant flow of air bubbled through a

tetrachloroethane vaporization unit. The tetrachloroethane concentration was determined by gas chromatography every 30 minutes during the exposure period. Groups of six mice were killed at 0, 4, and 8 hours after termination of exposure; their livers were removed, weighed, and analyzed for adenosine triphosphate (ATP), total lipids, and triglyceride content. Eight female mice were used as controls. The author [48] concluded that tetrachloroethane inhalation caused fatty liver by increasing the total liver lipid and triglyceride contents during, and up to 8 hours after, exposure. Compared with the controls, total liver lipids increased to 115, 155, and 216% of control values at 0, 4, and 8 hours, respectively; triglyceride content increased to 163, 288, and 518%, respectively; and hepatic ATP content decreased to 75, 59, and 46% of the control values, respectively.

In a subsequent study, Tomokuni [49] exposed 35 female mice to tetrachloroethane at 800 ppm for 3 hours. The triglyceride and phospholipid contents of the liver and plasma were measured in five mice each at 5, 20, 25, 30, 45, 70, and 90 hours postexposure. Eight female mice were used as controls. The hepatic triglyceride content increased after exposure, reached a maximum of 50.4 mg/g liver at 20 hours, then decreased to near the control level of 8.4 mg/g by 90 hours. The hepatic phospholipid content decreased after exposure, reached a minimum of 16.7 mg/g at 25 hours, and then slowly increased to near the control level of 23.2 mg/g by 90 hours. Both plasma triglycerides and phospholipids decreased until 25 hours after exposure. Triglyceride content decreased from 0.98 mg/ml to 0.39 mg/ml plasma, and phospholipids decreased from 0.84 mg/ml to 0.54 mg/ml. Both then gradually increased, the phospholipids to

the control level and the triglycerides to above the control level, between 70 and 90 hours after exposure. Judging from the increase in hepatic triglyceride levels, the author [49] concluded that the development of fatty liver reached a peak in the period between 20 and 25 hours postexposure. The decreased values observed for both liver and plasma phospholipids were not adequately explained.

Navrotskiy et al [50] tested the chronic inhalation toxicity of several chlorinated hydrocarbons including tetrachloroethane in 350 rats and rabbits. It was the authors' intent to show that upon continual exposure to low concentrations of an environmental contaminant, the "blood chemistry" of the tested species would be altered. Tetrachloroethane at 2, 10, or 100 mg/cu m (0.3, 1.46, or 14.6 ppm) was administered 3-4 hours "daily" for 7-11 months. No further details of the experimental and analytical procedures were reported. At 100 mg/cu m (14.6 ppm), hemagglutinin (antibody that agglutinates erythrocytes) production was progressively suppressed with continued exposure; phagocytic activity was increased 15-30% at 1-1.5 months, and suppressed (amount not specified) at 2-3 months after exposure. During the first 2-4 months of exposure at this concentration, the rabbits excreted 30-40% more 17-ketosteroids than they had excreted initially; after further exposure, there was a reduction to 10-20% below the initial rate. Other findings at the 14.6-ppm concentration were increased total serum proteins, moderate hyperurobilinogen, phasic fluctuations in acetylcholine content and cholinesterase activity in the blood, decreased hemoglobin content, and reduced erythrocyte counts. At autopsy, rabbits exposed to tetrachloroethane at 14.6 ppm showed signs of incipient liver and kidney

degeneration, but no further details were provided. The only effects specifically reported at 1.46 ppm were suppression of hemagglutinin production and phasic fluctuations in the whole blood acetylcholine content and cholinesterase activity. No effects were reported in rabbits exposed to tetrachloroethane at 0.3 ppm.

Insufficient information on the experimental procedures as well as on the test results was the major limitation of this 1971 paper [50]. Although it is difficult to thoroughly evaluate the authors' conclusions, the reported structural changes in the liver and kidneys of rabbits exposed chronically at 14.6 ppm are noteworthy, as are the apparent dose-effect relationships in the blood and urine parameters checked. Deviations from normal values at 14.6 ppm, for example, were greater than at 1.46 ppm, and no effects were reported at 0.3 ppm.

In 1972, Schmidt et al [51] described the toxic effects of low concentrations of tetrachloroethane to which rats were exposed by inhalation, with and without ethanol treatment. A total of 294 male rats (60 days old) weighing 210-270 g were used, 84 in a subacute experiment, and 210 in a chronic experiment. The animals were exposed in 200-liter chambers to a continuous flow of a tetrachloroethane-air mixture. Airborne concentrations of tetrachloroethane were determined both colorimetrically [52] and by calculation of the ratio of the weight of tetrachloroethane volatilized to the total air volume. The average tetrachloroethane concentration determined in both the subacute and chronic experiments was 13.3 ± 0.24 mg/cu m (1.94 ppm).

In the subacute study [51], 42 rats were exposed to tetrachloroethane at the test concentration for 4 hours/day on 8 of 10 days. Another group

of 42 rats was similarly exposed to air only. To study the effects of ethanol on tetrachloroethane-induced toxicity, the authors gave ethanol (4 g/kg, with an equal volume of isotonic saline) by intubation to 21 of the tetrachloroethane-exposed rats and to 21 of the controls. Seven rats each were intubated after their first, third, or seventh exposure. The other 42 rats were given saline only. The rats were thus subdivided into four groups of 21 animals each: those exposed to tetrachloroethane alone, those exposed to ethanol alone, those exposed to tetrachloroethane plus ethanol, and those exposed to air alone. Measurements performed in each group after the second, fourth, or eighth exposure indicated no significant differences among the groups in body weight, white blood cell counts, SGOT and SGPT activities, BSP excretion test values, and total fat content of the liver. Although significant fluctuations were noted in serum proteins and adrenocorticotropic hormone (ACTH) in the pituitary gland, the results were inconclusive because no consistent pattern or relationship could be established from the data.

In the 9-month chronic exposure experiments, Schmidt et al [51] exposed 105 rats each to tetrachloroethane and to air alone "daily" for 4 hours/day. The exposure chambers and the tetrachloroethane concentration (1.94 ppm) were identical to those of the subacute study, but no ethanol was used. Groups of seven each of experimental and control rats were examined after 110 and 265 days of exposure. At the end of 110 days, the exposed rats weighed significantly less than the controls (415 ± 5.3 g versus 435 ± 4.9 g), while their white blood cell counts averaged 90% higher than the control values. After 265 days, there was wide variation in group body weights and differences were no longer significant. No white

blood cell count data were given. The ACTH content of the hypophysis was significantly increased in the exposed rats at both intervals, and the total fat content of the liver was about 34% higher in the exposed than in control rats after 265 days. There were no significant differences between exposed and control mortality rates.

Schmidt et al [51] also investigated the effect of chronic exposure to tetrachloroethane on the reproductive capacity of male rats. One week prior to the end of the 9-month chronic exposure, seven control and seven exposed male rats were each mated with five unexposed, virgin female rats. The 1.94-ppm exposure of the male rats was continued during the mating period. Gross examinations of the F1 generation were carried out for 12 weeks. No differences of note were found in percentage of females littering and litter size, average weight, male-to-female sex ratios, growth rates, and percent mortality in the young.

Tetrachloroethane was one of several chlorinated hydrocarbons tested by Plaa and Larson [53] for potential kidney toxicity in mice following ip injection. Indicator paper dipped in the urine and compared to standard color charts was used to quantitate glucose and protein contents. Ten mice were injected ip every other day for 6 days with tetrachloroethane-corn oil solutions equivalent to doses of either 0.5 or 1.0 ml/kg (0.8 or 1.6 g/kg) tetrachloroethane. A group of 60 mice was used as a control. At 0.8 g/kg, all 10 mice survived, but 2 of them had a significant urinary protein increase (over 100 mg%), although none showed significant urinary glucose (over 250 mg%). At 1.6 g/kg, only one of the 10 mice survived, and it had significant increases in both urinary protein and glucose. No evidence of kidney necrosis or swelling in the proximal convoluted tubules was noted in

the five mice receiving 0.8 g/kg that were examined. No details were given on kidney effects for the group receiving 1.6 g/kg. The authors [53] classified tetrachloroethane as a weaker nephrotoxin in mice than either chloroform or carbon tetrachloride.

There have been several reports [24,54,55] describing the metabolism and excretion of tetrachloroethane in animals. In 1939, Barrett et al [24] reported the results of administering tetrachloroethane, either by inhalation or by subcutaneous injection, to unspecified numbers of dogs, rats, guinea pigs, and rabbits. The dogs were exposed at an unspecified concentration in an enclosed chamber for 1 hour, the period necessary to produce narcosis, for 20 successive days. The rats, rabbits, and guinea pigs were administered tetrachloroethane by subcutaneous injection; again, however, the dose was not stated. Concentrations of chlorinated hydrocarbons in the urine were determined by the Fujiwara reaction [52]. Not more than 0.5 mg/liter of chlorinated hydrocarbons was detected in dog urine; similar results were obtained in the other species. This amount was about 0.1% of that reported after similar experiments with trichloroethylene by the same authors [24].

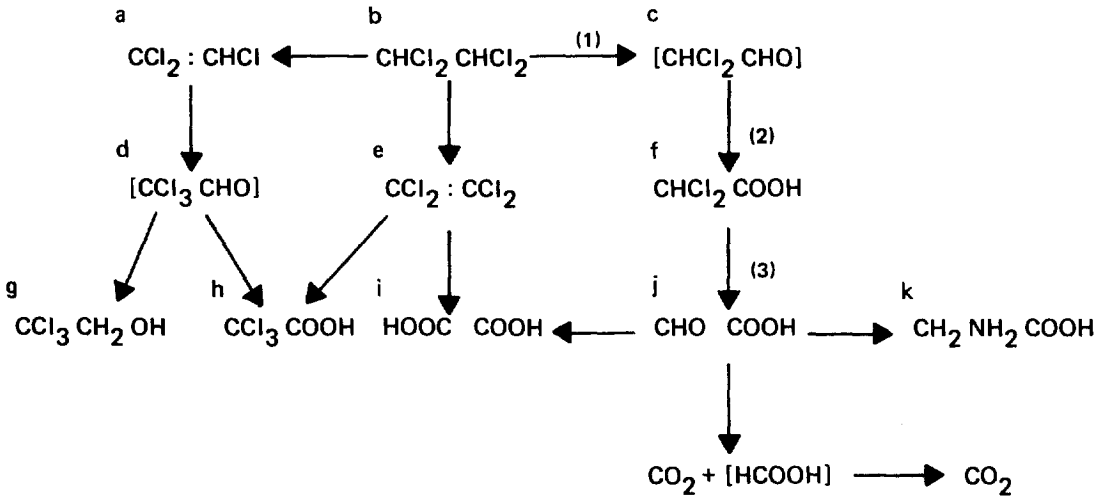
In 1971, Yllner [55] reported experiments in which 0.21-0.32 g/kg of 14C-labeled tetrachloroethane was injected ip into an unspecified number of female albino mice after which the elimination of radioactivity was monitored for 3 days. Of the total radioactivity measured, about 50% (range 45-61%) was accounted for in the expired carbon dioxide, about 28% (range 23-34%) was excreted in the urine, about 16% (range 11-19%) remained in the animal, and less than 4% was expired as tetrachloroethane. Dichloroacetic acid, trichloroacetic acid (TCA), trichloroethanol (TCE),

oxalic acid, and small quantities of glyoxalic acid and urea were identified in the urine by paper chromatographic and isotope dilution techniques. Half of the activity in the urine could not be identified. From these studies, a metabolic scheme for tetrachloroethane was developed; it is presented in Figure III-1. The primary pathway (1, 2, 3) was proposed to consist of a stepwise hydrolytic cleavage of the chlorine-carbon bonds yielding glyoxalic acid and then carbon dioxide. A nonenzymatic oxidation of tetrachloroethane produced a small amount of tetrachloroethylene. It was also demonstrated in vitro that tetrachloroethane could be dehydrochlorinated to form small amounts of trichloroethylene. The trichloroethylene was suggested as the precursor to the TCA and TCE found in the urine. Glycine production was indicated by the significant amounts of labeled hippuric acid excreted after a simultaneous injection of 14C-labeled tetrachloroethane and sodium benzoate [55].

In 1972, Ikeda and Ohtsuji [54] reported that rats exposed to tetrachloroethane excreted very small amounts of TCA and TCE in their urine. Eight groups of six immature Wistar rats (50 g) each were exposed to tetrachloroethane at 200 ppm for 8 hours. Urine samples were collected and pooled for each group for 48 hours after exposure and analyzed by a modification of the Fujiwara reaction [52]. Results indicated an average of 8.2 ± 3.0 mg/kg total trichlorocompounds, 1.7 ± 0.9 mg/kg TCA, and 6.5 ± 2.7 mg/kg TCE. These values were less than 1/20 of those observed for rats exposed to the isomer, 1,1,1,2-tetrachloroethane. Another eight groups of five Wistar rats each were injected ip with 2.78 mmole/kg (467 mg/kg) of

FIGURE III-1

PROPOSED TETRACHLOROETHANE METABOLIC SCHEME IN MICE



a) Trichloroethylene
b) Tetrachloroethane
c) Dichloroacetaldehyde
d) Trichloroacetaldehyde
e) Tetrachloroethylene
f) Dichloroacetic acid
g) Trichloroethanol
h) Trichloroacetic acid
i) Oxalic acid
j) Glyoxalic acid
k) Glycine

Derived from Yllner [55]

the tetrachloroethane isomers diluted with soybean oil (total dose of 1 ml/kg body weight). Urine samples were collected for two successive 48-hour periods and analyzed as before. Results were consistent with the inhalation experiment that showed much lower total trichlorocompounds, TCA, and TCE values for rats administered 1,1,2,2-tetrachloroethane than for those administered 1,1,1,2-tetrachloroethane. It was postulated that the rate and means of excretion are determined largely by the ease of biotransformation. A simple hydrolytic dehalogenation is required by 1,1,1,2-tetrachloroethane, while the symmetrical isomer requires a chlorine atom shift. The slow elimination of 1,1,2,2-tetrachloroethane from the body may be a definite factor in its high toxicity. Volatile compounds can also be exchanged into the lungs and expired effectively, but the authors [54] pointed out that elimination through the breath is low for these two isomers because of their relatively low vapor pressures.

Reported data on the possible carcinogenicity or teratogenicity of tetrachloroethane have not been found. The National Cancer Institute is conducting a study of the carcinogenic potential of tetrachloroethane, the results of which will be evaluated by NIOSH when they become available. Brem et al [56] used two different bacterial assay techniques to investigate the mutagenic potential of several haloalkanes, including tetrachloroethane. With one assay method, the growth inhibition by haloalkanes of a strain of E. coli lacking DNA polymerase I was compared with that of an E. coli strain having the enzyme. The two strains of E. coli (pol A+ and pol A-) were grown on separate agar plates. A sterile paper disc was laid on each plate and 10 μl of the haloalkane were placed on the disc. The plates were incubated at 37 C for 8 hours, after which

the zones of inhibition around the discs were measured. This was done in duplicate at least three different times for each test chemical. The ratio of the diameters of inhibition zones (pol A-/pol A+) was 1.00 for a control using 30 μg chloramphenicol. Ratios of the diameters of the zones in excess of 1.00 were considered indicative of some preferential inhibition of the pol A- strain. DNA polymerase I was claimed to play an important role in DNA repair. The polymerase-deficient strain (pol A-) was more sensitive than the parent strain (pol A+) to the inhibitory or toxic action of the haloalkanes. The degree of preferential inhibition was considered an indicator of the mutagenic potential of the test chemicals. The tetrachloroethane ratio of 1.88 indicated moderate mutagenic activity in E. coli relative to the other test chemicals. Ratios for the two most active haloalkanes tested were 3.39 for 1,1,2,2-tetrabromethane and 2.70 for 1,1-dibromoethane.

In a second mutagenesis study [56], three strains of Salmonella typhimurium were used. Strains TA 1530 and TA 1535 each had a base substitution in the histidine G gene, while strain TA 1538 had a single base deletion in the histidine D gene. Each of the three strains was inoculated on separate minimal agar plates containing only trace amounts of histidine. A paper disc impregnated with 10 μmol of test substance was deposited on the surface of each plate. Water (10 μl) and chloramphenicol (30 μg) were used as control substances. The plates were then incubated in darkness at 37 C for 54 hours and the histidine-independent colonies (mutants) were then counted. The use of duplicate plates could not be determined for this part of the study. In the presence of tetrachloroethane, mutant colonies totaled 77, 49, and 28 in strains TA

1530, TA 1535, and TA 1538, respectively; on control plates, they numbered 23, 26, and 19 for water and 20, 31, and 14 for chloramphenicol. The results indicated that tetrachloroethane was more active in inducing mutations of the base-substitution than of the frame-shift type in these bacterial test systems.

In these two assays [56], tetrachloroethane was more active than the controls and it was intermediate in effect among the other test substances--1,2-dibromoethane, 1,2-dichloroethane, 1-bromo-2-chloroethane, 1,1,2,2-tetrabromoethane, etc. Additional mammalian mutagenicity experiments in vitro and in vivo should be performed before a definite conclusion is reached concerning the mutagenic potential of tetrachloroethane in mammals.

Correlation of Exposure and Effect

The pronounced anesthetic properties of tetrachloroethane have been shown in both human and animal studies [26,40-43]. In humans, the effects of acute exposures to tetrachloroethane have been mainly observed in several reports of nonoccupational poisonings by ingestion. Rapid loss of consciousness, progressive CNS depression, and death within 20 hours after consumption of unknown amounts of tetrachloroethane were reported in five suicide cases [15-19]. Sherman [20] and Ward [21] reported two incidents in which 3 ml of tetrachloroethane were mistakenly given orally to each of 10 adults. Within 2 hours, five of the subjects became comatose while the other five lapsed into various degrees of semiconsciousness. All recovered and no aftereffects were reported. Ward [21] also mentioned a young girl

who ingested 2 ml of tetrachloroethane without adverse effects.

The report of Lehmann and Schmidt-Kehl [26] in 1936 described human experiments on the effects of tetrachloroethane after short-term inhalation exposures. Two men were exposed simultaneously by inhalation to the chemical at concentrations ranging from 2.9 to 335 ppm. At 2.9 ppm both men detected tetrachloroethane by its odor. Exposure at 116 ppm for 20 minutes produced dizziness and mild vomiting; at 146 ppm, both subjects experienced dizziness after 10 minutes, mucosal irritation at 12 minutes, and fatigue at 20 minutes. At concentrations of 262 and 335 ppm, these same symptoms were reported after progressively shorter exposure periods. Olfactory fatigue, which became apparent at the higher concentrations, indicated that odor is not a reliable indicator of the presence of tetrachloroethane.

Inhalation experiments on cats [26,40], rabbits [26,36], and mice [41,42] have confirmed the anesthetic effectiveness of tetrachloroethane. Lehmann [40] reported a dose-dependent anesthetic effect in one cat exposed to tetrachloroethane at each of seven test concentrations ranging from 830 to 8,300 ppm. At the lowest concentration, salivation, sneezing, and licking were observed after 17 minutes; prostration was evident after 3 hours, as was light narcosis after 4 hours, and deep narcosis was seen after 5 hours. Exposure times necessary for the onset of anesthesia decreased with each incremental increase in concentration; at 8,300 ppm, the cat salivated after 5 minutes, was prostrate after 7 minutes, was narcotized lightly after 25 minutes, and was narcotized deeply after 40 minutes. Lehmann [40] also exposed two cats and one rabbit to tetrachloroethane at 160-335 ppm for 6-7 hours/day on 18 of 28 days. The

animals exhibited varying degrees of "numbness" and sleep during the experiment.

Besides the anesthetic effects, tetrachloroethane has been reported to cause other neurologic effects in occupationally exposed workers. Grimm et al [12] reported a number of poisonings in German aircraft factory workers who experienced tremors, headaches, pains in the limbs, "numbness," sensation of pins and needles in the extremities, knee-jerk areflexia, and excessive sweating after long-term exposures to tetrachloroethane. Leri and Breitel [13] described the poisoning of two young women who worked in an artificial pearl factory where tetrachloroethane was used. Both experienced paralysis of the interosseous muscles of their feet and hands, obliteration of their ocular and pharyngeal reflexes, and paralysis of their jaw and ocular muscles. Poisonings of this type have not usually been fatal; however, the victims were seriously incapacitated, and they continued to experience effects long after their exposure to tetrachloroethane ended.

Lobo-Mendonca [29] found that a high percentage of workers in India's bangle industry had neurologic and gastrointestinal signs and symptoms; the measured concentrations of tetrachloroethane in air ranged from 9 to 98 ppm. There was considerable dermal contact with the liquid in at least two of the manufacturing processes and there was possible mixed exposure to acetone as well. The most frequently reported symptoms were hand tremors (35%), vertigo (30.5%), headache (26.6%), abdominal pain (23.7%), and anorexia (22.6%). In a four-factory comparison in which he related measured tetrachloroethane in air concentrations (values represented averages of unspecified numbers of samples) and the percentage of workers

having hand tremors, Lobo-Mendonca [29] reported hand tremors in 50% of the workers at the factory with the highest measured concentrations (65 and 98 ppm) of tetrachloroethane, compared with 40% at the factory with measured concentrations of 50 and 61 ppm, 33% at the third factory (40 and 74 ppm), and 14% at the factory with the lowest measured concentrations (9 and 17 ppm).

The main concern with occupational exposure to tetrachloroethane results from the numerous reported poisonings [7,8,12,57] due mainly to chronic inhalation exposures which resulted in liver damage and gastrointestinal disturbances. Most of these occupational case reports described a consistent clinical picture including initial symptoms of general malaise, anorexia, exhaustion, headache, and nausea. After continued exposure, jaundice was observed, frequently accompanied by vomiting, pale stools, and bile-stained urine. Finally "jaundice with toxemia" was seen including intensified jaundice, delirium, convulsions, coma, and death [9]. Unfortunately, the sparse occupational exposure data which were presented in these reports permitted little correlation of gastrointestinal and hepatic effects with tetrachloroethane exposure. Descriptions of the work operations [8,12] indicated the probability of dermal contact in addition to respiratory exposure in some of these poisonings.

The potent liver toxicity of tetrachloroethane has been also documented in numerous studies in rabbits [36,44,50], rats [43,47,51], mice [43-45,48,49], and guinea pigs [44]. Several of these studies were of short exposures at high concentrations. Horiuchi et al [43] exposed 20 male mice, 10 at 5,900 ppm and 10 at 6,600 ppm, to tetrachloroethane for a

single 3-hour period. After 1 week, three and four deaths had occurred, respectively, in the two groups. At autopsy, fatty degeneration of the liver along with "tissue congestion" was consistently evident. The same investigators [43] exposed six rats at 9,000 ppm for 2 hours/day, twice a week. One rat died after 2 exposures, 2 more died after 4 exposures, and the remaining 3 rats died after 11 exposures. Microscopic examination again showed fatty degeneration of the liver and generalized "tissue congestion."

Concentrations of airborne tetrachloroethane ranging from 1.5 to 247 ppm were measured in a penicillin-manufacturing plant [28] where there was an outbreak among the workers of signs and symptoms indicative of liver dysfunction. This 3-year study demonstrated the effectiveness of bimonthly medical screening examinations and improved ventilation; however, the author stated that some workers exposed to tetrachloroethane at concentrations ranging from 15 to 34.6 ppm still suffered liver damage. Effects seen at these concentrations included enlarged liver, urobilinogenuria, increased serum bilirubin, and general and digestive organ complaints.

Five of the more recent animal studies [47-51] have reported toxic liver effects after exposures at concentrations from 800 to as low as 1.94 ppm of airborne tetrachloroethane. Tomokuni [48,49] found fatty liver changes in mice exposed by inhalation to tetrachloroethane at 800 and 600 ppm for 3 hours. At 600 ppm, liver triglycerides increased almost linearly from the beginning of exposure until 8 hours postexposure. At 800 ppm, liver triglycerides increased for up to 20-25 hours after exposure, while at the same time there was a decrease in plasma triglycerides; although

they later decreased, liver triglyceride levels did not return to preexposure values even 90 hours after exposure.

Rats were found to have elevated SGOT values 24 hours after exposure to tetrachloroethane at 10 or at 100 ppm for 6 hours, and four of six rats exposed at 1,000 ppm for 6 hours died within 18 hours after the end of exposure [47]. The average SGOT values for the rats exposed at 10 ppm increased from a control value of 110 units to 144, 214, 245, 160, and 140 units at 24, 48, 72, 96, and 120 hours after exposure, respectively. The average SGPT values increased only minimally after exposure.

Navrotskiy et al [50] reported that rabbits exposed to tetrachloroethane at 14.6 ppm, 3-4 hours/day, for 7-11 months had signs of incipient liver and kidney degeneration at autopsy. There were also alterations in the rabbits' immunoresponse system as indicated by abnormal variations in blood and urine parameters at 14.6 ppm and, to a lesser extent, at 1.46 ppm.

Chronic inhalation exposure of male rats to tetrachloroethane at 1.94 ppm, 4 hours/day for 265 days resulted in significant increases in total liver fat content (34% more than controls) [51]. Body weights were lower, white blood cell counts higher, and pituitary ACTH greater in exposed than in control rats. No effects on the reproduction or mortality rates were observed. This long-term inhalation study is important in that 1.94 ppm is the lowest tetrachloroethane exposure concentration at which liver effects have been found in animals.

Carcinogenicity, Mutagenicity, and Teratogenicity

No data were found in the available literature which address the question of whether tetrachloroethane is carcinogenic or teratogenic. The mutagenic potential of tetrachloroethane was tested in two different bacterial assay systems by Brem et al [56]. Tetrachloroethane was more active than the controls (water, chloramphenicol) in both assays and intermediate in effect among the other haloalkanes tested. While the observations of small increases of point mutation frequency in bacteria are cause for concern, they are insufficient to establish the existence of any significant risk of genetic hazards to the human population exposed to tetrachloroethane.

Summary Tables of Exposure and Effect

Summaries of the human and animal data correlating tetrachloroethane exposure and effect are given in Tables III-4 through III-6.

TABLE III-4

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO TETRACHLOROETHANE

Route of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	18 men	75 - 224 ppm	Lymphocytosis, erythropenia, reduced whole blood specific gravity	31
"	34 - 75 men	15 - 36.4 ppm	Gastrointestinal disorders, enlarged liver, urobilinogenuria, increased serum bilirubin	28
"	75	0.37*- 1.33* ppm 7.7 yr, av time worked	No cardiovascular effects	32
Respiratory and dermal	380	9* - 98* ppm	Gastrointestinal and neurologic disorders (mixed exposure to acetone in some cases); dose-dependent occurrence of hand tremors	29

*Average values

TABLE III-5

SUMMARY OF EFFECTS OF INHALED TETRACHLOROETHANE
ON TWO MEN EXPOSED EXPERIMENTALLY

Exposure Concentration	Duration	Effects
335 ppm	10 min	Dizziness at 3 min; fatigue, mucosal irritation at 10 min; odor not discernable after 3 min
262 ppm	"	Dizziness, mucosal irritation at 5 min; odor not discernable after 5 min
146 ppm	30 min	Dizziness at 10 min, mucosal irritation at 12 min, fatigue at 20 min
131 ppm	10 min	Dizziness at 10 minutes (exposure terminated)
116 ppm	20 min	Dizziness, mild vomiting; odor not discernable after 10 min
2.9 - 13 ppm	-	Detection of odor, no complaints

From Lehmann and Schmidt-Kehl [26]

TABLE III-6

SUMMARY OF EFFECTS OF TETRACHLOROETHANE EXPOSURE ON ANIMALS

Route of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mouse	-	11,400 ppm 6 hr x 2 d	Deep anesthesia with rapid recovery after 1st exposure, death after 2d; fatty degeneration of liver and kidney	44
"	Rat	6	9,000 ppm 2 hr twice/wk	Unconsciousness within 1-1.5 hr; death of 1 after 2d exposure, 2 after 4th, 3 after 11th; fatty degeneration of liver, decreased RBC and Hgb content	43
"	"	9	7,000 ppm 2 hr	Death of 5 after 1st exposure, 3 after 3rd, 1 after 5th; fatty degeneration of liver	43
"	Mouse	10	6,600 ppm 3 hr	Death of 4 within 1 wk, fatty degeneration of liver, tissue congestion	43
"	"	10	5,900 ppm 3 hr	Death of 3 within 1 wk, fatty degeneration of liver, tissue congestion	43
"	Monkey	1	1,000- 4,000 ppm 2 hr/d 6 d/wk 190 total in 9 mo	Weakness after 7th exposure, diarrhea and anorexia after 12th, anesthesia after 15th; fluctuations in RBC, WBC, and Hgb content; marked vacuolation of liver	43
"	Rat	6	1,000 ppm 6 hr	Death of 4 within 24 hr; no histologic changes in remaining 2 after 24 or 120 hr	47

TABLE III-6 (CONTINUED)

SUMMARY OF EFFECTS OF TETRACHLOROETHANE EXPOSURE ON ANIMALS

Route of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Rat	6	1,000 ppm 4 hr	Death of 3 within 14 d	38
"	Mouse	35 F	800 ppm 3 hr	Increased hepatic and decreased plasma triglycerides	49
"	"	18 F	600 ppm 3 hr	Increased hepatic triglycerides and total lipids, decreased hepatic ATP content	48
"	Rat	6 M	100 ppm 6 hr	Increased SGOT levels 24-96 hr postexposure; no histologic changes	47
"	Rabbit	-	14.6 ppm 3 - 4 hr/d 7 - 11 mo	Suppressed hemagglutinin production and phagocytosis, altered blood chemistry, signs of liver and kidney degeneration	50
"	Rat	6 M	10 ppm 6 hr	Increased SGOT levels 24 hr postexposure; no histologic changes	47
"	"	105 M	1.94 ppm 4 hr/d 110 or 265 d	Increased WBC, pituitary ACTH, total fat content of liver; decreased body weight	
"	Rabbit	-	1.46 ppm 3 - 4 hr/d 7 - 11 mo	Suppressed hemagglutinin production, decreased RBC and Hgb content, fluctuating blood chemistry	50
"	"	-	0.3 ppm 3 - 4 hr/d 7 - 11 mo	None reported	50

TABLE III-6 (CONTINUED)

SUMMARY OF EFFECTS OF TETRACHLOROETHANE EXPOSURE ON ANIMALS

Route of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Dermal	Rabbit	1	Liquid of unknown dose to shaved abdomen (22 sq cm) 13 hr total	Complete anesthesia after both a 6-hr and an added 7-hr exposure, fatty degeneration of liver and kidneys	36
"	"	1	Liquid of unknown dose to shaved abdomen (22 sq cm) 5 hr total	Obliterated corneal reflex and excitability after the 3-hr exposure, mild paralysis after the added 2-hr exposure, death in 3 d	36
"	"	-	-	LD50 = 6.38 g/kg	38
Oral	Dog	4	0.70 g/kg (in acaia gum)	Minimum lethal dose	37
"	Rat	-	-	LD50 = 0.3 g/kg	38
iv, ip, or sub-cutaneous	Guinea pig	-	0.7 ml total (in paraffin) in 5 doses over 14 d	Weight loss, convulsions, death, histologic changes similar to effects in mice inhalation study	44
"	"	-	0.2 ml	Convulsions and death	44
iv	Rabbit	1	0.2 g	Immediate narcosis with recovery in 15 min, death in 30 hr, enlarged liver with fatty degeneration	44
"	Dog	7	60 mg/kg (in olive oil)	Minimum lethal dose	37
Sub-cutaneous	Rabbit	5	0.5 g/kg	"	43

TABLE III-6 (CONTINUED)

SUMMARY OF EFFECTS OF TETRACHLOROETHANE EXPOSURE ON ANIMALS

Route of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Subcutaneous	Monkey	1	1 - 5 ml (in olive oil) x 5 in 29 d	Minimum lethal dose	43
ip	Mouse	10	1.6 g/kg (in corn oil) on 3 alterate d	Death of 9, increased urinary protein and glucose in survivor	53
"	"	10	0.8 g/kg (in corn oil) on 3 alternate d	Increased urinary protein in 2	53
"	"	5	800 mg/kg*	Ataxia, prostration, dyspnea; death within 1 d	39
"	"	3	400 mg/kg*	Ataxia; death within 3 d	39
"	"	3	200 mg/kg*	Ataxia; death within 7 d	39
"	"	3	100 mg/kg*	Death of 1 within 2 d	39
"	"	3	48 mg/kg*	Death of 2 within 3-4 d	39
"	"	3	24 mg/kg*	No deaths	39
-	Dog	1	1 ml x 150 in 1 yr	Diarrhea, intestinal hemorrhage, jaundice, marked ascites; after 1 yr, liver hypertrophy but returned to normal after 3 mo	46

*Dissolved in propylene glycol