

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION OF EXPOSURE

Environmental Concentrations

In 1935, Smyth and Smyth [57] reported concentrations of carbon tetrachloride in the air of 23 drycleaning establishments, 5 carbon tetrachloride manufacturing plants, 3 fire extinguisher manufacturing plants, and 5 plants where carbon tetrachloride was either repacked or used in chemical processes, one of which used a mixture of 30% carbon tetrachloride and 70% ethylene dichloride. Fifteen of the drycleaning plants used an unspecified mixture of carbon tetrachloride and trichloroethylene in open type drycleaners. A portable 50-cm interference refractometer, calibrated for the appropriate mixture, was used for all determinations. The measurements, which were essentially instantaneous observations of carbon tetrachloride concentrations, were taken at intervals of 10 seconds to 5 minutes, depending on the variation of the process. The method was not specific for carbon tetrachloride. Tables XI-3 and XI-4 summarize the concentrations found in different workplaces in plants where the exposure was to carbon tetrachloride. Average carbon tetrachloride concentrations were 59-84 ppm near closed systems, 21-650 ppm near half-closed systems, and 72-300 ppm near open processes. In general, most concentrations were less than 100 ppm, but on some excursions they were as high as 7,900 ppm. [57]

A study of carbon tetrachloride concentrations in a film-coating room of a motion picture plant, using a portable combustion apparatus, [23] was reported by Heimann and Ford. [21] The coating wax was carried in a solution of 85% carbon tetrachloride and 15% ethyl alcohol. Carbon

tetrachloride exposure concentrations of 33, 61, 67, 72, 117, and 124 ppm (average, 79 ppm) were found.

The Kentucky Bureau of Industrial Hygiene investigated an outbreak of an illness resembling food poisoning in a parachute factory in 1944 and discovered that it was associated with the use of carbon tetrachloride for cleaning the parachute fabric. [60] One week after measures were taken to alleviate the situation, air samples were taken with a halogenated hydrocarbon indicator commonly used in plant surveys at that time and the carbon tetrachloride concentrations found in the vicinity of the inspection tables were 163 and 194 ppm.

Concentrations of carbon tetrachloride at which workers were exposed in 7 plants using carbon tetrachloride for various purposes were studied by Elkins. [54] The samples were collected in amyl acetate, the solution was burned, and the liberated chloride was determined by titration with silver nitrate. [55] The findings in these plants are summarized in Table IV-1.

In 1959, Elkins [108] published additional data on carbon tetrachloride exposure concentrations found in 30 work places. These data are presented in Table IV-2.

Breathing zone exposures to carbon tetrachloride were studied with a portable halide meter in a plant where carbon tetrachloride was used in the manufacture of polyfluorocarbon refrigerants. [36] The process was virtually automated and enclosed, but exposures of workers occurred when road tankers were unloaded or when storage tanks were cleaned or repaired. Draining of contaminated water from a carbon tetrachloride storage tank resulted in exposure concentrations in excess of 600 ppm. Fitters dismantling recovery columns during a maintenance operation were exposed to

carbon tetrachloride at 75-600 ppm, with "the main" exposure level at 210 ppm. Concentrations of carbon tetrachloride in the breathing zone of a tank-truck driver on top of the tanker and during the hose-connecting process ranged up to 30 ppm.

TABLE IV-1
CONCENTRATIONS OF CARBON TETRACHLORIDE
IN 7 INDUSTRIAL PLANTS

Type of Operation	CCl ₄ Concentration, ppm Average	Range
Drycleaning (spotting)	35	10-80
Drycleaning	65	35-115
Drycleaning	25	15-60
Drycleaning	20	5-40
Multigraph cleaning	85	40-375
Multigraph	--	10-25
Unspecified	25	10-30

Derived from Elkins [54]

Paulus et al [109] surveyed the fumigation procedure used by government employees involved in shelled corn storage. The fumigant used was composed of 80% carbon tetrachloride and 20% carbon disulfide. Carbon tetrachloride concentrations were determined in the bins after fumigation with a halide detector. Because of wide fluctuations in the halide meter responses at higher concentrations, the ratio of carbon tetrachloride to carbon disulfide in duplicate samples was used to estimate carbon tetrachloride concentrations during application. The data presented in Table IV-3 show that during fumigation, when the fumigators wore full-face gas masks with organic vapor canisters, about 40% (14 of 36 measurements)

TABLE IV-2

CONCENTRATIONS OF CARBON TETRACHLORIDE IN 28 PLACES OF WORK

Type of Operation	Concentration, ppm		Comment
	Avg.	Max.	
Balloon cementing	40	50	No illness
	65	70	Nausea
	45	45	
Carburetor jet testing	115	130	Illness reported
Cement mixing	25	...	Illness reported
Drycleaning	20	40	Nausea
	25	30	Complaints
	25	60	Complaints
	35	155	Much illness
	35	45	Illness
	10	15	
	120	200	Compensation case
	45	90	
Gasoline tank cementing	15	25	No illness
	30	35	No illness
	40	50	
Gas mask cleaning	3	...	
Jewel cleaning	40	45	Nausea
Metal cleaning	45	95	
Motor cleaning	50	70	
Multigraphing	15	25	
	80	375	Illness
	190	225	Illness
Nozzle cleaning	10	16	
Pitch spraying	20	40	
Tape coating	25	30	Complaints
Jacket cleaning	130	350	Serious illness
Broaching	30	40	Nausea, vomiting

Derived from Elkins [108]

TABLE IV-3

FREQUENCY OF OCCURRENCE OF CCl₄ CONCENTRATIONS
IN BREATHING ZONES OF GRAIN FUMIGATORS

Concentration Range, ppm	Operation		
	Spraying (masks)	Tending Equipment	Inspecting Bins
0-25		15/43	18/33
26-50		9/43	2/33
51-150		9/43	12/33
151-375		7/43	1/33
375+		3/43	
0-1,500	14/36		
1,501-4,500	8/36		
4,501-15,000	9/36		
15,000+	5/36		

Adapted from Paulus et al [109]

of the estimated concentrations were reported to range from 0 to 1,500 ppm. Five of the 36 measurements were estimated at more than 15,000 ppm.

Workers tending the equipment did not wear respiratory protection. About 33% (15 of 43 measurements) of the estimates of the concentrations to which they were exposed ranged from 0 to 25 ppm and 3 of the 43 estimates were greater than 375 ppm. Workers inspecting previously fumigated grain bins also did not wear respiratory protection. About 50%, (18 of 33 measurements) of the directly measured concentrations at which they were

exposed were in the range of 0-25 ppm and only 1 measurement was greater than 150 ppm.

Environmental Sampling and Analytical Method

(a) Collection Methods

Most analytical methods are dependent on the effectiveness and reproducibility of the uptake of carbon tetrachloride by different collection media. Air samples are usually collected and transported to a laboratory, then desorbed or chemically treated, and finally analyzed quantitatively. Silica gel, which has been used as a collection medium, is a polar adsorbent and shows pronounced selectivity in adsorbing polar molecules, particularly in preference to nonpolar molecules such as carbon tetrachloride. [110] A laboratory study indicated that water vapor in the workroom could displace carbon tetrachloride when sampling more than 3 liters of air through 1-inch silica gel tubes. [111]

More recently, activated charcoal has been used as a collection medium in conjunction with analysis by gas chromatography. [112] Charcoal is nonpolar and will generally adsorb organic vapors in preference to water vapor resulting in less interference from atmospheric moisture than with silica gel. [111]

Williams and Umstead [113] reported the use of porous polymer beads as a collection medium. With this sampling method, the same column was used for sample collection and gas chromatographic analysis. This method consolidated collection and analysis into one operation, but only one analysis could be made on each sample. The method has not been developed for field use.

Liquids have been used to collect chlorinated hydrocarbons from contaminated atmospheres. Elkins et al [55] used amyl acetate in a sampling train to collect carbon tetrachloride from sampled air. Midget impingers containing m-xylene have been used for collection in conjunction with gas chromatographic analysis. [114] Bubbler bottles containing a pyridine solution have been used for collection in conjunction with colorimetric analysis. [115] Impingers and bubblers present hazards from glassware and chemicals when used in personal sampling units for collection of breathing zone samples.

Other investigators have collected grab samples of contaminated atmospheres directly in a variety of containers ranging from plastic bags to hypodermic syringes. [116]

(b) Desorption Methods

When solid collection media are used, it is necessary to desorb the collected contaminant from the medium. Desorption from charcoal was studied by Otterson and Guy. [116] They recommended the use of different desorbing agents depending upon the comparative gas chromatograph retention times for the desorber and the contaminant. Carbon disulfide was determined to be the best desorbent for carbon tetrachloride collected in charcoal tubes.

(c) Analysis

Several methods have been used to quantify carbon tetrachloride in air samples. The analytical methods can be divided in 2 broad categories: 1) methods based on carbon tetrachloride chemical reactions, and 2) methods based on carbon tetrachloride physicochemical characteristics.

(1) Chemical methods

The 3 chemical methods that have been used extensively are: 1) dechlorination of collected vapor samples with strong alkalis followed by titration of the chloride ion (alkaline hydrolysis) [108]; colorimetric measurement of the reaction products of carbon tetrachloride and pyridine heated in alkali solution (Fujiwara reaction) [117]; and 3) direct reading colorimetric indicators. [118]

The dechlorination method (alkaline hydrolysis) requires collection of the carbon tetrachloride-contaminated air by a suitable collection medium followed by alkaline hydrolysis in isopropyl alcohol, and titration of the liberated chloride with silver nitrate. [108] The percentage of chlorine hydrolyzed is determined by comparison between samples and known controls. A disadvantage is that it is not specific for carbon tetrachloride.

In the colorimetric analytical method based on the Fujiwara reaction, a stream of air containing carbon tetrachloride is passed through a bottle containing pyridine. [117] Potassium hydroxide and methylethyl ketone are then added to an aliquot of the sample, and this mixture is heated in a boiling water bath, cooled during a fixed time period, and the color developed is determined with a spectrophotometer. This method requires less time than the dechlorination method, but the problem of specificity with mixtures of chlorinated hydrocarbons remains.

The third chemical method utilizes direct reading detector tubes. [118] These are glass tubes packed with solid chemicals that change color when a measured and controlled flow of air containing carbon tetrachloride passes through the packed material. Depending on the type of detector

tube, the air may be drawn directly through the tube and compared with a calibration chart, or the air may be drawn into a pyrolyzer accessory prior to the detection tube. [118] In either case, the analysis is not specific for carbon tetrachloride since liberated halogen ions produce the stain and any halogen or halogenated compounds will interfere. Regulations on detector tubes (42 CFR 84.50) provide that measurements with colorimetric indicator tubes shall be correct within $\pm 25\%$ of the values read. There are commercially available detector tubes which fulfill this criterion.

(2) Physicochemical methods

Photodetection (halide meters), [119] infrared spectrometry, [120] and gas chromatography [116] are among the analytical methods that are based on the physicochemical properties of carbon tetrachloride.

Halide meters are made to detect the increased brightness of an a-c arc across metal electrodes when they are enveloped by an atmosphere contaminated with halogenated compounds other than fluorides. These instruments are sensitive to all halogens and halogenated compounds except fluorides and consequently they are not specific for carbon tetrachloride. Halide meters are suitable for continuous monitoring if carbon tetrachloride is the only halogenated contaminant present in the sampled air. [119]

An infrared spectrophotometer in conjunction with a suitable recorder can be used to record concentrations relatively instantaneous or continuously. With this method, concentrations are measured directly and it is not necessary to collect individual samples or to transport them to a laboratory for analysis. Infrared spectrophotometry has been used for continuous monitoring of industrial operations for chlorinated hydro-

carbons. There is the need to ensure that the atmosphere of relevant working stations is sampled, and that such samples correspond to the breathing zone of the workers at the working stations. [120] Infrared analysis is subject to interferences from other air contaminants and these interferences are not easily detected or resolved without substantial knowledge of infrared spectrophotometry.

Gas chromatography provides a quantitative analytical method which can be specific for different chlorinated hydrocarbons. [121] Every compound has a specific retention time in a given chromatograph column, but several compounds in a mixture may have similar retention times. This problem is easily overcome by altering the stationary phase of the chromatograph column or by changing the column temperature or other analytical parameters. Altering conditions will usually change the retention times and separate the components.

A mass spectrometer can be used subsequent to gas chromatography to more positively identify the substance present in a gas chromatographic peak. Linked gas chromatograph-mass spectrometer instruments perform this identification automatically. A charcoal capillary tube has been used to trap and transfer the material associated with a gas chromatographic peak to a mass spectrometer for qualitative identification when only unlinked units were available. [122]

(d) Conclusions and Recommendations

(1) Compliance Method

Based on review of air sampling and analytical methods, it is recommended that carbon tetrachloride in air samples be collected with activated coconut shell charcoal, desorbed with carbon disulfide, and

analyzed by gas chromatography. Although this system of measurement is indirect and requires collection and desorption prior to analysis, it has the following attributes:

(A) Charcoal tubes are easy to prepare, ship, and store.

(B) Estimation of exposure with personal samplers is easily achieved.

(C) Desorption with carbon disulfide is efficient and reproducible.

(D) Carbon tetrachloride can be identified in combination with many other compounds.

(E) At the sample volumes recommended, ie, 5-80 liters, interference by moisture is minimal.

(F) Sampling tubes and personal pumps are commercially available.

(2) Monitoring Methods

Exposure to carbon tetrachloride associated with its continuous and constant use can be monitored by infrared spectrophotometry or, if it is the only halogenated hydrocarbon in the workroom air, halide meters can be used. Air from representative work sites can be drawn directly into the infrared spectrophotometer or halide meter by a multiprobe sampling apparatus. A time-location study of the workroom at the different probe locations can be used to estimate peak, ceiling, and TWA exposures to carbon tetrachloride.

Direct reading colorimetric tubes (gas detection tubes) can be used as an inexpensive way to monitor carbon tetrachloride concentrations. The tubes must be used as instructed by the manufacturer.

Biologic Evaluation of Exposure

Carbon tetrachloride was found by Hamburger et al [41] in the blood of patients who had developed anuria following carbon tetrachloride poisoning. They used the reaction of carbon tetrachloride with pyridine as described by Fabre et al [44] for whole blood. The concentrations in the blood of 9 individuals ranged from 0.09-2.30 mg/liter. No information was available about the amount of carbon tetrachloride which had been absorbed by these patients. [43] Carbon tetrachloride was not detected by infrared analysis by Stewart et al [26] in the blood or urine of subjects exposed to carbon tetrachloride at 49 ppm for 70 minutes or 10-11 ppm for 180 minutes. The minimum amount of carbon tetrachloride added to either blood or urine which could be detected by the method they used was 5 ppm (5 mg/liter). There was no measurable excretion of carbon tetrachloride in the urine of monkeys exposed to carbon-14 labeled carbon tetrachloride at 46 ppm for up to 344 minutes by McCollister et al. [85] The concentration of carbon tetrachloride in the blood of these monkeys ranged up to 3.1 mg/liter. Most of the carbon tetrachloride absorbed by these monkeys was excreted unchanged in the expired air. Wells [18] found that most of the carbon tetrachloride he ingested was exhaled. He was able to measure carbon tetrachloride in his exhaled air up to 38.5 hours after he ingested 3 ml of carbon tetrachloride.

Carbon tetrachloride was measured by Stewart and Dodd [48] in the exhaled air of 3 human subjects who each immersed one thumb in beakers of carbon tetrachloride. The concentration ranges in the exhaled air were 0.03-0.09, 0.3-3.3, and 0.7-5.8 $\mu\text{g/liter}$ at 10, 20, and 30 minutes of immersion, respectively. The thumbs were removed from the liquid at the end of 30 minutes and breath samples collected 5 hours later still had measurable amounts of carbon tetrachloride (0.1 $\mu\text{g/liter}$).

Concentrations of carbon tetrachloride in exhaled air of human subjects were studied by Stewart et al [26] during 5 hours following exposures to carbon tetrachloride at 49 ppm for 70 minutes and at 10-11 ppm for 180 minutes. Twenty-five minutes after the end of exposure at 49 ppm, carbon tetrachloride averaged about 20 $\mu\text{g/liter}$ in the exhaled air, and in the subjects exposed to 10-11 ppm it averaged about 6 $\mu\text{g/liter}$. Five hours after the exposures, carbon tetrachloride ranged from 1 to 2.5 $\mu\text{g/liter}$ regardless of the exposure concentration.

Concentrations of carbon tetrachloride in the breath of 2 patients who were accidentally exposed to carbon tetrachloride, 1 by inhalation and the other by ingestion, were studied by Stewart et al. [46,47] The amount of carbon tetrachloride absorbed was not known in either case. The initial concentration of carbon tetrachloride in the breath of the inhalation case following the exposure was 56 $\mu\text{g/liter}$. Carbon tetrachloride was still detectable in the patient's breath 2 weeks later. In the ingestion case, the concentration of carbon tetrachloride found in the breath about 3 hours after the ingestion was 2.0-2.5 mg/liter . A series of breath samples showed a progressive decrease in carbon tetrachloride concentration to 1.2 $\mu\text{g/liter}$. Analytical methods for carbon tetrachloride in air may be

sensitive enough to evaluate exposures by breath analysis at the recommended environmental standard, but experimental data to determine this have not been found. Carbon tetrachloride has a long life in the body and a variety of exposure conditions can result in the same exhaled breath concentrations. Data from experimental animals must be obtained and correlated with human data in order to estimate the magnitude of carbon tetrachloride exposure from concentrations in the breath. However, as a complement to air sampling, breath analysis can be useful to qualitatively determine carbon tetrachloride exposure.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The Sub-Committee on Threshold Limits of the National Conference of Governmental Industrial Hygienists (NCGIH) published a list in 1942 entitled, "Maximum Permissible Concentrations of Atmospheric Contaminants as Recommended by Various State Industrial Hygiene Units." [123] Thirteen states were listed as recommending 100 ppm for carbon tetrachloride. The listing was presented without comment other than that the tabulated values were not to be construed as recommended safe concentrations.

Various standards for carbon tetrachloride were the subject of discussion at the 7th Annual Meeting of NCGIH in 1944. [124] Manfred Bowditch, Director, Massachusetts Division of Occupational Hygiene, gave "temporary indisposition," indicated by nausea, as reason for a standard lower than 100 ppm. (Some of the data that were the basis for this statement were published by Elkins [54] in 1942, and by Bowditch [125] in 1943.) He reported that as a consequence, the Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries proposed lowering the standard for carbon tetrachloride to 40 ppm. Other governmental agencies also considered 100 ppm ineffective and recommended a lower standard. [124,126]

A list of maximum allowable concentrations of atmospheric industrial contaminants compiled by Cook [126] in 1945 included the carbon tetrachloride values of 7 governmental agencies. These are presented in Table V-1.

TABLE V-1
 CARBON TETRACHLORIDE STANDARDS OF GOVERNMENTAL AGENCIES

Agency	MAC, ppm
California Industrial Accident Commission	100
Connecticut Bureau of Industrial Hygiene	100
Massachusetts Department of Labor and Industries	50
New York State Department of Labor	75
Oregon State Board of Health	50
Utah Department of Health	100
United States Public Health Service	100

Derived from Cook [126]

These concentrations were all recommended as allowable for prolonged exposures, usually assuming a 40-hour workweek. [126]

In addition to tabulating these values, Cook [126] reported 100 ppm to be an accepted or tentative value based on the work published by Smyth et al [56] in 1936. However, in his discussion of carbon tetrachloride, Cook [126] wrote that since that publication there was an increasing amount of evidence of injury to health at lower concentrations and he recommended that exposures be at less than half the 100 ppm then being used.

The American Conference of Governmental Industrial Hygienists (ACGIH) (formerly NCGIH) adopted a list of "Maximum Allowable Concentrations of Air Contaminants for 1946" which was prepared by the Subcommittee on Threshold Limits [127] and selected a value of 50 ppm for carbon tetrachloride based on Cook's recommendation. [126]

The ACGIH Committee on Threshold Limits reported in 1949 that it had received comments from outside the Conference that a value of 50 ppm for carbon tetrachloride was too low. [128] On the other hand, carbon tetrachloride was included in a list of substances for which a reduction of the limit had been suggested by members of the Conference.

The ACGIH recommended a TLV of 25 ppm for carbon tetrachloride in 1953. [129] A preface to future tables of threshold limits was adopted which defined the values as "maximum average atmospheric concentration of contaminants to which workers may be exposed for an 8-hour working day without injury to health." [129] The preface was modified in 1958 and included the statement that "They [threshold limit values] represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect." [130]

The American Standard Maximum Acceptable Concentration of Carbon Tetrachloride (ASA Z37.17-1957), published in 1957, was 25 ppm for exposures not exceeding 8 hours daily with the understanding that variations should fluctuate around 10 ppm. [131] The 25 ppm was understood to be a ceiling below which all concentrations were to fall. It was partly based on the animal experiments reported by Adams et al [69] and partly on industrial experiences of members of the Committee.

The Documentation of Threshold Limit Values [132] which was published in 1962 by the ACGIH referred to the reports of Adams et al, [69] Heimann and Ford, [21] Kazantzis and Bomford, [59] and Elkins [54] in its support of the TLV for carbon tetrachloride of 25 ppm. From these data, it was considered that 25 ppm was low enough to prevent irreversible injury. [132]

At the annual meeting of the ACGIH in 1962, the Threshold Limit Committee recommended reducing the TLV for carbon tetrachloride to 10 ppm because there were "increasing indications" that exposure to carbon tetrachloride at 25 ppm was excessive. [133]

Tables of "Permissible Levels of Toxic Substances in the Working Environment" for many countries were published by the International Labour Office in 1970. [134] The reported carbon tetrachloride standards are presented in Table V-2. The USSR values (MAC) are absolute values never to be exceeded. They are set at a value which will not be expected to produce in any exposed person any disease or other detectable deviation from normal. Some other countries tend to follow this concept in setting their standards, while still others tend to follow the concepts of the ACGIH. The intent is indicated for some of the standards presented in Table V-2.

TABLE V-2
CARBON TETRACHLORIDE STANDARDS OF 10 COUNTRIES

Country	Standard mg/cu m	ppm	Qualifications
Czechoslovakia	50	8	Normal MAC
	250	40	Single short exposure
Finland	160	25	8 hours continuous exposure
Hungary	20		8-hour average
	100		30 minutes
Japan	10		
Poland	20		
Rumania	50		
UAR and SAR		100	
USSR	20		MAC
Yugoslavia	65	10	

Derived from reference 134

The most recent documentation of the threshold limit values was published by the ACGIH in 1971. [135] The reports of Heimann and Ford, [21] Elkins, [54] Barnes and Jones, [36] Kazantzis and Bomford, [59] Markham, [45] Adams et al, [69] and Stewart et al [26] were referred to in support of the TLV of 10 ppm which had been adopted in 1962. Information that some workmen experienced nausea when average daily carbon tetrachloride exposures approached 25 ppm, whereas no difficulties were experienced at 10 ppm, based on a personal communication to the Committee, was used as additional support for the TLV. The TLV of 10 ppm was recommended with the caution that peak exposures, even of short duration, should not exceed 25 ppm.

The Occupational Safety and Health Administration, US Department of Labor, adopted ANSI standard Z37.17-1967 [136] as the federal standard for carbon tetrachloride (29 CFR 1910.1000). This standard is 10 ppm for an 8-hour TWA exposure, with an acceptable ceiling exposure concentration of 25 ppm, and an acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift of 200 ppm for 5 minutes in any 4 hours.

This ANSI standard was based on human experience and extensive animal investigations. References cited to support it were Adams et al, [69] Stewart et al, [26] Stewart et al, [46] Stewart and Dodd, [48] von Oettingen, [137] and Irish. [138]

Basis for Recommended Environmental Standard

The recommended environmental standard is based on reports of liver and eye changes found in workers chronically exposed to carbon tetrachloride. [13,20,22,27-29,36,37,39,41,50,56,57,59,61] Concentrations

of carbon tetrachloride to which the workers had been exposed were not available in some of the reports and were not extensively documented in any of them. However, the findings of liver and eye damage at the carbon tetrachloride concentrations reported are supported by comprehensive studies of animals chronically exposed to carbon tetrachloride, 7 hours/day, 5 days/week for up to 2 years. [56,57,69]

Elkins [54] found that workers' symptoms of gastrointestinal and central nervous system disturbances generally were alleviated when exposures were reduced below 20 ppm. He did not, however, report studies which would detect liver injury. The observations of Kazantzis and Bomford [59] support those of Elkins, [54] but they also did not make measurements to detect chronic liver injury.

Alcohol consumption was common both in fatalities and in severe cases of liver and kidney involvement from carbon tetrachloride exposure. [29,31,32,34,40,49-53] Observations that alcohol enhances the hepatotoxic effect of carbon tetrachloride have been verified by animal studies. [98,99,106,107] Two-hour exposures of rats to carbon tetrachloride at 100 ppm, 16-18 hours after they were given ethyl alcohol, increased SGOT activity compared to that of either control rats exposed to carbon tetrachloride at 100 ppm without alcohol pretreatment or rats given only ethyl alcohol. The toxicity from single 8-hour exposures to carbon tetrachloride at 25 and 50 ppm was not increased by pretreatment of the rats with ethyl alcohol. [98]

Elevated icteric indices and enlarged livers were found by Gray [29] in 4 workers who had used carbon tetrachloride in their work for from 2 months to 11 years. The carbon tetrachloride concentrations to which these

workers were exposed were not reported, but Smyth et al [56] and Smyth and Smyth [57] found elevated icteric indices in 11 workmen chronically exposed at 8-hour TWA concentrations estimated at 26-39 ppm. In the same investigation, they [56,57] did not find elevated icteric indices in 14 other workmen with estimated 8-hour TWA exposures at 5-24 ppm.

Elevated serum transaminases, elevated BSP retention, and an enlarged, discolored liver with fatty degeneration were found by Dellian and Wittgens [37] in a man who had been using carbon tetrachloride in his work for 4 years. Carbon tetrachloride concentrations found at 16 locations in the plant where the man worked were 10-100 ppm. Two other workers reported chronic symptoms of central nervous system and gastrointestinal disorders.

Elevated SGOT was found by Kazantzis and Bomford [59] in a man who worked in an environment where measured carbon tetrachloride concentrations were between 45 and 97 ppm. The SGOT returned to normal after corrective measures reduced carbon tetrachloride concentrations to less than 10 ppm. Of 18 employees in the factory, 17 reported having had symptoms of central nervous system or gastrointestinal disturbances before these corrective measures were taken.

Statistically significant increases were found in zinc and thymol turbidity, SGOT, and serum bilirubin, indicative of liver injury, in a group of 16 workers who handled carbon tetrachloride compared to a group of 11 workers who did not handle it in a modern plant manufacturing polyfluorocarbons. [36] Urinary urobilinogen was normal in the unexposed workers but was positive in 6 of the 16 exposed workers. There was no report of concentrations of carbon tetrachloride in the factory.

The durations of exposure to carbon tetrachloride and biochemical test data of 51 workers were compared by Rabes. [61] The workers had used carbon tetrachloride for 3-27 years to clean equipment in an electrical generating plant. Carbon tetrachloride was the only solvent used in the cleaning process which occurred 2-3 times a year. Each cleaning process required about 14 days. Concentrations of carbon tetrachloride in the work environment, determined from 2 measurements taken on 1 day, were 6.3 ppm at the beginning of a work shift and 9.5 ppm at the end of the work shift.

Biochemical test data from the 51 exposed workers were classified into 5 groups according to the number of years of employment and compared with 27 unexposed workers. Serum iron and GDH changes indicative of liver injury were found in the exposed workers. The average serum GDH value of the group exposed for 3-5 years was increased 92% above the average of the control group, and for the group exposed 20 or more years, it was increased 182%. Serum iron of the group exposed for 3-5 years was increased 40% and 25.5% for the total group of exposed workers. [61]

Restricted visual fields and other eye abnormalities have occurred with occupational exposures to carbon tetrachloride. [13,20,22,27-29,56-58] Smyth et al [56] and Smyth and Smyth [57] described 9 cases of definitely restricted visual fields and 26 cases of slightly restricted visual fields in 77 workmen exposed to carbon tetrachloride. Of the 9 cases of definitely restricted visual fields, 4 occurred in workmen for whom estimated 8-hour TWA exposures were 7, 10, 10, and 24 ppm with respective estimated peak exposures of 66, 22, 173, and 232 ppm. Moeller [58] found a high percentage of restricted visual fields in 62 workmen who dipped cleaning mops into buckets of carbon tetrachloride without skin or eye

protection. The measured concentrations of carbon tetrachloride in the air were in the 7-10 ppm range. The fundi and visual fields were normal in 17 individuals examined by Kazantzis and Bomford [59] after exposures at 45-97 ppm for up to 2 years.

The indications of liver changes in workers chronically exposed to carbon tetrachloride at estimated concentrations of 5-10 ppm were based on only 2 environmental measurements, [61] so it is unlikely that their exposures were confined to the 5-10 ppm range. However, the possibility that liver involvement, as reported, could have occurred is supported by other occupational observations reported by Barnes and Jones, [36] Dellian and Wittgens, [37] Smyth et al, [56] Smyth and Smyth, [57] and Moeller, [58] and by animal experimentation. The finding of degenerative fatty changes in the livers of both rats and guinea pigs exposed to carbon tetrachloride at 10 ppm for 7 hours/day, 5 days/week for 26 weeks suggests that the present standard TWA of 10 ppm for an 8-hour workday is too high.

Pathologic changes have been found in animals exposed 7 hours/day, 5 days/week to carbon tetrachloride at 5 ppm or more. [69] Increased liver weights relative to body weights were found in female guinea pigs after 143 exposures to carbon tetrachloride at 5 ppm. Guinea pigs may be more sensitive to carbon tetrachloride than other species, [56,57] and in this study, [69] rats were the only other species exposed at 5 ppm. However, increased liver weights and fatty degeneration of the liver were found in both rats and guinea pigs exposed at 10 ppm, 7 hours/day, 5 days/week for 136-139 exposures. Total lipid, neutral fat, and esterified cholesterol in livers of these animals were more than twice the control values. Cirrhosis of the liver and fatty degeneration of the liver, nerves (optic and

sciatic), and eye muscle were found in guinea pigs intermittently exposed at 25 ppm. [57,69] Fatty degeneration of the liver without cirrhosis was found in rats and rabbits intermittently exposed at 25 ppm. [69] Liver cirrhosis and degenerative changes in the eye muscle and sciatic nerve were found by Smyth et al [56,57] in rats after chronic exposures to carbon tetrachloride at 50 ppm.

When exposure concentrations were below 100 ppm, Adams et al [69] did not find significant liver effects in monkeys. However, Smyth et al [56] and Smyth and Smyth [57] did observe fatty changes without degeneration in the livers and degenerative changes in the eye muscle of monkeys exposed at 50 ppm for 8 hours/day, 4-6 days/week for 62 days. Fatty degeneration of the liver and slight cloudy swelling of the kidney tubules were found by Adams et al [69] in 2 monkeys exposed at 100 ppm.

Three cases of liver cancer in humans following carbon tetrachloride exposure were found in the literature. [38-40] In these cases a definitive causal connection could not be made to carbon tetrachloride. However, in all three cases there was evidence of severe liver injury from acute exposures to carbon tetrachloride.

Hepatomas following administration of carbon tetrachloride to a variety of experimental animals have been reported. [70-83] They have been found in animals following inhalation, ingestion, or subcutaneous or intrarectal administration of carbon tetrachloride.

Hepatomas induced by carbon tetrachloride were successfully transplanted between mice of the same strain. [77,79] Transplantations of hepatomas from a single host were successful when 8 months had elapsed

between carbon tetrachloride administration and tumor transplantation, but were unsuccessful when only 11 weeks or less had elapsed. [79]

Carcinomas larger than 5 mm were found in livers of 3 strains of rats subcutaneously injected, twice weekly until they died, with doses of 1.3 ml/kg carbon tetrachloride. [81] Carcinomas were found in 12 of 15 Japanese strain rats, 8 of 13 Osborne-Mendel rats, and 4 of 12 Wistar rats.

Incipient or established carcinomas were found by Costa et al [83] in the livers of 10 of 30 rats that completed 7-month inhalation exposures. The concentrations of carbon tetrachloride were not given.

Liver necrosis due to carbon tetrachloride seems to be a necessary precursor to development of tumors or cancers in the liver. A positive correlation was found between the degree of liver necrosis and the incidence of hepatomas in mice given 30 oral doses at different intervals. In the chronic inhalation experiments of Smyth et al, [56] Smyth and Smyth, [57] and Adams et al, [69] there was no evidence, in any species, of liver necrosis where the carbon tetrachloride exposure concentrations were less than 200 ppm. Evidence of liver necrosis has not been found by examination of workers where the exposures were less than 25-50 ppm. [26,59,61] There have been no reports of liver cancer in humans who have been chronically exposed but without evidence of liver necrosis having occurred.

The findings in the eyes of workers exposed to carbon tetrachloride at 5-10 ppm indicate that exposures should be limited to less than 5 ppm to protect the eyes as well as the liver from chronic injury. There is no evidence from human experience to determine what level of exposure below 5 ppm is safe. However, to provide for a margin of safety it is recommended that worker exposures be limited to 2 ppm determined as a time-weighted

average exposure for up to a 10-hour workday, 40-hour workweek. The evidence indicates that the recommended standard will be sufficiently restrictive of carbon tetrachloride exposure that adverse effects will not result from the allowable environmental exposures.

Exposure to carbon tetrachloride other than by inhalation can occur in the work environment. Absorption of liquid carbon tetrachloride through the skin has been shown to occur in humans and animals. [48,66,67] Skin contact with carbon tetrachloride can also result in irritation and dermatitis. [13,25]

Stewart and Dodd [48] estimated that the amount of carbon tetrachloride absorbed during topical exposure of both hands for 30 minutes would be equivalent to vapor exposure of about 10 ppm for 3 hours.

Exposure of the skin was a definite factor which was not evaluated in a number of occupational reports, but it was evident from the type of work involved. [45,54,59,60] Farrell and Senseman [22] considered a case of polyneuritis to have been caused by absorption of carbon tetrachloride through the skin. It is recognized that many workers handle small amounts of carbon tetrachloride or work in situations where, regardless of the amount used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect worker health under more hazardous circumstances. Concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, "occupational exposure to carbon tetrachloride" has been defined as exposure above half the environmental limit, thereby delineating

those work situations which do not require the expenditure of health resources for environmental and medical monitoring, and associated recordkeeping. Half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, because of nonrespiratory hazards such as those resulting from skin absorption or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the air concentration.