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Human Exposure to Tetrachloroethylene: Inhalation and Skin Contact

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There is considerable potential for worker exposure to tetrachloroethylene, both by skin contact and by inhalation, during its use in dry cleaning and degreasing operations. This paper reviews accounts of both accidental overexposures of workers and controlled exposures of human subjects by these two routes of exposure. Several reported cases of accidental overexposure to anesthetic doses of the chemical reveal that recovery was generally complete but prolonged, and accompanied by many days of measurable levels of the chemical in the patient's alveolar breath. Chronic overexposures of workmen have lessened since the general acceptance by the Western world of the recommended TLV of 100 ppm for 8 hr of daily exposure. Controlled inhalation studies with volunteer subjects at this level of exposure revealed no effects upon health but did indicate a slight decrement in performance on a coordination test. Additional behavioral and neurological tests revealed no interactive effects when alcohol or diazepam, two depressant drugs, were added singly to tetrachloroethylene exposures. Individual susceptibility to the vapor of this chemical, as evidenced by subjective complaints, was noted in approximately one of ten subjects. The authors conclude that the TLV concentration of 100 ppm in the workplace has a negligible margin of safety regarding unimpaired performance during repeated exposures which could be especially hazardous if the worker is physically active or is in a situation where skin absorption presents an added burden.

Tetrachloroethylene, also known as perchloroethylene or more commonly as perc, is an unsaturated ethylenic molecule containing four chlorine and no hydrogen atoms. Because of its lipophilic properties and relatively high boiling point of 121°C, it has found widespread use in dry cleaning and degreasing operations. Because of the nature of these two uses, there is great potential for human exposure to tetrachloroethylene, both through inhalation and skin contact. In this paper I will briefly review the human toxicology associated with such exposures.

Skin Contact

The skin is often overlooked as an organ that absorbs or can be affected by solvents. Among the chlorinated industrial solvents, human skin reaction to tetrachloroethylene is relatively mild, and therefore workers can become careless in handling this liquid. A mild to moderate burning sensation is experienced with direct skin contact for 5–10 min, and a marked erythema, and finally blistering can occur upon prolonged contact. Soft tissue contact increases the sensation of irritation and burning. Repeated insults to the skin produce a defatting effect which may result in chapping and cracking, allowing infection to set in. Allergic skin responses are uncommon and not to be expected with this solvent.

Stewart and Dodd (*1*) carried out a study several years ago to demonstrate the absorption of chlorinated solvents by human skin. Exposure was by dipping one thumb into the undiluted chemical, and absorption was demonstrated by analyzing for the solvent in serial breath samples. Figure 1 shows the mean breath concentrations of five volunteer subjects during and for up to 5 hr after exposure. Of the five solvents tested, tetrachloroethylene, though reaching the lowest maximum concentration with the longest exposure, exhibited the slowest decay in the breath. The latter property is quite distinctive for tetrachloroethylene, as we shall see later. This study demonstrated the importance of skin exposure in assessing the hazard of these solvents, and though ab-

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sorption through the skin is usually not of as great consequence as through the lungs, it should not be overlooked as a contributory factor to the tetrachloroethylene body burden in a work environment.

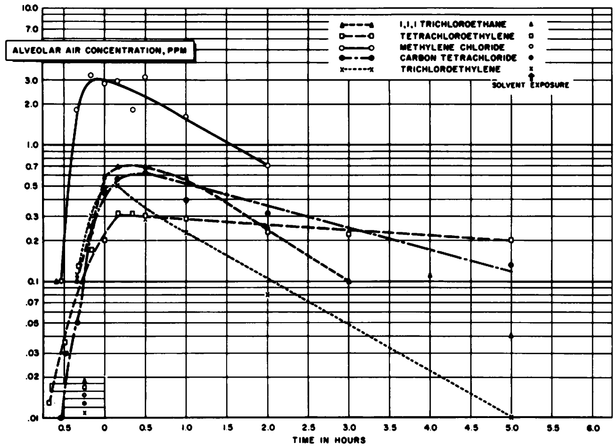

FIGURE 1. Mean alveolar air concentrations during skin exposure and in the early post exposure period plotted for five solvents. The thumb of one hand was immersed in the solvent for the period of time charted. From Stewart and Dodd (*1*).

Inhalation and Skin Contact

Acute intoxications with tetrachloroethylene have been reported where inhalation of the vapors was the primary route of entry, though in several cases, skin absorption also occurred. As far back as 1943, Foot and co-workers (*2*) tested tetrachloroethylene as an anesthetic agent on four healthy volunteers and fourteen patients. The desired anesthesia was somewhat difficult to achieve because of the low vapor pressure of this chemical, and during anesthesia the patients demonstrated poor muscle relaxation.

Stewart et al. (*3*) in 1961 were the first to confirm an acute overexposure to tetrachloroethylene by the use of breath analysis. Identification of the chemical in the patient's breath was done by infrared spectroscopy. A worker had been using a solvent in an enclosed work situation, and when found was in a semicomatose state. Although the patient recovered rather rapidly with no abnormality of function, the authors identified tetrachloroethylene and followed the chemical in the breath for 20 days. They attributed laboratory evidence of impaired liver function, which surfaced 9 days after exposure, to the prolonged body burden of the chemical.

In 1969, Stewart (*4*) reported a second confirmed overdose case in which the worker experienced marked CNS depression followed by transient, minimal liver injury. Morgan (*5*) reported a case where a worker was anesthetized and lay unconscious for a half hour in a coin-operated launderette in England before being rushed to the local hospital. Erythema and blistering occurred over 30% of his body, but no other untoward effects were reported. Ling and Lindsay (*6*) reported an almost identical case of a worker being overcome in a British launderette with resultant erythema and blistering of the skin. Lackore and Perkins (*7*) described the unusual case wherein a patient on a respirator became anesthetized after a workman had inadvertently washed the filters for the supplied air to the hospital's respirators with tetrachloroethylene. Other than temporary anesthesia and drowsiness during exposure, the patient's clinical condition did not change. Patel et al. (*8*), reported a case involving overexposure to a dry cleaning agent.

We have recorded an additional case recently that exemplifies a gross tetrachloroethylene overexposure. A 60-year old male dry cleaning operator arrived at the local hospital early one morning after having been discovered lying in a pool of solvent. It was assumed that he had been lying there unconscious for approximately 12 hr. A physical examination 2.5 hr after removal from the exposure revealed that the patient was comatose but responsive to painful stimuli. He had a systolic blood pressure of 70 mm Hg, pulse rate of 96 beats/min, respiration rate of 28/min, was cyanotic in appearance; pupils were constricted and reactive, and the chest was clear. Several large patches of skin were exfoliating where he had been in direct contact with the liquid solvent. During the exam he underwent a mild seizure involving his left side. Laboratory studies revealed renal damage as indicated by a proteinurea, which lasted for 20 days, and hematuria for eight days. Mild liver injury was evidenced by elevated serum enzymes. His initial hypotension, atelectasis, right hemiparesis, and extensive first and second degree burns all responded to supportive treatment. Serial breath samples were obtained and assayed for tetrachloroethylene by gas chromatography. As seen in Figure 2, we could easily see the chemical in his breath until his discharge from the hospital. This graph compares his breath levels to the two previously reported cases, and to the mean breath decay curve after exposures to the time-weighted average threshold limit value (TLV) of 100 ppm. After 21 days, the patient was discharged from the hospital, fully recovered from this accidental overexposure, and as of a few months ago was back at his dry cleaning establishment. We believe that the three examples from our experience, all well documented, demonstrate the reversibility of the narcotic effect and the liver and kidney injury due to gross overexposure to tetrachloroethylene.

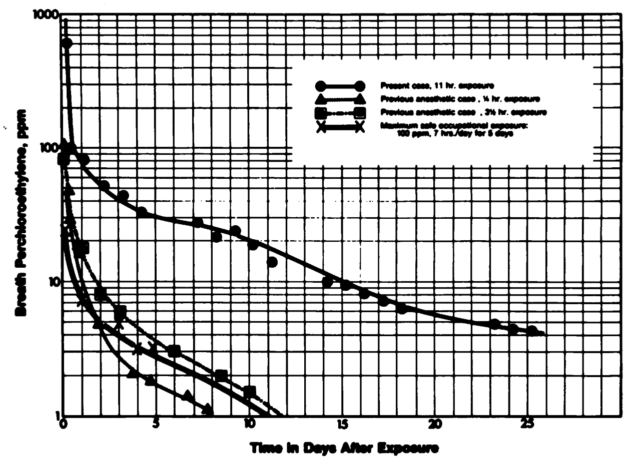

FIGURE 2. Breath analysis decay curves representing three cases of acute accidental overexposure to anesthetic concentrations of tetrachloroethylene, and the mean of sedentary subjects exposed to 100 ppm of the chemical vapor for 7.5 hr/day for 5 days.

Despite the use of this solvent in an industry characterized by thousands of small independent businesses wherein industrial hygiene is often lacking, relatively few reports of chronic toxicity have appeared in the literature. In the 1950s, when continuous inhalation exposure concentrations of > 200 ppm were not uncommon, Coler and Rossmiller (*9*) and Lob (*10*) reported multiple cases of intoxication. Symptoms ranged from headache, nausea, lightheadedness, dizziness, tiredness, hang-over and intoxication feelings, to serious neurological symptoms and signs of liver disfunction. Since the general acceptance by the Western world of the recommended TLV of 100 ppm, reports such as those by Dumortier et al. (*11*), Meckler and Phelps (*12*), Gold (*13*), and Trense and Zimmerman (*14*), wherein individual intoxications are reported, the exposures have generally been uncontrolled and can be assumed to have been grossly over the TLV.

Controlled Inhalation Studies

We believe that controlled inhalation studies afford the most reliable data for assessing physiological, behavioral, and pharmacodynamic responses to tetrachloroethylene vapor.

The first controlled inhalation study reported was that of Rowe et al. (*15*) in 1952. The exposed human subjects to tetrachloroethylene concentrations ranging from 1060 ppm for 1 min to 106 ppm for 1 hr. The latter exposure was not objectionable to any of six persons, while the penultimate concentration of 216 ppm resulted in eye irritation and slight dizziness or inebriation. Higher concentrations were unacceptable.

In 1961, Stewart et al. (*16*), published the first of their series of papers on controlled human exposures to tetrachloroethylene. Sedentary subjects breathed concentrations of approximately 100 or 200 ppm for periods of time up to 3 hr. The work confirmed the earlier report of Rowe et al. regarding subjective and physiological responses, and the authors concluded that vapor exposures to this compound "should never exceed 200 ppm, because of the rapid onset of lightheadedness and, hence, the increased risk of accidental injury resulting therefrom." The authors also pointed out the prolonged exponential decay in the post exposure expired air.

A second controlled inhalation study by Stewart and co-workers (*17*) was published in 1970. In this study, as in all studies from this laboratory, great care was exercised in the analysis of the air in the controlled-environment chamber, making certain that the time-weighted average exposure concentration was accurately assessed. A second consideration of importance to the interpretation of results from these studies is the sedentary activity level of the subjects. A third consideration that must be kept in mind is that only healthy individuals were selected as volunteers. Fifteen subjects were exposed to air containing 100 ppm tetrachloroethylene vapor for 7 hr of one day, and five subjects were repeatedly exposed for 7 hr to this level for five consecutive days. Although several of the subjects reported various subjective symptoms, of greater importance was the one individual who seemed to be more susceptible to the central nervous system depressant effect than others. He experienced some loss of equilibrium, complained of dizziness, and of slight impairment of intellectual faculties, and was thus removed from the exposure after 3 hr. Normalcy returned within 30 min. The concentration of tetrachloroethylene in the breath of the five subjects repeatedly exposed to the vapor is shown in Figure 3. Here again we see the long decay of the chemical as it is being excreted by the lungs, and we also see the trend to a higher breath level as the week progresses, indicating an increase in the body burden.

We have conducted two additional studies with tetrachloroethylene. These were primarily funded by the National Institute for Occupational Safety and Health and have appeared or will appear shortly as NIOSH reports. Table 1 relates some of the parameters for these studies. Study A was simply carried out to demonstrate that light exercise, or physical activity, increases the body burden of tetrachloroethylene. A faculty member exercised on a bicycle ergometer for 0.5 hr at a concentration of 150 ppm on two separate days, and was sedentary while

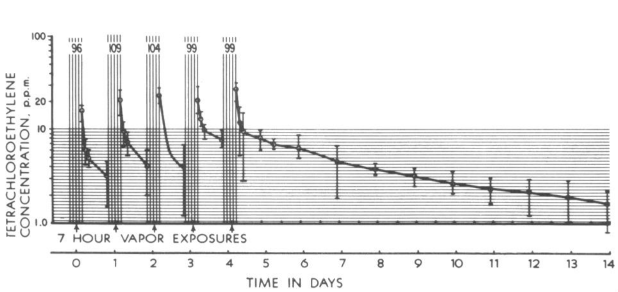

FIGURE 3. Mean and range breath concentrations are plotted for each post exposure time interval. The first decay curve represents lung excretion following first day's exposure. Following fifth day's exposure, prolonged exponential decay of solvent in subjects' breath was observed. From Stewart et al. (17).

days. The subjects entered the exposure chamber in pairs, and carried out their routine of testing, 30 min of moderate exercise, consumption of alcohol, diazepam, or placebo, 30 min of rest, and final retesting on all days in an identical manner. The 30 min of moderate exercise increased the venous blood concentrations to levels higher than one would expect from a sedentary exposure to 100 ppm for 8 hr.

Figure 4 shows the postexposure breath concentrations of the single subject (Study A) exposed to 150 ppm tetrachloroethylene with and without exercise; it is obvious that his body burden was greater with exercise. Åstrand (18) from the Swedish National Board of Occupational Safety and Health has reported similar results for several other industrial solvents.

Table 1. Study parameters.

Study	Subjects Number	Subjects Sex	Tetrachloroethylene concentration, ppm	Exposure Duration	Exposure hr/day	Remarks
A	1	M	150	3 days	0.5	Sedentary vs. exercise
B	4	M	0, 20, 100, 150,		7.5	
	3	M	and 100 fluctuating	5/wk	3	Sedentary
	3	M	0 and 100		1	
C	4	F			7.5	
	3	F		5/wk	3	Sedentary
	2	F			1	
D	6	F	0 (M&Tu), 25 (Th)	11 wk	5.5	Combined study
	6	M	and 100 (W&F)	11 wk	5.5	with drugs, 0.5 hr exercise

undergoing the same exposure on a third day. In studies B and C, male or female volunteer subjects were exposed for 7.5, 3, or 1 hr/day, 5 days/week, to several concentrations of the vapor. The subjects were generally sedentary during these two studies. Neurological, physiological, behavioral, and the volunteer's own subjective responses were assessed during the exposures, and blood, breath, and urine samples were assayed for tetrachloroethylene or metabolites. Study D was carried out primarily to determine the interactive effect of tetrachloroethylene exposure and alcohol consumption or tetrachloroethylene exposure and diazepam dosing upon behavioral and neurological responses. Diazepam is the generic term for Valium, a mild tranquilizer. All three of these chemicals have a general "depressant" effect on the central nervous system, and the combination exposures no doubt occur daily in industries where tetrachloroethylene is used. This study was fairly complicated, and, because of the need to study responses after several days of medication and after placebo dosing, it required 11 weeks of daily exposures wherein Monday and Tuesday were generally control days, Thursday was an intermediate exposure day, and Wednesday and Friday were 100 ppm exposure

In study B, wherein male subjects were repeatedly exposed to control and three concentrations of tetrachloroethylene bracketing the TLV, and in study C wherein female subjects were exposed to the TLV for five consecutive days, all of the subjects continued in good health and performed normally on all physiological tests including pulmonary function tests. However, the EEG tracings scanned subjectively by a neurologist suggested altered patterns indicative of cortical depression in both male and female subjects exposed to 100 ppm tetrachloroethylene for 7.5 hr. Visual evoked responses (VER) and equilibrium tests were normal. In behavioral tests (males only) math skills, time discrimination, inspection, and reaction time remained normal. However, coordination scores as measured by the Flanagan coordination test (FACT 7A, Coordination, published by Science Research Associates, Inc., 259 East Erie Street, Chicago, Illinois 60611) were significantly decreased on at least one day during the weeks of 100 ppm and 150 ppm exposure. This coordination test required the performer to rapidly follow with a pencil a prepared spiral on a sheet of paper without touching the lines of the spiral. Figure 5 demonstrates the mean daily scores with standard deviations of the four subjects with 7.5 hr exposure.

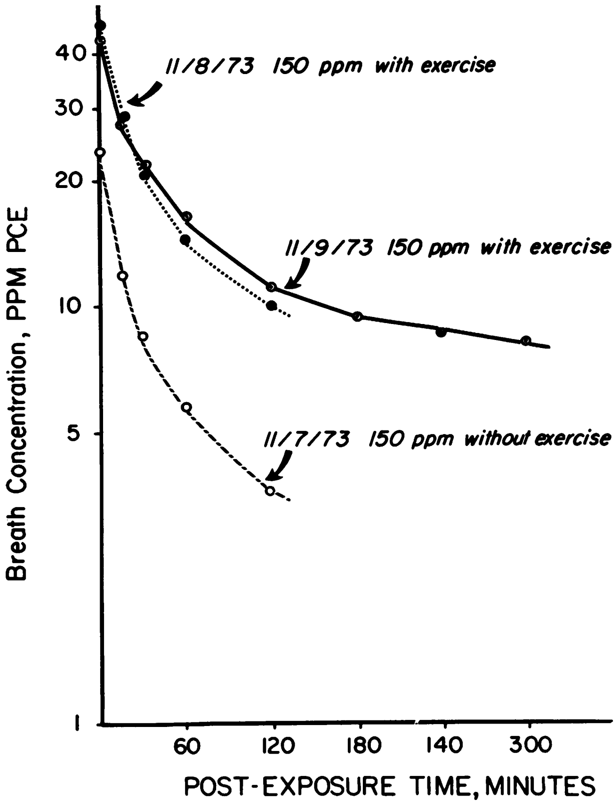

FIGURE 4. Effect of 30 min of light exercise upon post-exposure tetrachloroethylene (PCE) breath analysis decay curves, study A.

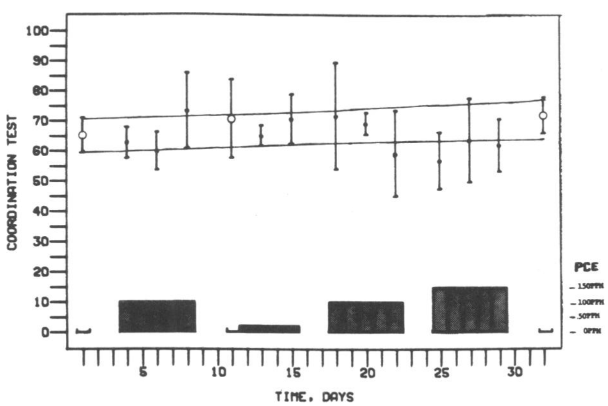

FIGURE 5. Mean daily scores with standard deviations of Flanagan coordination test related to tetrachloroethylene (PCE) vapor exposures, four male subjects, 7.5 hr/day, study B. The curved longitudinal brackets indicate the 95% confidence limits of the scores from the three control days which are noted by open circles.

The curved longitudinal brackets indicate the 95% confidence limits of the scores from the three control days which are noted by open circles. The exposure concentrations are indicated on the right hand side of the graph. Using linear adjusted scores corrected for the training effect, plus scores from the two days at 20 ppm exposure as additional control days, significant ($p < 0.05$) decrements in performance were established for the Monday and Friday scores during 150 ppm and the Wednesday score of the first 100 ppm exposure concentration. Other outliers were not significantly different from control plus 20 ppm scores.

Other observations made during this study were that almost all subjects reported a tachyphylactic type of response regarding subjective complaints and odor detection; that is, complaints and/or the chemical odor usually became less noticeable or disappeared entirely as an exposure progressed both daily and on a weekly basis. And in addition, one subject accounted for a disproportionate number of subjective complaints. There was no direct relationship of subjective complaints to increasing magnitude of tetrachloroethylene exposure concentration.

Regarding urinary metabolites of tetrachloroethylene, we could find no trichloroethanol and only traces of trichloroacetic acid in 24-hr urine collections during these exposures. Our assays for these metabolites were carried out by gas chromatography, with a detection limit of 1 ppm.

Figure 6 illustrates the venous blood levels, for the four studies. In study A, light exercise increased the blood level somewhat. With both male and female subjects (studies B and C), the concentration of the chemical in the atmosphere had a greater effect on the blood level than the length of the exposure. In most cases, blood levels did not seem to increase much after 3 hr of exposure. However, 30 min of moderate exercise during exposure to 100 ppm tetrachloroethylene (study D) increased the venous blood levels about fourfold over that expected after an equivalent time of sedentary exposure. Alcohol blood levels of 30 to 100 mg-% or diazepam at 7 to 30 mcg-% had no effect on tetrachloroethylene blood or breath levels during exposure to 100 ppm, as shown in Table 2. The significant decrease ($p = < 0.01$) at 30 min postexposure after alcohol is interesting but unexplained. This is actually 4 hr after alcohol ingestion, and the effect was reversed on 25 ppm exposure days.

Behavioral studies, including the Flanagan coordination test and four new tests not included in the previous study, the Michigan eye-hand coordination, rotary pursuit, the dual tasks test, and the saccade velocity measurements, were carried out im-

Table 2. Effects of alcohol and diazepam upon tetrachloroethylene (PCE) blood and breath levels, 5.5 hr exposure.

PCE in chamber, ppm	PCE in blood 2 hr into exposure, ppm			PCE in breath, ppm At 2 hr in exposure			PCE in breath, ppm At 30 min post exposure		
	PCE alone	PCE + alcohol[a]	PCE + diazepam[b]	PCE alone	PCE + alcohol[a]	PCE + diazepam[b]	PCE alone	PCE + alcohol[a]	PCE + diazepam[b]
25	1.65	2.92[c]	1.76	11.03	12.35[d]	11.72	6.40	7.49[c]	6.96[d]
100	8.25	7.96	8.47	33.2	32.3	35.5	17.62	13.83[c]	17.35

[a]Alcohol blood levels of 30 to 100 mg-%.
[b]Diazepam blood levels of 7 to 30 mcg-%.
[c]Significantly different from PCE alone at $p < 0.01$.
[d]Significantly different from PCE alone at $p < 0.05$.

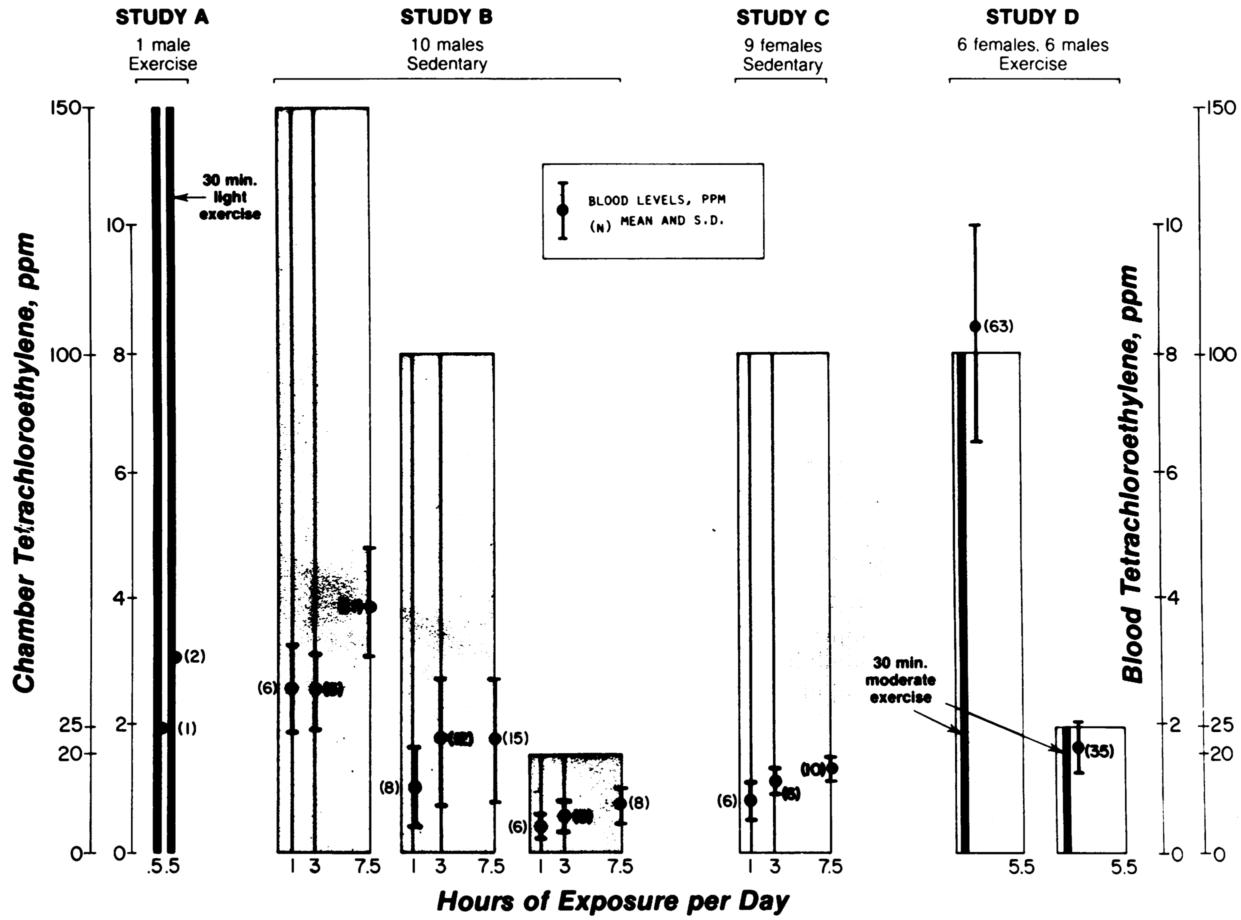

FIGURE 6. Tetrachloroethylene blood levels at the conclusion of each exposure for studies A, B, and C, and 30 min after moderate exercise for study D. Numbers in parentheses represent number of values available to calculate mean and one standard deviation as presented.

mediately following the blood and breath sampling at 2 hr. A significant decrement in performance scores due to tetrachloroethylene alone was found only in the Flanagan coordination test (Fig. 7), and again only on a limited number of days. Alcohol had a significant detrimental effect upon performance in several behavioral tests. This effect is especially noticeable on the coordination scores during the two weeks of alcohol intake. Diazepam effects were seen only on the rotary pursuit test, and on EEG responses. Analysis of variance and multiple regression equations demonstrated no interactive effect between tetrachloroethylene and either alcohol or diazepam. EEG epoch analysis by computer revealed no tetrachloroethylene effect at 100 ppm during this study. This result lends some doubt to the significance of the EEG changes noted subjectively in the previous study. As found in previous studies, one subject seemed to be peculiarly susceptible to the subjective effects of tetrachloroethylene.

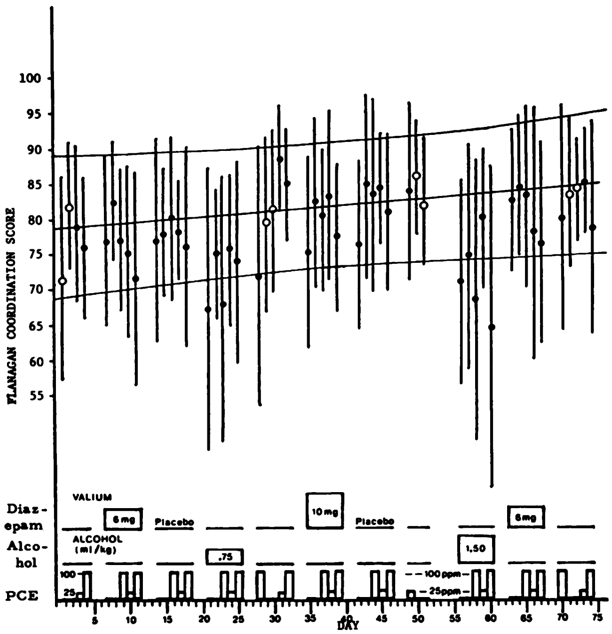

FIGURE 7. Daily mean scores (± 1 SD) from Flanagan coordination test, study D, with daily exposure conditions shown at bottom of graph (PCE = tetrachloroethylene). Open circles represent zero exposure days. The straight line describes the trend of scores for the zero exposure days only, and the outer lines describe 95% confidence limits of expected mean scores under zero exposure conditions.

Summary

In summary, from our studies and from studies reported in the literature, we consider tetrachloroethylene to be a relatively safe solvent regarding its acute overexposure effects. However, the margin of safety regarding unimpaired performance during repeated exposures at the present TLV concentration of 100 ppm is negligible, especially if a worker is physically active or is in a situation where skin absorption is likely. Additionally, a worker may be peculiarly susceptible to tetrachloroethylene, experiencing daily subjective complaints. Figure 8 depicts the breath analysis decay curve that we have developed from sedentary exposures associated with minimal decrements in coordination at 100 ppm. A breath sample obtained 8 to 16 hr, or 500 to 1000 min, postexposure reflects the magnitude of a previous exposure. The upper 95% confidence limit of this curve could be considered as a biological threshold limit value for tetrachloroethylene. The use of biological sampling to ascertain the body burden of this chemical in individuals in the workplace is highly recommended.

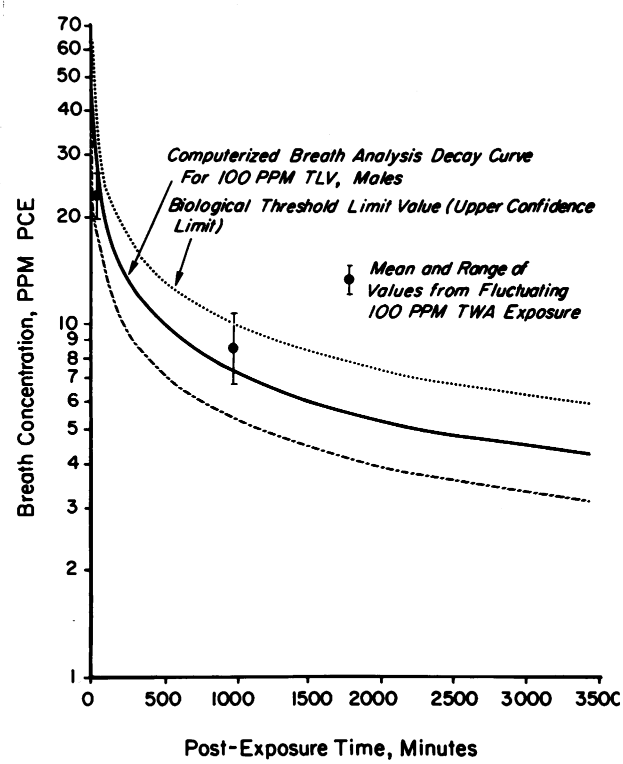

FIGURE 8. Tetrachloroethylene (PCE) breath analysis decay curve (BADC) constructed from values obtained from male subjects repeatedly exposed to tetrachloroethylene vapors for 7.5 hr/day, 5 days/week, 100 ppm. Superimposed are mean and range values from experimental exposure to a fluctuating but time-weighted average concentration of 100 ppm tetrachloroethylene vapor.

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