DRAFT CRITERIA DOCUMENT FOR TRICHLOROETHYLENE

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PREFACE

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The objective of this document is to assess the health effect information of the contaminant trichloroethylene in drinking water and to recommend a maximum contaminant level. To achieve this objective, data on pharmacokinetics, assessment of human exposure, acute and chronic health effects in animals, human health effects including epidemiology and mechanisms of toxicity were evaluated. Only the reports which were considered pertinent for the derivation of the maximum contaminant level are cited in the document. Particular attention was paid toward the utilization of primary references for the assessment of health effect. Secondary references were used rarely. For comparison, standards and criteria developed by other organizations are included in Section IX, Quantification of Toxicological Effects, and are discussed.

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I. SUMMARY

Trichloroethylene, $Cl_2C = CHCl$, is a colorless solvent. It has been used as a degreasing solvent in metal industries and in drycleaning shops and as an inhalation anaesthetic during certain short-term surgical procedures.

The widespread use of trichloroethylene has resulted in its detection in air, in food and in human tissues. It has also been detected in the surface as well as ground water supplies of several states across the Continent of the United States.

On ingestion, either from food or in drinking water, trichloroethylene is expected to be readily absorbed from the gastrointestinal tract and enter the blood stream. After entering the blood stream, it distributes into various tissues and organs. The extent of distribution depends largely on the fat content of the tissues. Trichloroethylene may be transported across placental barriers in pregnant women.

Trichloroethylene is metabolized to monochloroacetic acid, trichloroacetaldehyde (chloral), trichloroethanol, trichloroacetic acid and trichloroethanol glucuoronide. There is strong evidence that trichloroethylene is metabolized to the above-mentioned metabolites via an epoxide intermediate--2,2,3-trichlorooxirane. This intermediate is thought to be responsible for the mutagenic and carcinogenic

potential of trichloroethylene. However, interaction of the epoxide with the nuclear material--a step towards carcinogenesis--has not been studied. It is noteworthy that TCE-epoxide does bind with tissue macromolecules. This is characteristic of other carcinogens.

Among the acute and chronic adverse effects in animals, hepatotoxicity appears to be of importance. Nephrotoxic effects have also been reported in rats and mice. At very high dosages, it depresses myocardial contractility. The teratogenic and reproductive effects of trichloroethylene need to be substantiated. There are two reports on the teratogenic effects of trichloreothylene. These reports indicated no tetratogenic abnormalities in mice or rats.

Trichloroethylene is mutagenic in bacterial test system, utilizing liver microsomal fractions for activation. Trichloroethylene was found carcinogenic in $B_6C_3F_1$ strain mice; however, it was not carcinogenic in Osborne-Mendel rats. The validity of the study was questioned because carcinogenic impurities were detected in the test compound. In a repeat experiment with pure TCE, it was again found to be carcinogenic in $B_6C_3F_1$ mice.

Central nervous system, cardiotoxic, hepato- and nephrotoxic effects have been reported in humans exposed to trichloroethylene in workplace, inhalation-abuse and by accidental ingestion. The reports are clouded by the fact

that the subjects were exposed either to the contaminated trichloroethylene and/or to its decomposition products. However, some of the effects have been observed in animals under experimentally controlled conditions with reasonably pure trichloroethylene. Furthermore, dose-response relationships have been observed.

Based on the mechanism of toxicity--specifically mutagenesis and carcinogenesis--trichloroethylene, has the potential of being carcinogenic. TCE has been reported to bind with mouse liver DNA in an in vivo experiment. Covalent binding of calf thymus DNA with TCE in an in vitro experiment, further provides support to the carcinogenic potential of TCE.

The National Academy of Sciences (NAS) and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water by mathematical extrapolation from high-dose animal studies (Table I-1). Using the risk estimates generated by the NAS (1977-1979) where the multi-stage model was utilized, that range of trichloroethylene concentrations was computed which would nominally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) and per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption at the stated exposure level. From the NAS model it is estimated that, at the 95% confidence limit, consuming two liters of water having trichloroethylene

concentrations of 450 ug/l, 45/l or 4.5 ug/l per day over a lifetime, would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, respectively. Using the revised CAG approach and thus the "improved" multi-stage model, it can be estimated at the 95% confidence limit that consuming two liters of water having trichloroethylene concentrations of 280 ug/l, 28 ug/l or 2.8 ug/l per day over a lifetime, would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, respectively. The numerical differences observed after utilizing the NAS and the CAG risk estimates are partly due to the fact that the dose extrapolation model used by the two groups is similar but not identical. The NAS has used the multi-stage model whereas the CAG has used the "improved" version of the multi-stage model recently discussed by Crump (U.S. EPA, 1980). In addition, the selection of the data and other parameters in each model will also result in some differences.

Table I-1

Drinking Water Concentrations and Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)*		
	CAG (95% confidence limit)	NAS (95% confidence limit)	NAS (point estimate)
10^{-4}	280	450	1400-450
10^{-5}	28	45	140-45
10^{-6}	2.8	4.5	14-4.5

*Assume 2 liters of water are consumed per day.

II. INTRODUCTION

Trichloroethylene (1,1,2-trichloroethylene; TCE), C_2HCl_3, is a clear colorless liquid, used mainly as a degreasing solvent in metal industries. TCE is also used as a household and industrial drycleaning solvent, an extractive solvent in foods, and an inhalation anesthetic during certain short-term surgical procedures (Huff, 1971).

TCE has a molecular weight of 131.4; is non-flammable; has chloroform-like order; d^{20} 1.4649 bp_{760} 86.7°; vapor density, 4.53 (air = 1.00) (Windholz, 1976); 1 ppm in air at 25° C is equivalent to 5.45 mg/m^3; odor threshold 0.5 mg/kg water (Van Gemert and Nettenbreijer, 1977).

The solvent used in industry before the mid-1960's contained impurities, such as 1,1,2,2-tetrachloroethane, and some of the stabilizers, such as epichlorhydrin. A more pure product was obtained in the early 1960's, because a change was made in the manufacturing process (MRI, 1979).

The US produced approximately 234,000 metric tons a year (40 FR 48907 - October 1975). TCE volatilization during production and use is the major source of environmental levels of this compound. TCE has been detected in air, in water, and in marine organisms.

Its detection in rivers, municipal water supplies, the sea, and aquatic organisms indicates that TCE is widely distributed in the aquatic environment. The authors concluded that it is not persistent in the environment and that there is no significant bioaccumulation in marine food chains (Pearson and McConnell, 1975).

Recently, TCE has been detected in the groundwater of several states across the continent of the United States. Region III, U.S. EPA, reported high concentrations of TCE in Pennsylvania and Delaware at several locations. The concentration of TCE in these waters ranged from 18 ppb to 22,000 ppb. How TCE entered groundwater in these areas has not been determined.

III. PHARAMACOKINETICS

Absorption

Several reports indicate that TCE is absorbed into the bloodstream by all the three routes of entry--inhalation, oral and dermal. However, information on the quantitative aspects of TCE absorption is limited.

Soucek and Vlachova (1960) exposed three men and two women of an average age of 21 years to trichloroethylene vapors for 5 hours in an exposure chamber. The concentrations of TCE used in these experiments were: 500, 850, 820, and 830 ug/l. The concentration of the trichloroethylene retained by the test subjects was calculated by subtracting the levels of TCE in the expired air from the concentrations in the exposure chamber. The method of analysis of TCE was not described. The authors calculated that the body retains an average 65% of inhaled TCE. Soucek et al. (1952) recorded a range between 51% and 64%, with an average of 58%.

Data on ingestion of TCE are limited. Several reports concern the accidental ingestion of TCE that resulted in poisoning (Kleinfeld & Tabershaw, 1954; Gibitz and Ploechal, 1973). These reports provide evidence that TCE is absorbed via the gastrointestinal tract. Quantitative absorption data are not available.

Stewart and Dodd (1964) demonstrated that the alveolar breath concentration from skin exposure to TCE was only 0.5 ppm after subjects had immersed their thumb in a beaker containing the compound for 30 minutes. Using alveolar breath levels to measure absorption and assuming no body retention, the authors stated that unless TCE was trapped against the skin, it was not absorbed in any significant quantities. Frant and Westendorp (1950) showed that when a volunteer's hands had been dipped into the solvent for 10 minutes, absorption through the skin was of minor importance and that 3 days later the trichloroacetic acid content in the urine was found to be only 1.5 mg/l. To insure that the only mode of entry of TCE was through the skin the subject wore a protective gas mask during the experiment. Schwander (1936) demonstrated that TCE penetrated the skin of rabbits and was detected in the expired air.

Distribution

After absorption, TCE enters the blood and is distributed to the various tissues and organs. Most of the data on tissue levels have been obtained through inhalation studies. There are no data available on disposition of ingested TCE, although there is substantial evidence that TCE after ingestion enters the bloodstream.

Kulkarni (1944) determined TCE blood and tissue levels of dogs, rabbits, guinea pigs and cats after exposure to TCE vapors. The lethal TCE blood concentration in dogs was found to be 100-110 mg per 100 ml blood; for chloroform anesthesia, it was 60-65 mg/100 ml blood. At the anesthetic stage, TCE blood levels were 24-37, 23-28, 14-18 and 25-32 mg/100 ml blood for dogs, rabbits, guinea pigs and cats, respectively. The blood-brain ratio at anesthetic dosages was approximately 1:2 for both guinea pigs and dogs. Guinea pigs and rats were used by Fabre and Truhaut (1952) to determine how TCE vapors distributed to the tissues. Guinea pigs were exposed to 600-900 mg/m^3 for 5-23 days (4.5-5.25 hrs/day). Biological effects, per se, were not evaluated in this study. Rather, tissue distribution was assessed. However, a trend for distribution of TCE in this study can be observed. TCE was present in most of the examined tissues; the greatest concentrations were in fat, followed by adrenals, ovaries, kidneys, lungs, brain and liver. A metabolite, trichloroacetic acid, was found in the greatest concentrations in the adrenals, ovaries, spleen, kidneys, lungs, adipose tissue and the brain. After acute exposure to TCE, the greatest amount of trichloroacetic acid was present in the spleen. After repeated exposure, the largest amount of acid was present in the lungs.

To study the effect of embalming on TCE tissue concentration, Stewart et al. (1964) administered 1 and 2 ml TCE orally to dogs, weighing 8 and 10.2 kg, respectively. The animals were sacrificed 16 hours after exposure and the tissue levels were determined four, ten and 21 days later, utilizing gas chromatographic technique. Omental fat contained highest level of TCE.

TCE tissue distribution in humans has been studied by several investigators (Powell, 1945; Astrand and Ovrum, 1976; Versterberg and Astrand, 1976; Clayton and Parkhouse, 1962; Laham, 1970 and Beppu, 1968). These data were collected both from patients under anesthesia and from autopsies of human subjects. As with animals, inhaled TCE vapors are readily absorbed into the bloodstream of humans.

In an inhalation study by Powell (1945), 12 patients (during anesthesia) were exposed to 1.5 to 2.5 vol. % TCE for at least one half-hour. Concentrations in venous blood varied between 6.5 and 12.5 mg (100 ml). The blood concentration was reduced to 1 mg % within 3 hours and to 0.1 mg % within 24 hours. However, lower TCE blood concentration [2.8±1.14 mg/100 ml] was reported in women after TCE anesthesia during vaginal deliveries. These women inhaled

TCE vapors for an average time period of 34.7 minutes (Beppu, 1968). When the inhalation time for TCE anesthesia was reduced to 10-19 minutes, maternal venous blood ranged from 0.67-8 mg TCE per 100 ml blood (Laham, 1970). Clayton and Parkhouse (1962) recorded 2.2-11.3 mg TCE per 100 ml in venous blood of subjects who inhaled 0.5 to 1.0 TCE concentration volume/volume percent for 20-25 minutes.

TCE is readily transported from mother to fetus. Beppu (1968) noted that TCE may be transported across placental barriers in pregnant women. The mean inhalation time of thirty-four subjects was 34.7 minutes; the mean concentration of TCE was 2.80±1.14 mg/100 in the femoral (cubital) arteries of mothers, 2.36±1.17 mg/100 ml in the cubital veins of mothers and 1.83±1.08 mg/100 ml in the umbilical veins and 1.91±0.95 mg/100 ml in the umbilical arteries. The concentration of TCE in fetal blood was lower than that of the mother's blood. Laham (1970) obtained similar results from studies on placental transfer of trichloroethylene. Ten case studies involving women between 20-28 years were reported. Intermittent inhalation technique was used for producing anesthesia. Duration of inhalation was between 10 and 19 minutes. Material venous blood contained 0.67-8 mg trichloroethylene per 100 ml of blood, whereas fetal blood concentrations of trichloroethylene ranged from 1-5.20 mg/100 ml.

TCE has been detected in human tissues. Specimens from eight humans were examined post-mortem by McConnell et al. (1975) and found to contain TCE in the body fat, liver, kidney and brain tissue samples, indicating uptake by these tissues (Table III-1).

Table III-1

Occurrence of Trichloroethylene in Human Tissue

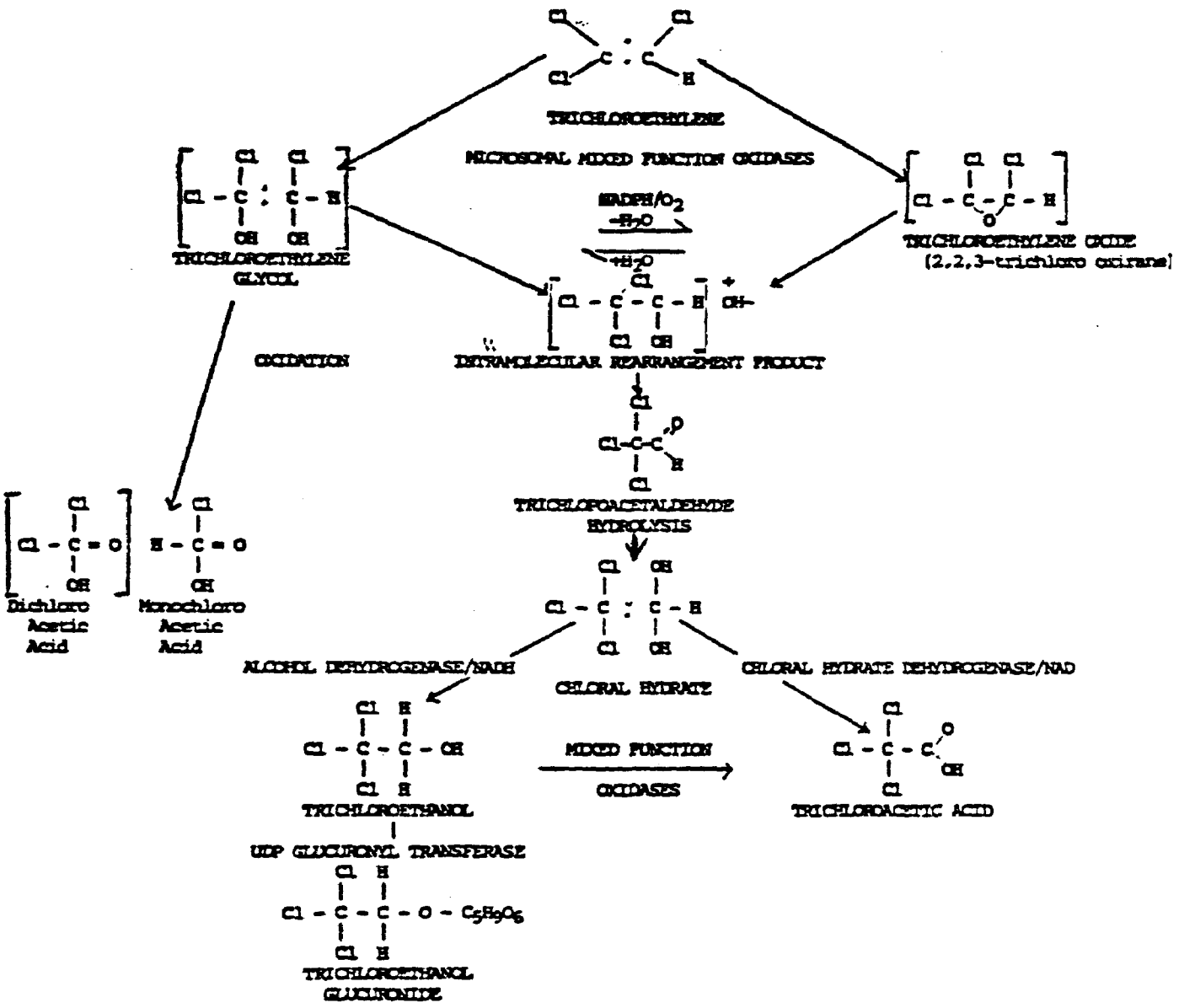
Age of Subject	Sex	Tissue	ug/kg
76	F	Body fat	32
		Kidney	<1
		Liver	5
		Brain	1
76	F	Body fat	2
		Kidney	3
		Liver	2
		Brain	<1
82	F	Body fat	1.4
		Liver	3.2
48	M	Body fat	6.4
		Liver	3.5
65	M	Body fat	3.4
		Liver	3.5
75	M	Body fat	14.1
		Liver	5.8
66	M	Body fat	4.6
74	F	Body fat	4.9

Post-mortem samples taken from subjects of unreported work history or trichloroethylene exposure, who had lived in northwestern England; isolation accomplished by solvent extraction and column chromatography; samples analyzed by gas-liquid chromatography using an electron capture detector with confirmation by mass spectroscopy (Source: McConnell et al. (1975).

Metabolism

Studies indicate that TCE is metabolized to trichloroethylene oxide (2,2,3-trichloro-oxirane), trichloro acetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol, trichloroethanol glucuronide). These metabolites have been obtained both in in vivo and in vitro experiments, utilizing both experimental animals and human systems. In general, the metabolites reported in the animal systems were qualitatively similar to those found in humans.

A proposed pathway for the metabolism of trichloroethylene is given in Figure 1. According to this pathway, the first step in the biotransformation of TCE is the formation of 2,2,3-trichloro oxirane by the epoxidation of the double bond. Uehleke and Poplawski-Tabarelli (1977) compared the absorption spectrum at 451-452 nm of both the incubated rabbit liver microsomes with trichloroethylene and 2,2,3-trichloro oxirane added to reduce suspension of rabbit liver microsomes. Both preparations had identical spectra. Trichloroethylene did not form a ligand absorption spectrum with hepatic microsomes reduced by dithionite or in anaerobic incubates in the presence of NADPH. 2,2,3-trichloro oxirane has not been isolated and characterized in either in vitro or in vivo experiments probably because of the unstable nature of the compound.



PROPOSED INTERMEDIARY METABOLISM OF TRICHLOROETHYLENE

Figure 1

The intramolecular rearrangement of trichloroethylene oxide and hydrolysis may result in the formation of chloral hydrate. Experiments conducted by Daniel (1963) suggest that the rearrangement favors the pathway leading to the formation of chloral hydrate and the subsequent metabolites--trichloroethanol and trichloroacetic acid. The author showed that chlorine attached to TCE is not removed during biotransformation in rats exposed to ^{36}Cl-labelled compound. Approximately 93% of the ^{36}Cl-labelled TCE administered by stomach tube was excreted unchanged through the lungs or in the urine as trichloroethanol and trichloroacetic acid. The specific activities of metabolic trichloroacetic acid and trichloroethanol were shown to be the same as that of the administered trichloroethylene, thus demonstrating an intramolecular rearrangement of chloride.

Chloral hydrate has been suggested as an intermediate in the metabolic pathway of TCE since 1949. Later, Liebman (1965), and Byington and Leibman (1965) demonstrated the transformation of trichloroethylene to chloral hydrate. These workers utilized liver microsomes of rats, rabbits and dogs, in a reaction requiring NADPH and oxygen. Ikeda and Imamura (1973) confirmed this finding, using rat liver microsomes. In vivo identification of chloral hydrate was done by Kimmerle and Eban (1973), using rats exposed to TCE vapors.

Chloral hydrate as a metabolite of TCE in the plasma of human subjects following trichloroethylene anesthesia was demonstrated by Cole, et al., 1975.

The next step in the metabolic process of TCE involves biotransformation of chloral hydrate to trichloroethanol by a reduction reaction and to trichloroacetic acid by oxidation processes. Trichloroacetic acid was identified by Fujiwara test in the urine of dogs exposed to TCE vapors (Barret and Johnston, 1939). The identity of trichloroacetic acid was confirmed by its m.p. and mixed m.p. with an authentic sample of trichloroacetic-acid, (Powell, 1945). Quantitative relationship of formation and the course of elimination in the urine of the metabolites including trichloroacetic acid were determined by Soucek and Vlachova (1959, 1960). Three men and two women with an average age of 21 years were exposed to TCE vapors. Their urine was analyzed for monochloroacetic acid, trichloroacetic acid and trichloroethanol. Sex-related differences in the metabolism of TCE were not noted.

Ogata and Saeki (1974) reported the presence of monochloroacetic acid and chloral hydrate in the blood serum after oral administration of TCE to rabbits. However, because of its short half-life chloral hydrate does not remain in the body for a long length of time.

Elimination

TCE and its metabolites are excreted in urine, by exhalation, and to a lesser degree in sweat, feces, and saliva. Trichloroethanol, trichloroethanol glucuronide, monochloroacetic acid, and trichloroacetic acid appear in the urine immediately after exposure begins. Monochloroacetic acid is excreted from the organism the fastest, followed by trichloroethanol, trichloroethanol glucuronide and trichloroacetic acid. On the other hand, TCE is excreted in the urine in small amounts (Soucek and Vlachova, 1959).

Urinary elimination of TCE metabolites in experimental animals has been investigated by several researchers (Friberg et al., 1953; Forssmann and Holmquist, 1953; Kimmerle and Eben, 1973; and Ogta and Saeki, 1974). Rats exposed to TCE vapors excreted Fujiwara positive reaction products which were calculated as trichloroacetic acid (Friberg et al., 1953; Forssmann and Holmquist, 1953). Kimmerle and Eben (1973) detected trichloroacetic acid and trichloroethanol glucuronide in the urine of rats given trichloroethylene by inhalation. Trichloroacetic acid was determined colorimetrically whereas trichloroethanol glucuronide was analyzed by gas chromatographically after enzymatic hydrolysis of the urine samples. After oral administration of trichloroethylene to rabbits, the following metabolites, in order of decreasing concentration were detected

After oral administration of trichloroethylene to rabbits, the following metabolites, in order of decreasing concentration were detected in the urine: chloral hydrate <tri- and monochloroethanol and monochloroacetate <trichloroacetate (Ogata and Saeki, 1974).

Human volunteers and/or patients were used to study the elimination of TCE after inhalation exposures. Dependent on the concentration and the exposure time, significant quantities of TCE were eliminated by the lungs, following the general rule that low molecular weight compounds are preferentially excreted from the lungs. The amount of TCE excreted through the lungs ranged from 40 to 70 percent. (Bartonicek, 1962, Ogata, et al., 1971, Soucek and Vlachova, 1960).

Soucek and Vlachova (1960) examined the excretion time and percent excretion of monochloroacetic acid, trichloroacetic acid, and trichlorethanol in humans (three men and women) exposed to dosages ranging from 440-850 mg/m^3 TCE for 5 hours. The excretion of the metabolites was measured over the next 7-14 days. The quantities of the metabolites excreted were not related to individual dosages. Monochloroacetic acid was shown to be excreted in the first few minutes after exposure. Excretion of monochloroacetic acid was maximal at the end of the exposure and continued for 48 to 168 hours, 4.8 days (average 112 hours). Monochloracetic acid comprised about 4% of the

retained TCE. Trichloroacetic acid appeared in the urine immediately after inhalation, and its concentration slowly rose due to its ability to accumulate in the body. Maximal excretion occured within 24-48 hours and lasted for 520 hours. The fall in the rate of excretion was considered to be the sum of two exponential rates (phases). The first phase lasted about 5 days, and the second phase lasted approximately 14 days. Trichloroacetic acid comprised 10% to 30% (19% average) of the retained vapor. Trichloroethanol was also excreted within the first few minutes of exposure. Excretion of trichloroethanol reached its maximum a few hours after exposure and rose very rapidly. The excretion time was 312-390 hours (average 350 hours). A decrease in the excretion rate appeared as the sum of two exponential rates. The first phase lasted 3-4 days, while the second phase lasted 7-9 days. The total quantity of trichloroethanol excreted was between 32% and 59% of the TCE retained; the average was 50%. The total quantity of these three metabolites excreted in the urine of humans amounted to from 43% to 100% of the absorbed TCE. The ratio of these three metabolites was found to be monochloroacetic acid: trichloroacetic acid: trichloroethanol = 1:5:12.

Bartonicek (1962) and Ogata et al. (1971) confirmed Soucek and Vlachova's findings. Eight volunteers (both males and females) were exposed to 1,042 mg/m^3 TCE for 5 hours by

Bartonicek (1962). Of the retained TCE, 38.0% to 49.7% and 27.4% to 35.7% was excreted in urine as trichloroethanol and trichloroacetic acid, respectively. The amount of trichloroethylene eliminated via the lungs was not determined. Bartonicek, in the same experiment, found that trichloroethanol and trichloroacetic acid were excreted in the feces, for a total of 8.4%. The time and the time intervals at which expired air was analyzed for TCE were not provided. Therefore, the amount amount of TCE absorbed cannot be determined accurately; there is a possibility of reaching a steady state between the blood concentration and the inhaled TCE concentration.

Ogata, et al. (1971) conducted two separate experiments on 13 male subjects exposed to approximately 474 mg/m^3 and 927 mg/m^3 TCE. One group of five people (A) remained in the exposure chamber for 3 hours in the morning and 4 hours in the afternoon at an exposure of 927 mg/m^3. A second group of four people (B) were exposed to 474 mg/m^3, but they remained in the chamber for only 3 hours (in the morning). Urine was collected for 100 hours after the initial exposure. In Groups A and B, the concentration of trichloroethanol was maximum 1-3 hours after exposure, and trichloroacetic acid concentrations were maximum 42-69 hours after exposure. The excretion rate of trichloroacetic acid and trichloroethanol returned to normal after 92 hours. The

total amounts of trichloroethanol and trichloracetic acid recovered in the urine were 44% and 18.1%, respectively, for the 7-hour exposure. Fifty-three percent of the trichloroethanol and 21.9% of the trichloroacetic acid was the final amount recovered in the 3-hour exposure to 927 mg/m^3.

The levels of TCE metabolites in the urine of humans have been recorded by many researchers. Ikeda and Ohtsuji (1972) conducted two separate experiments on male workers exposed to TCE vapors (1090 mg/m^3) for 8 hours, and recorded the excretion of the metabolites in the urine. In the first experiment six workers were exposed intermittently to 54.5 to 272.5 mg/m^3 of the solvent. Total trichloro-compounds varied from 38 to 376 mg/liter, trichloroethanol varied from 11 to 281 mg/liter, and trichloroacetic acid varied from 18-95 mg/liter in the urine. In the second experiment, 14 workers were exposed intermittently to a range of 650 to 1363 mg/m^3 TCE. The urinary metabolites ranged from 55-487 for total trichloro-compounds, 33-347 for trichloroethanol, and 22-177 for trichloroacetic acid. The overall time during which these urinary metabolites were measured was not given.

Surveys were conducted by Ikeda et al. (1972) on 85 male industrial workers (36 control) under working environments. The urinary excretion of metabolites was recorded as total trichloro-compounds. The results are summarized in Table III-2

and show that metabolite concentration increased as exposure concentration increased.

Sukhanova and Burdygina (1971) measured the metabolite level in the urine of students during their 4 months' apprenticeship in a plant which used TCE. The content of metabolites in the urine increased significantly. After 4 months, the metabolites found in the urine of students ranged from 2.3 to 65.6 mg/liter.

Five male volunteers were subjected to 1090 mg/m^3 TCE 7 hours/day for 5 days (Stewart, 1968). Twenty-four hour urine samples were collected and analyzed for trichloroacetic acid and trichloroethanol before, after, and during exposure. The results are summarized in Table III-3.

A study conducted by Friberg, et al. (1953) showed similar results. Three people were exposed to TCE concentrations ranging from 100-150 ppm for 7 hours daily for 1 week. During the later days of the study, 250-500 mg of trichloroacetic acid per liter of urine was excreted. Frant and Westendorf (1950) calculated that if people were exposed to 100 ppm of TCE for several days, they would excrete about 200 mg/liter of trichloroacetic acid in the urine. Grandjean, et al. (1955) reported that workers, most of them exposed to 20-40 ppm TCE, excreted about 8% of inhaled TCE as trichloroacetic acid in a ratio of 3:1 (3 mg/liter trichloroacetic acid in the urine to 1 ppm TCE in the

Table III-2

Average Metabolite Concentrations in Urine of Workers
Exposed to Various Concentrations of Trichloroethylene (mg/l)

Number of People Exposed	Concentration (ppm) [a]	Time Exposed	Metabolite Concentrations		
			Total Trichloro-Compounds	Trichloro-ethanol	Trichloro-acetic Acid
36	0	8 hr/day, 6 days/wk	1	0	1
9	3	8 hr/day, 6 days/wk	39.4	25.1	12.7
5	5	8 hr/day, 6 days/wk	45.6	24.9	20.2
6	10	8 hr/day, 6 days/wk	60.5	42.0	17.6
4	25	8 hr/day, 6 days/wk	164.3	77.3	77.2
4	40	8 hr/day, 6 days/wk	324.9	220.3	90.6
5	45	8 hr/day, 6 days/wk	399.0	256.7	138.4
5	50	8 hr/day, 6 days/wk	418.9	267.3	146.6
5	60	8 hr/day, 6 days/wk	468.0	307.9	155.4
4	120	8 hr/day, 6 days/wk	915.3	681.8	230.1
4	175	8 hr/day, 6 days/wk	1,210.9	973.1	235.8

[a] The parts per million of solvent in the air was measured using Kitagawa (1961) detection tubes. At least five determinations were made and the averages were recorded.

Source: Ikeda *et al.* (1972).

Table III-3

Urinary Excretion of Trichloroacetic Acid and Trichloroethanol in Five Subjects During and Following Trichloroethylene Exposure [a]

Time	Metabolite Concentration (mg/l)	
	Trichloracetic Acid	Trichloroethanol
1st Exposure day	51 (34 - 84)	308 (179-480)
2nd Exposure day	175 (113-238)	359 (294-480)
3rd Exposure day	229 (148-416)	399 (296-546)
4th Exposure day	306 (249-439)	538 (294-822)
5th Day following last exposure	50 (35 - 61)	15 (10 - 18)
12th Day following last exposure	8 (2 - 22)	14 (1 - 37)

[a] Subjects were exposed to 200 ppm trichloroethylene, 7 hr/day for 5 days.

Source: Stewart (1968).

urine to 1 ppm TCE in the air). This ratio was larger in younger people (6:1) than in older people (2:1).

Results from two experiments described below indicate there may be a variation in the urinary excretion of TCE metabolites depending on the sex of the subject. More specifically, there may be a sex difference in human metabolism of TCE. However, there is not enough evidence to substantiate this theory.

Nomiyama (1971) exposed five male and five female students to between 250 and 380 ppm TCE for 160 minutes. Males and females excrete trichloroacetic acid and trichloroethanol in different amounts during the first 24 hours after exposure. Females excreted more trichloroacetic acid in their urine than did males, while males excreted twice as much trichloroethanol as females. Of the retained TCE in males, 32.6% was excreted as trichloroacetic acid and 48.6% as trichloroethanol, whereas in females, 49.3% of retained TCE was excreted as trichloroacetic acid and 42.7% as trichloroethanol.

Similar results were obtained by Kimmerle and Eben (1973b). After exposing eight volunteers (four male and four female) to either 44±4 ppm or 50±7 ppm of TCE for 4 hours,

a difference in the amount of excretion products was noted. Females showed a higher excretion of trichloroacetic acid than males. No other differences between sexes in urinary excretion levels or concentrations of TCE and trichloroethanol in the blood were observed.

Four male volunteers inhaled 70 and 140 ppm TCE for 4 hours during exercise and at rest. Monster et al. (1976) reported that exercise increased the quantity inhaled but not the distribution of metabolism. Analysis accounted for 67% of the dose: 10% unchanged from lungs and 39% trichloroethanol plus 18% trichloroacetic acid in the urine.

Storage-Biological Half-life

Many articles have been published on the biological half-life ($T_{1/2}$) of TCE and its metabolites in humans. Ikeda and Imamura (1973) collected and summarized these previous citations of biological half-lives; an expanded version of these citations is presented in Table III-4. Additional studies on the half-lives in the urine, not cited by Ikeda and Imamura, have been collected and added.

Ikeda and Imamura noted a wide variance in biological half-lives (26-51 hours) of total trichloro-compounds in urine of factory workers exposed to TCE (Table III-4). There appears to be no correlation between the number of exposures

and variance in biological half-lives. However, Ikeda and Imamura observed that the total mean value calculated was about 41 hours. This value closely correlates to the experimental values of half-lives in subjects not previously exposed to TCE vapors.

Two other observations based on data from Table III-4 were made by Ikeda and Imamura. First, no sex related differences were observed in the half-life of total trichlorocompounds; second, the half-life in an "addicted" patient was higher than in the factory workers.

Few data have been published on the biological half-lives of TCE in the blood. Table III-5 summarizes the biological half-lives of metabolites of TCE in the blood of human subjects exposed occupationally to vapors of trichloroethylene.

The biological half-life in the serum and urine of rabbits was reported by Ogata and Saeki (1974) (Table III-6). Results show that, except for TCE and chloral hydrate, the half-lives of metabolites in urine are longer than in serum.

Four subjects were repeatedly exposed to TCE, 4 hours/day for 5 days, at 50 ppm (48±3 ppm) (Kimmerle and Eben, 1973). It was noted that trichloroethanol could be detected in the human blood up to 4 days following a single exposure to 50 ppm.

Table III-4

Biological Half-Life of Metabolites in the Urine of Human Subjects Exposed to Vapors of Trichloroethylene

Group Affected	Number of People	Sex	Exposure Load and Time	Biological Half-Life (hr.) Total Trichloro-Compounds	Trichloroethanol	Trichloroacetic Acid	References
Factory workers	6	M	10 to 150 ppm for 4 hr, 1 or 2 times/mo	42.7 ± 4.5[a]/ (37.3 ± 6.2)	— —	— —	Ikeda and Imamura (1973)
	6	M	5 to 170 ppm for 2 hr, 1 or 2 times/mo	48.8 ± 11.7 (47.5 ± 7.7)	—	—	Ikeda and Imamura (1973)
	6	M	Intermittently exposed to 200 ppm 5 days/week	26.1 ± 4.8 (22.7 ± 4.6)	15.1 ± 2.2 (14.2 ± 2.3)	39.7 ± 8.7 (36.5 ± 17.3)	Ikeda and Imamura (1973)
	6	M	20 to 40 ppm for 8 hr/day for 5 days/wk	33.7 ± 6.8 (26.9 ± 5.0)	—	—	Ikeda and Imamura (1973)
	6	F	Intermittently exposed to 50 ppm 5 days/ week	50.7 ± 7.7 (38.3 ± 7.5)	42.7 ± 9.1 (12.6 ± 8.9)	57.6 ± 19.8 (50.9 ± 22.6)	Ikeda and Imamura (1973)
Volunteers	2	F	186 ppm for 5 hr	50.3	29.2	55.3	Bartonicek (1962)[b]/
	5	M	250 to 380 ppm for 160 min	31.4	19.0	38.0	Nomiyama and Nomiyama (1971)
	5	F	250 to 380 ppm	36.1	25.8	36.1	Nomiyama and Nomiyama (1971)

Table III-4 (Continued)

Group Affected	Number of People	Sex	Exposure Load and Time	Biological Half-Life (hr.) Total Trichloro-Compounds	Trichloroethanol	Trichloroacetic Acid	References
Volunteers	5	M	170 ppm for 7 hr	35.8	—	—	Ogata et al. (1971)[b]
	4	M	170 ppm for 3 hr	48.6	—	—	Ogata et al. (1971)[b]
	5	M,F	50 ppm for 6 hr	—	12.0	100.0	Muller et al. (1972)[b]
Addict	1	M	—	72.6 (95.1)	49.7 (49.8)	72.6 (95.0)	Ikeda et al. (1971)[b]

a/ Values are mean ± SE calculated from metabolite concentration corrected for a specific gravity of urine of 1.016 together with those corrected for creatinine concentration in parenthesis.

b/ Values are calculated by the present authors from results of referred authors.

Table III-5

Biological Half-Life of Metabolites in the Blood of Human Subjects Exposed Occupationally or Experimentally to Vapors of Trichlorethylene

Compound	Groups	Type of Exposure	Biological Half-Life (hr.) TTC[a]	TCE[b]	TCA[c]	Reference
Trichloroethylene	Volunteers (5 subjects)	Experimental	—	12[d]	—	Ertle et al. (1972)
	Volunteers (5 subjects)	Experimental	—	13.3[e] 12.4[f]	85.6[e] 99.0[f]	Muller et al. (1974)

a/ Total trichloro-compounds.

b/ Trichloroethylene.

c/ Trichloroacetic acid.

d/ 6 hr/day for 5 days at either 50, 100, or 250 ppm for 12 min/hr (high peak concentration, average 50 ppm).

e/ 100 ppm trichloroethylene, 6hr/day for 10 days.

f/ 500 ppm TCE, 6 hr/day for 5 days.

Biological Half-Life of TCE
and Metabolites in Rabbits[a]/

Compound	Half-life (hr.) Urine	Serum
Trichloroethylene	—	3.8
Chloral hydrate	—	6.4
Free trichloroethanol	30.5	8.4
Total trichloroethanol	38.0	8.5
Conjugate trichloroethanol	42.0	8.5
Monochloroacetic acid	36.0	14.0
Trichloroacetic acid	43.5	18.5

a/ Rabbits were given 13 moles/kg TCE orally.

Source: Ogata and Saeki (1974).

Summary and Conclusion

Information on the quantitative absorption of TCE via ingestion is not available. However, TCE is expected to be completely absorbed after ingestion, because of the physico-chemical nature of the chemical. The extent of absorption by the inhalation route has been reported to be between 51 and 64 percent. This appears misleading because it is reasonable to believe that at a given concentration of TCE in air, equilibrium between the concentration in air and concentration in blood is established. After the equilibrium is established, the absorption is dependent upon the disposition and metabolism of the chemical. TCE has been reported to distribute in tissues according to their fat contents. It crosses the placental barrier and has been detected in fetal blood.

TCE is biotransformed in the mamillian system probably via the formation of an epoxide. The metabolites identified include trichloroacetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol and trichloroethanol glucuronide. In general, the metabolites reported in the animal systems are qualitatively similar to those found in humans.

TCE and its metabolites are eliminated in urine, by exhalation and to a lesser degree in sweat, feces, and saliva. Urinary excretion of the metabolites--trichloroethanol and trichloroacetic acid appears to be dose dependant--higher the dose, larger the amount of these metabolites excreted in the urine. The metabolite, trichloroacetic acid has been reported to bind with plasma protein. On repeated exposure, this metabolite may stay in the body for a long time.

V. ACUTE AND CHRONIC HEALTH EFFECTS IN ANIMALS

A. Hepatotoxicity

Several inhalation studies, after single or multiple exposures, have provided observations on hepato-toxic effects. Kylin et al. (1962) compared the hepatotoxicity of chloroform, trichloroethylene and tetrachloroethylene. Mice were given a single 4-hour exposure by inhalation. The animals were sacrificed on the third day; the livers were analyzed for fat by histological examination and by acetone-hexane extraction. In addition, activity of serum ornithine carbamyl transferase was determined. Trichloroethylene, at a concentration level of 6,400 ppm produced no significant damage to the liver. In this study, trichloroethylene was the least hepatotoxic, whereas chloroform was the most. Similar results were obtained by Plaa et al. (1958) and Gehring (1968) when animals were exposed to halogenated hydrocarbon solvents by subcutaneous injection and by inhalation. The results of these workers indicate that the halogenated hydrocarbon solvents rank in the order of their decreasing capacity to cause liver dysfunction: carbon tetrachloride, chloroform, 1,1,2-trichloroethane, tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane.

Multiple inhalation exposure studies have been reported utilizing mice, rats and dogs. Seifter (1944) observed degeneration of liver parenchyma cells in dogs that were exposed either

to 750 ppm TCE 8 hours/day, 6 days/week for 3 weeks or 500 to 750 ppm TCE 6 hours/day, 5 days/week for 8 weeks. Slight fatty infiltration of the liver of mice was detected by Kylin et al. (1965). The female albino mice were exposed to 1,600 ppm TCE by inhalation for 4 hours daily, six days a week, over periods of one, two, four and eight weeks. The increase in liver fat content was detectable after one week's exposure and subsequently the liver fat showed no further increase. In terms of fatty degeneration, the authors noticed that tetrachlorethylene was approximately 1/10 times less toxic than trichloroethylene. Male Wistar II rats inhaling 55 ppm TCE for 14 weeks, exhibited elevated liver weights but did not cause pathological changes measured by hematological examinations, liver function tests, renal function tests and blood glucose (Kimmerle and Eben, 1973). Four animal species--rabbits, guinea pigs, rats and monkeys--were exposed to 100-3,000 ppm TCE vapors seven hours daily, 5 days a week, for periods up to approximately six months by Adams et al. (1951). Rats exposed to 300-3,000 ppm TCE for a period of 36 days (total of 27 exposures) showed an increase in liver and kidney weights. However, histopathological examination of the tissues failed to reveal any abnormality in male rats, but some female rats showed fat vacuoles in the cytoplasm of the liver. Rats exposed to 200 ppm TCE for 205 days (total exposures 151) showed no significant abnormality from the controls. The authors concluded that the maximum concentrations

without adverse effects were as follows: monkey, 400 ppm; rat and rabbit, 200 ppm; guinea pig, 100 ppm.

B. Nephrotoxicity

There are conflicting reports in the literature regarding renal damage resulting from parenteral and inhalation exposure of animals to TCE. Kidney damage was observed in rats (maintained on a high protein diet) exposed to 5 mg/liter (935 ppm) TCE, 5 hours/day for 7 days (Kalashnikova et al., 1974). Investigators observed focal dystrophic changes in the renal tubule epithelium. A long-term inhalation study on rats, guinea pigs, dogs, rabbits, and monkeys by Pendergast et al. (1967) showed that no nephrotoxicity occurred at continuous concentrations of 35 ppm (189 mg/m^3) for 90 days and 730 ppm (3825 mg/m^3) for 8 hours/day, 5 days/week for 6 weeks.

Plaa and Larson (1965) found that after injecting mice intraperitoneally with 0.6 ml/kg of TCE, no renal toxicity was observed. The acute nephrotoxic properties were studied using phenol sulphthalein excretion, the presence of proteinuria and glucosuria, and histopathology. However, when Bartonicek and Soucek (1959) injected six rabbits (av. wt. 4.2 kg) intramuscularly with 33-55 g of TCE over a period of 55-100 days, two of the rabbits died from renal failure.

C. Nervous System

Because of its effects on the nervous system, TCE has been used as a general anesthetic agent. Studies performed as early as 1944 give information concerning the blood concentration of TCE for lethal as well as anesthetic effects. Dogs, rabbits, guinea pigs and cats were administered TCE by inhalation. Blood levels were determined at death and at anesthesia stages. Lethal blood TCE concentration in dogs were found to be 100-110 mg/100 ml blood. At the anesthetic stage, TCE blood levels were 24-37, 23-28, 14-18, 25-32 mg/100 ml blood for dogs, rabbits, guinea pigs and cats, respectively. The blood-brain ratio at anesthetic dosages was approximately 1:2 for both guinea pigs and dogs (Kulkarni, 1944).

Histopathological changes have been observed on acute and long-term exposure of animals to TCE. A single exposure of dogs to 30,000 ppm TCE in air resulted in death within 20 minutes. No obvious changes were found in the nervous system. In a longer term experiment, the animals were subjected to TCE concentration ranging from 500-3,000 ppm for periods varying 2-8 hours daily, often for 5 days weekly. The total exposure period was between 60-162 hours. The exposures appear to selectively destroy the Purkinje layer of the cerebellum. The cerebral hemispheres showed mild changes--scattered cortical neurons became swollen or pyknotic and the white matter of

the myelin developed a mild focal swelling (Baker, 1958). Bartonicek and Brun (1970) injected TCE intramuscularly in female rabbits and observed moderate neurological changes in the exposed animals. The dosage regimen included subacute exposure for 29 days. Animals were injected with 2.47 g/kg body weight three times a week. For the chronic exposure experiment, animals were injected intramuscularly for 41-247 days with 1.62 g/kg twice a week. The rabbits were sacrificed at different times during the test and the brains examined histologically and histochemically for any pathological change. Round cell infiltration around blood vessels and in the parenchyma occured in all animals of the subacute and in one of the chronic experiments but not in the controls. Disappearance of Purkinje cells and basket cells was definitely shown only in the chronic experiment.

Grandjean (1960) exposed male rats to 200 and 800 ppm TCE vapors for 4-11 weeks. The rats were subjected to a single 3-hour TCE exposure just before testing. After the exposure, trained rats responding to signals climbed up a rope to reach a feeding trough where they found a small dextrose pellet as a reward. The results indicate that the increase in the number of spontaneous climbs after exposure to the solvent is significant in comparison with the control

tests. The observed effect was not dose-dependent. The authors conclude: TCE in doses studied modified the psychological equilibrium of rats by increasing excitability. The author in the 1963 report described the effect of TCE vapors on the swimming performance and on the motor activity of rats. The animals were exposed for six hours and swimming tests were performed 5-15 minutes later. At 400 ppm, TCE retarded only the rats swimming with an additional load in a manner barely significant while 800 ppm adversely affected the performance both with the load and without, in a significant manner. One hour after termination of exposure, no significant changes in the swimming times could be observed.

D. Cardiovascular Effects

TCE causes depression in myocardial contractility (Aviado et al., 1976). The minimum inhaled concentration of 500 ppm caused a depression in the myocardial contractility in dogs. Transitory arrythmia was observed in the isolated guinea pig heart at a concentration of 5,300 ppm.

E. Teratogenic Effects

Trichloroethylene does not appear to be tetratogenic in animals. Pregnant rats and mice were exposed to 300 ppm TCE vapor for 7 hours daily on days 6-15 of gestation. This exposure resulted in a slight but statistically significant reduction in mean body weights of maternal rats, but not mice during

and/or following exposure. No teratogenic abnormalities were observed in either of the species.

In another study, Dorfmueller, et al. (1979) exposed, by inhalation, female Long-Evans hooded rats to trichloroethylene at a concentration of 1800 ± 200 ppm (9810 ± 1090 mg/m^3) for two weeks before mating and during the first twenty days of pregnancy. Rats were observed for changes in the body weight every 4 days. Fetuses were weighed and examined for skeletal and soft tissue anomalies. Postnatal behavioral changes were examined by activity measurements with aid of electronic Motility Meters. The most frequent, skeletal anomaly observed was incomplete ossification of sternum, indicative of delayed skeletal ossification rather than a true malformation. No overt maternal toxicity, embryotoxicity or teratogenicity were seen as a result of TCE treatment.

F. Mutagenic Effects

There have been a number of recent studies using various assay techniques to determine the mutagenic potential of TCE. Current results are tabulated (Table V-1) with both positive and negative results depending on the test system and whether or not the system was metabolically activated.

Table V-1

Mutagenicity Testing — Trichloroethylene

Test System	Reaction Tested	Result	Reference
Microbial:			
Salmonella typhimurium	Gene mutation	Mutagenic in activated system	Greim *et al.* (1975)
Salmonella typhimurium	Gene mutation	Mutagenic in activated system	Bartsch *et al.* (1975)
Salmonella typhimurium	Gene mutation	Non-Mutagenic	Waskell (1978)
Escherichia coli K-12	Gene mutation	Mutagenic in activated system	Griem *et al.* (1977)
Sacchromyces cerevisiae	Mitotic gene conversion	Positive	Bronzetti *et al.* (1978)
Sacchromyces cerevisiae SV185-14C	Gene mutation Frameshift mutation	Positive	Shahin and VonBorstel
Animal:			
Fischer Rat embryo	Cellular Transmation	Positive	Price *et al.* (1978)

Bacterial mutagenesis system is most commonly used as a screening technique to determine the mutagenic and carcinogenic potential of chemicals. Trichloroethylene was found mutagenic in salmonella typhimurium strains and the E. coli K 12 strain, utilizing liver microsomes for activation (Greim et al., 1975; 1977). Bartsch et al. (1979) used S-9 fractions from liver specimens for activation instead of microsomes for mutagenesis test. The authors reported trichloroethylene as marginally mutagenic. Waskell (1978) reported trichloroethylene nonmutagenic in Ames test system with activation. The negative response obtained by later researchers cannot be explained at the present time.

Sacchromyces cerevisiae (yeast), and Fischer rat embryo, have also been used to study mutagenic response. After activation with liver microsomal fractions trichloroethylene was mutagenic in strains of yeast in such as sacchromyces cerevisiae strains D_4, D_7 and XV185-14C (Bronzetti et al. 1978, Shahin and von Borstel 1977). Price et al. (1978) tested TCE for in vitro cell transforming potential in a Fischer rat embryo system (F1706). The transformed cells grew in a semisolid agar and produced undifferentiated fibrosarcomas when inoculated into newborn Fischer rats.

G. Carcinogenic Effects

The National Cancer Institute (NCI, 1976) conducted a study to delineate the carcinogenic potential of trichloroethylene. They used both sexes of Osborne-Mendel rats and $B_6C_3F_1$ mice. For rats, the initial doses were 1,300 and 650 mg/kg body weight. The dosages were changed, based upon survival and body weight data, so that "time-weighted" average doses were 549 and 1,097 mg/kg for both male and female animals. The time-weighted average daily doses were 1,169 and 2,339 mg/kg for male mice and 869 and 1739 mg/kg for female mice. Animals were exposed to the compound by oral gavage 5 times per week for 78 weeks. They were observed until the terminal sacrifice at 110 weeks for rats and 90 weeks for mice. A complete necropsy and microscopic evaluation were conducted on all the animals (except 7 out of the original 480, who died at unscheduled times).

No significant difference was noted in neoplasms between experimental and control groups of rats. However, in both male and female mice, the higher dose-induced primary malignant tumors in the liver. For males, 26 of 50 mice who received the low dosage and 31 of the 48 mice who received the high dosage developed hepatocellular carcinomas while only 1 out of 20 of the controls showed neoplasms. In female mice, 4 of the 50 receiving the low dosage and 11 out of 47 receiving

the high dosage developed neoplasms as compared to zero out of 20 of the controls.

The results of this experiment indicate that trichloroethylene induced a hepatocellular carcinoma response in mice. Under the conditions of this experiment, the rats did not elicit the carcinogenic response.

In the NCI study cited above, the test chemical, trichloroethylene was later found to contain epichlorohydrin-a carcinogen. Therefore, NCI repeated the bioassay with epichlorohydrin-free trichloroethylene. Rats (F344/N) and mice ($B_6C_3F_1$) of both sexes were used. Trichloroethylene was mixed with corn oil and administered by gavage five times per week for 103 weeks. Rats received dosages of 500 and 1,000 mg/kg. These dose levels were lower than the initial doses used in the earlier bioassay in Osborne-Mendel rats (650 and 1,300 mg/kg for both sexes). As with the rats, the dosage levels used in the mice were lower than in the earlier study. The dose selected for the study in mice was 1,000 mg/kg for both sexes.

Trichloroethylene was not found to be carcinogenic for female F344/N rats. The experiment with male rats was considered inadequate because these rats received dose levels of trichloroethylene which exceeded the maximum tolerated dose.

Trichloroethylene was carcinogenic for both sexes of $B_6C_3F_1$ mice, producing hepatocellular carcinomas.

In another study by Rudali (1967), oral doses of TCE were administered by gavage to 28 NLC mice (age not specified). Dosages of 0.1 ml of a 40% solution of TCE in oil were administered twice weekly for an unspecified time. No liver lesions or hepatomas were observed. In a similar set of experiments, chloroform was slightly oncogenic.

H. Synergistic and/or Antagonistic Responses

There are a few reports which suggest interaction of TCE and the drugs/chemicals, when given concurrently and/or in sequence. The interactions have been reported at very high dose levels for short durations. Interaction studies for longer durations are not available. Therefore, information cited below should not be used for making any adjustment to the standard.

Cornish and Adefuin (1966) found that the hepatoxic response was markedly potentiated by prior ingestion of ethanol. These workers exposed rats to TCE (10,000 ppm) for 1.5 hours. Pretreatment of rats with phenobarbital (50 mg/kg, 2.p.) or 3 methylcholanthrene (40 mg/kg) increased TCE-induced liver damage as indicated by SGOT and SGPT (Carlson, 1974). The possible mechanism behind these observations have been described in the Section "mechanisms of toxicity."

Summary and Conclusions

1. Trichloroethylene has been reported to adversely affect the livers of the exposed animals. In acute exposures, it is ranked in the following order of decreasing capacity to cause liver dysfunction: Carbon tetrachloride, chloroform, 1,1,2-trichloroethane, trichloroethylene and 1,1,1-trichloroethane.

2. Animal species which have been reported to respond to the toxic effects on liver are mice, rats, rabbits, guinea pigs, dogs, and monkeys; however, which of the species is the most sensitive, has not been precisely determined.

3. Chronic exposure of animals to trichloroethylene induces nephrotoxic response.

4. At very high dose levels, TCE produces anesthesia. At the anesthetic stage, TCE blood levels have been reported as 24-37, 23-28, 14-18, and 25-32 mg/ml blood for dogs, rabbits, guinea pigs and cats respectively.

5. TCE was not found to be teratogenic.

6. TCE is considered a weak mutagen as indicated by microbial test system.

7. In a repeat study with epichlorohydrin free trichloroethylene, NCI found it carcinogenic in both sexes of $B_6C_3F_1$ mice. The

experiment with male rats was considered inadequate for establishing carcinogenicity.

8. Interaction of TCE with ethanol ingestion has been reported. This information cannot be used in deriving a standard for TCE in drinking water, because the duration of exposure was too short. In addition, it is reasonable to believe that the interaction was dose-dependent and at lower concentration, the interaction may not exist.

VI. HUMAN HEALTH EFFECTS

A. Acute Exposure

The following section includes information concerning the acute effects of trichloroethylene either by ingestion or by inhalation exposure. Special attention has been given to the dosages in mg/kg body weight which have been reported to produce an effect.

Single oral dosages ranging from 7.6 to 35 g have been reported to exhibit clinical symptoms in humans. A 4-1/2-year old child who ingested an estimated 7.6 g of trichloroethylene, vomited, became inebriated, and lost consciousness within a few minutes, but recovered after 4 hours (Gibitz and Plochl, 1973). Two persons, who each consumed 15-25 ml (21-35g) of trichloroethylene experienced vomiting and abdominal pain, followed by inebriation and transient unconsciousness (Stephens, 1945).

Morreale (1975) reported one 56-year old patient who drank 15 ml TCE and, along with neural intoxication, suffered a myocardial infarct, which was attributed to the TCE.

Bernstein (1954) stated that a 19-year old marine who underwent TCE anesthesia suffered cardiac arrest (due to an excessive concentration of TCE in the body), but subsequently

recovered. In another report, electrocardiographic abnormalities were seen in 15 of 30 patients exposed acutely to high levels of TCE. Arrhythmia was the most frequent effect (Pelka and Markiewicz, 1977).

Tomasini (1976) reviewed Italian case histories of TCE-related toxicity. In about one-fourth of a group of 35 patients, cardiac arrhythmia of some degree had occurred after TCE exposure. Accidental, intentional, and industrial exposures were included in the population. TCE levels that produced the fatalities ranged from oral introduction of 50cc pure TCE in a 21-year old male to a "pitcher" of Trilene in a 38-year old female. Cardiac histories of the industrial workers were not described, nor were quantities of TCE producing cardiac effects reported. The author suggested that the mechanism of cardiotoxicity was depression of normal rhythm which permitted any other ectopic foci present to break the normal myocardial rhythm. The fact was stated that TCE, as sold, is sometimes a mixture of several chlorinated solvents. The relationship, if any, of specific Italian additives to the cardiac effects described was not further developed.

Dependent upon the dosages, the inhalation of TCE results in a mild to severe central nervous system depression. Salvini et al. (1971) observed psychophysiological changes in

human volunteers in a controlled inhalation study using TCE at as low a level as 110 ppm for two four-hour periods. At 200 ppm TCE, Stopps and McLaughlin (1967) noted a slight decline in performance of subjects, which became increasingly pronounced at 300 and 500 ppm exposure levels.

Industrial accidents provide some information about the toxic effects of trichloroethylene, however, these reports do not provide precise dosages. Buxton and Haywood (1967) described four cases of industrial accidents that involved TCE. Four workers were required to climb inside tanks containing TCE and scoop the remaining liquid out with buckets. All four workers became ill, and one subsequently died. The symptoms of trichloroethylene intoxication noted in two men who spent less than 30 minutes inside the tanks were nausea and headaches. The symptoms observed in the third man who remained inside the tanks for 2-1/2 hours were nausea, diplopia, and facial displegia. The fourth man, exposed to TCE vapors for the longest time period, died after developing severe multiple cranial nerve palsies 51 days after initial exposure. The authors ascribed the effects to unidentified decomposition products of TCE.

Six women employed in the cleaning of optical lenses for binoculars used their fingers to apply TCE for removal of small spots of wax remaining on the lenses. After a few months, they reported difficulty handling the lenses because they could

no longer feel the lenses properly. Examination showed persistent loss of tactile sense, inability to grasp objects between thumb and fingers, and loss of motion. Disability lasted for several months (McBirney, 1954). No skin damage was noted in any of these cases.

Maloof (1949) reports a worker who, after entering a freshly drained, heated degreasing tank, became comatose, suffered convulsions and had to be treated for first, second, and third degree chemical burns. Upon awakening, the worker complained of blurred and double vision and burning sensation of the skin. He recovered 31 days later. Another worker involved in the incident became unconscious, but regained consciousness almost immediately.

A man employed for one month as a metal degreaser lost his sense of taste and after two months of employment, developed trigeminal analgesia. Non-recovery of taste and trigeminal sensation was reported ten months later (Mitchell and Parsons-Smith, 1969).

Trichloroethylene has been shown to cause hepatic necrosis in man following either inhalation or ingestion (Ossenberg et al., 1972; Chiesura and Corsi, 1961). However, liver damage does not always occur in TCE intoxication. Most occupational studies on man show an increase in serum transaminases,

which indicates damage to the liver parenchyma (Albahary et al., 1959; Lachnit, 1971). These increases are transient and usually disappear after exposure is terminated.

B. Chronic Exposure

Toxic hepatitis was observed in a patient who had been cleaning a tank in which trichloroethylene was used to clean machine parts. Evidence of liver damage was based on rising serum glutamic-oxalacetic transaminase (SGOT), serum glutamicpyruvic transaminase (SGPT), and lactic dehydrogenase (LDH) levels (Bauer and Rabens, 1974). These levels returned to normal 6 weeks later. It was not stated how long this person had been employed or whether he had cleaned more than one tank as part of his regular duties.

Milby (1968) reported a case of TCE intoxication of a 39-year old female employed for two years as a paint-stripping operator. Six months prior to medical attention she had been assigned to a newer model stripping machine. She showed no signs of liver injury even though she complained of daily nausea and vomiting, drunkenness, abdominal cramps, flushing, sleepiness, loss of appetite and swelling of the eyes, face, and hands. Her physician observed a nonspecifically abnormal electrocardiogram and excretion of 780 mg trichloroacetic acid per liter in her urine on the day of examination. One week later, she excreted 40 mg trichloroacetic acid per liter of urine.

Eight workers were exposed to TCE in an electroplating plant for 2-3 weeks. The concentrations in the workroom ranged from 115-384 ppm (627-2,093 mg/m^3). Symptoms began almost immediately after exposure and included headaches, muscle and joint pains, nausea, vomiting, loss of appetite, depression, dizziness, and narcosis. All eight subjects showed an increase in globulin fraction and a decreased albumin fraction. It was concluded that liver damage was present as indicated by the cephalin cholesterol flocculation test (CCF) and hyperglobulinemia observations (Nomura, 1962).

Guyotjennin and van Steenkiste (1958)* reported that 18 workers exposed regularly to TCE showed signs of abnormal lipid metabolism characterized by total lipid content determination, analysis of lipid fractions and unsaturated fatty acid content. There was also an increase in γ-globulins.

Joron et al. (1955) found massive liver necrosis in a patient exposed to TCE vapors previously and in an acute episode lasting 2-1/2 hours where no protective mask was used. The patient died more than 1 month after the last known exposure to the TCE.

Cotter (1950) examined 10 workers who were exposed for several days to TCE vapors arising from a spill on board a ship. Symptoms included dizziness, nausea and vomiting, mental agitation, and coma, and later persistent abdominal pain,

cramps, diahrrea, and pain in the lower back. None were clinically jaundiced and none of the 10 sera gave positive reactions in cephalin cholesterol flocculation test. Cotter suggested that liver damage was present because of changing globulin level despite the absence of bilirubin or phosphatase retention or a disturbance of the esterification of serum chlolesterol. A full recovery of the subjects within 2 months was noted.

It was noted that children are highly susceptible to TCE liver pathology when compared to adult susceptibility (Kusch et al., 1976)*.

Toxic effects of TCE on the urinary system in man are not well defined. Only a few incidences of renal damage due to TCE intoxication have been reported. Acute hepatic and renal damage was reported in three patients with histories of drug abuse. In one patient centrilobular hepatic necrosis was found (Baerg and Kimberg, 1970). These effects were attributed to sniffing Carbona cleaning fluid or Carbona No. 10 special spot remover, which may contain TCE, petroleum solvents, and 1,1,1-trichlorethane.

Gutch et al. (1965) reported that a needle biopsy test showed acute tubular degenerative changes in the kidney of

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*Foreign language article. The information was obtained from a secondary source.

a 41-year old man who had inhaled TCE vapors. The man had been replacing asphalt floor tile in a small, enclosed room (10 by 20 feet) with a small ventilation opening in one window. TCE (99.5% pure) was used as a solvent to clean tile cement. A gallon container of TCE remained open during the cleaning operations which lasted over 2 hours. Inhalation exposure was estimated to be between 166-3,700 ppm. After leaving work, the man complained of headache, shortness of breath, and vomiting. He admitted himself to a hospital 5 days later and was diagnosed as having acute renal failure. Kidney function returned to normal after a 5-week rest. It is important to note that consistent moderate to heavy use of alcohol had been reported in this case.

Another case of renal failure after accidental oral ingestion was reported by Kleinfeld and Tabershaw (1954). A patient who had ingested liquid TCE developed jaundice and oliguria and died as a result of acute hepato-renal failure. The amount ingested is unknown. The patient had been in good health, was a moderate beer drinker, and had consumed several bottles of beer on the morning of the accident.

Cardiac arrhythmia is the most frequent effect of TCE on the heart. The most direct proof that TCE can cause

ventricular fibrillation and cardiac arrest is that these changes can be demonstrated in electrocardiograms (ECGs) of subjects who have accidentally ingested TCE. There are also reports of TCE-related deaths occurring which were due to ventricular fibrillation.

TCE is believed to sensitize the heart to epinephrine, resulting in ventricular fibrillation; thus, any form of stress would help induce cardiac sensitization. Anesthetic concentrations of TCE have been shown to cause changes in the ECG indicating tachycardia and arrhythmias. The ECG changes that occur during TCE anethesia in man usually cease when exposure is terminated.

Radonov et al. (1973)* reviewed the cases of 200,000 women given TCE as an analgesic during therapeutic abortions. Seven deaths occurred; the deaths were attributed to cardiac arrest.

Starodubtsev and Ershova (1976)* successfully used TCE-air anesthesia in 128 cases of dental surgery in all three levels of stage 1 anesthesia. The electrocardiograms showed no apparent toxicity.

Four deaths were reported by Kleinfeld and Tabershaw (1954) from chronic exposure to TCE. Exposure concentrations

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*Foreign language article. The information was obtained from a secondary source.

were unknown for three of the four cases. In one case, the concentrations measured after the final incident were between 200 ppm and 8,000 ppm. All four workers continued to work at their jobs even though they complained of nausea and vomiting, drowsiness, and dizziness. They all died within a few hours after leaving the plant. The mechanism of death was considered to be ventricular fibrillation. Autopsies revealed no gross anatomical abnormalities, but toxicological analysis of the tissues revealed the presence of trichloroethylene.

C. Epidemiology

Grandjean et al. (1955) examined 50 workers exposed to trichloroethylene in degreasing operations in the Swiss mechanical engineering industry. Clinical exams, case histories, trichloroacetic acid analysis of urines and other clinical blood and urine analyses were done. Medical histories and urine samples were taken from an additional 23 workers. Of the 50 examined clinically, the average age was 43 years; length of exposure ranged from 1 month to 15 year; workplaces were at both open and closed degreasing tanks; air TCE concentrations in 96 samples ranged between 1 and 355 ppm; and TCA in urines ranged from 8-444 mg/l.

These authors found that the air measurements did not adequately reflect exposures due to great variations in concentration with ventilation and operating schedules for degreasers.

They found that the general health of the men examined was frequently bad; they felt this was related to the pay and the poor standard of living. Although the authors stated they were not acquainted with the normal incidence of disease in Swiss workmen, they did not examine an unexposed control or comparison group. Of greater importance they noted the following dose-effect relationships: neurological and vegetative nervous system disorders were more frequent in men with the longest history of work exposure; subjective symptoms were the same regardless of length of exposure; and subjective symptoms, vegetative and neurological disorders, were more frequent in the higher exposure groups as determined by the amount of trichloroacetic acid in urine. Persons with symptoms of chronic poisoning were from workplaces with measured air concentrations of trichloroethylene between 20 and 80 ppm, and had between 10 and 250 mg/l TCA in their urines. Finally, 10% of the workers examined (5) showed evidence of slight impairment of liver function but the authors were not sure if this could be related to trichloroethylene exposure.

Bardodej and Vyskocil (1956) examined 75 persons engaged in work with trichloroethylene, 12 of these in dry-cleaning establishments and 55 in degreasing metal parts.

Length of exposure varied between one-half year and 25 years. Air concentration in these plants varied between 0.028 and 3.4 mg TCE per liter (5-630 ppm). Eight disabled former employees were also followed clinically. Intolerance to alcohol, shivers, giddiness, neurasthenic syndrome with anxiety states, bradycardia, and conduction disturbance of the heart muscle were found to be significantly correlaterd ($P < 0.01$) with duration of exposure in years. The frequencies of lacrimation, reddening of skin, decreased sensitiveness of of hands, and disturbances of sleep among this mixed group of workers was also significantly correlated with duration of exposure ($P < 0.05$). No control group was observed, and the age and sex distribution in this group of workers was not given in the description of this study.

Takamatsu (1962) studied 50 male and female workers exposed to trichloroethylene during degreasing operations in communicating machine factory for approximately 2-1/2 years. Screening of workers in January and November, 1960, included a questionnaire, blood cell count, blood pressure measurement and analysis of urine for albumin, sugar, urobilinogen and TCA. Urines were collected twice for each worker, once in the morning and once in the afternoon. On the basis of these results, workers were selected for further examination, including fatigue tests. A control group of 48 non-exposed workers was referred

to in the paper but no information on their characteristics was given.

Eighty percent of the air values in January, and 70% in November fell between 25-100 ppm TCE. Variations in air concentrations were related to proximity to the degreasing apparatus and location of air currents. A mean value of urinary TCA found was 66 mg/l. Wide variations in TCA occurred, depending again on proximity to main currents of vapor. A majority of the 50 exposed workers had some complaints including headache, vertigo, diplopia, sleeplessness, fatigue, etc. Thirty-eight percent of the workers had slight or moderate visual disturbances and 15% had diplopia. Diastolic blood pressure exceeded the (unknown) control groups by 5 mm Hg. No significant differences in blood count were observed. Decreases in albumin concentration and increases in -globulin were observed in exposed workers and were more frequent in those exposed to highest air concentrations (150-250 ppm). Thirty percent of the workers had albumin in urine and elevated urobilinogen was found in 36% of workers. Some of the workers reported constriction of the visual field.

Six employees who worked in the degreasing room, had urinary TCA values from 370-1,000 mg/l, and frequent complaints but few other clinical findings after short-term (7-30 days) exposure. In workers with the highest exposures (150-250 ppm)

subjective complaints included headache, dizziness, giddiness, drunken feeling, flushing of the face, burning throat, and fatigue. TCA in urine was >100 mg/l and increased during the work week. Malfunctions of the liver were observed as were changes in serum protein fractions. Workers exposed to 50-100 ppm complained of headache, burning eyes, flushing of the face and fatigue. Half of these workers had urinary TCA exceeding 100 mg/l. Changes in serum protein fractions were observed and visual disturbances were found in workers exposed for several years. Work efficiency was reduced by the end of the work week. Workers exposed to less than 50 ppm TCE showed no apparent ill effects. Their urinary TCA was less than 50 mg/l.

Lilis et al. (1969) examined 70 workers in a Rumanian semiconductor manufacturing plant. Eighty-three percent of these workers were less than 30 years old and 74% were women. Duration of exposure of 55% of these workers was less than 2 years and not more than 6 years for the remaining workers. Two hundred fourteen air samples were collected at work places of which 40% exceeded 50 mg/m^3, and 12% were higher than 200 mg/m^3. Trichloroacetic acid concentrations in urines of these workers exceeded 20 mg/l in 46% of cases, 40 mg/l in 24% of examined workers, and exceeded 100 mg/l in 7.3% of workers. Examination included a detailed occupational history questionnaire with information on the onset of and occurrence of persistent symptoms.

The physical examination paid special attention to the nervous system, heart and vessels and liver, and included electrocardiograms and presence of a metabolite of catecholamine in the urine. Seventy-five percent of the workers examined reported prenarcotic symptoms during the work shifts, including dizziness (88% of cases), headache (74%), nausea (43%), euphoria (31%), palpitation (29%) disturbances of vision (21%), and sleepiness at end of shift (29%). These symptoms appeared daily in more than 1/3 of the examined workers. Persistent symptoms of the pseudo-neurasthenic type appeared after several months of exposure and included fatigue, headache, irritability, anxiety, loss of appetite and alcohol intolerance, along with signs of autonomic system inbalance such as excessive sweating, palpitation, and nausea. Physical exams showed few abnormalities. In 14% of cases moderate tachycardia was found. Electrocardiographic abnormalities did not appear to be related to their toxic exposure but were said to be similar in frequency to every population group.

Systemic hemodynamic parameters were compared in 44 exposed workers and 10 non-exposed controls similar in age and sex. Significantly raised mean values of stroke volume, cardiac output, cardiac index and heart work in the exposed workers were found and considered as signs of epinephrine type hypersympathicotonia. In support of this, the authors reported that urinary vanililmandelic acid (3-methoxy-4-hydroxymandelic acid) values

differed significantly between exposed workers and controls using a student test ($P < 0.01$).

The scanty description of the control group and their participation in only selected parts detracts from this otherwise interesting study. Also, the selection of exposed workers in this study is not described in detail.

Szulc-Kuberska et al; (1976) studied 50 Polish workers, 28 men and 22 women, age 25-50 years, with between 1 and 23 years of occupational exposure to trichloroethylene. Forty-four percent (22) of these workers complained of excessive somnolence, 18% (9) headaches, 20% drowsiness during work time. Two instances of loss of consciousness at work were reported. Thirteen workers (26%) reported intolerance to alcohol, 14 persons (28%) signs of vegetative dystonia (excessive sweating) were present. Four men reported impotency; 3 women reported disorders of menstruation including one with signs of menopause before age 35. Disturbances of affection like apathy and inclination to weeping were also observed. One person revealed signs of psycho-organic syndrome with disturbances of memory, loss of interest and bradyphrenia. A distinct correlation was found between the duration of work and the frequency of occurrence of symptoms in these workers.

These authors also examined the auditory and vestibular apparatus in 40 workers and reported perceptive hearing impairments in 60% of TCE-exposed workers. Workers with previous or

present exposure to noise were excluded from this portion of the study. Hearing disturbances found were always bilateral and symmetric in the high frequencies beginning from 2,000-3,000 hz. Hearing loss was not always correlated with vestibular pathology. Impairment of auditory and labyrinthine function was found more frequently among workers with longest period of work. These authors also stated that disorders of hearing and vestibular reactions are early signs of the adverse health status of workers exposed to trichloroethylene.

In all of these workers the trichloroacetic acid level in the urine exceeded 40 mg/l. No control group was examined, and the type of work or circumstances of the workplace were not described. Air concentrations of TCE in the workplace(s) were also not given. The possible confounding effect of age and length of employment on hearing loss is also not discussed. For these reasons it is difficult to evaluate the results of this study or to determine whether different results would be obtained in a similar but unexposed (to TCE) industrial population.

Axelson et al. (1978) examined causes of death in a small cohort of 518 men whose trichloroethylene exposure was estimated through trichloracetic acid (TCA) in the urine. Average TCA in urine above 100 mg/l was considered high exposure corresponding to more than 30 ppm in air. Close agreement was found between observed and expected numbers of cancer deaths

based on national Swedish cause-age-specific death rates. Five hundred forty-eight and 3,643 person-years of observation comprised the high and low exposure groups, respectively. Due to the small sample size, the cancer risk to man from trichloroethylene could not be ruled out by these investigators, particularly with regard to uncommon malignancies.

All of the epidemiologic studies described above examine workers exposed to trichloroethylene in their workplace. A frequent criticism of these studies is that they rarely have included an unexposed group for comparison. Secondly, the age and sex distribution in the groups of workers being examined was not always provided in the papers, nor were other demographic characteristics. Exposed groups were lumped together by intensity of exposure and it was difficult to separate out effects which may have been related to age, sex, or length of employment. Discussion of exposure to other chemical substances in these workplaces, and their possible influence on the findings was also scanty, and made the lack of control groups a greater deficiency. In view of these difficulties, information can best be derived by examining consistent findings among studies conducted under different circumstances. Four out of the six studies noted some dose-effect relationship. All but one were able to document exposure to trichloroethylene by measuring trichloroacetic acid

in the urine of workers. The most consistent findings were complaints of fatigue, alcohol intolerance, disturbances of sleep (both sleepiness and insomnia) headache, dizziness, excess sweating, tachycardia or palpitations, and visual disturbances. It should be noted that the studies may not have used comparable methods of ascertaining these symptoms. Some of the similarity of findings may have been related to historical experience of previous investigators and the particular objective of each study.

D. Synergistic and/or Antagonistic Response

Intolerance to alcohol has been reported among the TCE-exposed workers. Stewart, et al. (1974) performed experiments to substantiate this observation. They gave small oral doses of ethanol to seven subjects and exposed them to 20,100 and 200 ppm of TCE for 1, 3, or 7-1/2 hours. Transient vasodilation of the superficial skin vessels reaching maximum intensity at 30 minutes was noted.

Summary and Conclusions

1. Reports on the accidental ingestion of TCE are available. A single oral dose of 7.6 g in a 4-1/2 year old child produced toxic effects. Assuming a 20 kg body weight of the child, the estimated dose is approximately 380 mg/kg. In another incident, an adult who ingested 21 g trichloroethylene exhibited symptoms such as vomiting, abdominal pain, inebriation, transient unconsciousness and myocardial infarction. In the second case, the

dose is estimated at 300 mg/kg. Therefore, the lowest toxic dose in humans is 300-380 mg/kg.

2. Occupational exposures give some information with regard to exposure and obvert adverse health effects. However, these data do not provide precise exposure levels and are cofounded by the fact that the workers are also exposed concurrently to other chemicals. And it is not possible to associate adverse health effects with the chemical(s) with certainty. In an electroplating plant, when the exposure was between 627-2093 mg/m^3 for 2-3 weeks, the workers complained of headaches, muscle and joint pains, nausea, vomiting, loss of appetite, depression, dizziness and narcosis. The workers had liver damage as indicated by chloesterol flocculation test and hyperglobinemia.

3. Epidemiological evidence cannot be related to the exposure levels with confidence, however, exposure of workers to trichloroethylene and its association with observed health effects - fatigue, dizziness, alcohol intolerance, conduction of disturbance of heart muscle, nervous system disorders, increase in plasma Y -globulin and decrease in albumin concentration, is worth mentioning. Some workers had albumin and elevated urobilinogen in urine. These studies cannot be used for determing recommended maximum contaminant levels.

4. Intolerance to ethanol among the factory workers exposed to ethanol has been reported.

VII. MECHANISMS OF TOXICITY

Exposure to trichloroethylene has been reported to produce: disturbances in the central nervous system, arrhythmia (cardiotoxic effect), hepato- and nephrotoxic effects and carcinogenic response in animals. Very little is known about the mechanisms by which TCE exerts the bioeffects; however, several attempts have been made to elucidate the mechanisms for some of these bioeffects.

Information concerning the hepatotoxic and possibly potential carcinogenic effects have been generated by the experiments of several workers. The first step in this mechanism appears to involve epoxidation of trichloroethylene in the mammalian system. This system requires cytochrome P-450 and the NADPH-generating enzymes. The trichloroethylene-epoxide thus formed may interact: (1) with low molecular weight nucleophiles by conjugation reaction; (2) with cellular macromolecules by alkylation; and (3) with water to produce diols or undergo intramolecular rearrangement.

The evidence for macromolecule binding of TCE has been generated by Allemand et al. (1978); Uehleke and Poslawski-Tabarelli (1977); Van Duuren and Banerjee (1976); and Bolt and Filser (1977). In in vitro experiments, Allemand et al. (1978) incubated ^{14}C-trichloroethylene with rat liver microsomes, with

and without the NADPH-generating system. Without the NADPH-generating system, there was negligible radioactivity bound to microsomal proteins. This suggests that TCE itself does not bind to proteins. The TCE-binding was increased after pretreatment with microsomal enzyme inducers and decreased under the influence of CO/O_2 atmosphere and piperonyl butoxide--the inhibitor of microsomal enzymes. Intraperitoneal administration of 100 umol (13.14 mg/kg) of TCE to normal and phenobarbital-pretreated animals gave higher activity in the treated animal tissues; hepatic-protein bound radioactivity was 40 times more than that of the muscle protein. Inhalation exposure of male Wister rats to ^{14}C-TCE for 5 hours at concentrations of 9 ppm, 100 ppm, and 1,000 ppm (49, 545, 5,450 mg/m^3) demonstrated irreversibly-bound radioactivity maximum to the liver and minimum to the muscle (Bolt and Filser, 1977). These authors also carried out in vitro covalent-binding experiments utilizing ^{14}C-TCE. Incubating ^{14}C-TCE with NADPH-generating liver microsomes and albumins and globulins, Bolt and Filser (1977) found large amounts of radioactivity bound to albumin (bovine and rabbit). Binding was reduced by the addition of glutathione. This was in contrast to vinyl chloride where the metabolites preferentially bind to SH groups.

VanDuuren and Banerjee (1976) incubated rat liver microsomes with ^{14}C-TCE. The results showed that TCE binds covalently to microsomal protein. The binding was decreased by the addition of microsomal inhibitors--7,8-benzoflavone, blocked by compound SKF-525A and enhanced by pretreatment of the animals with phenobarbital. The experiments with 3,3,3-trichloropropene oxide (TCPO), a potent inhibitor of epoxide hydrase showed that this agent causes an enhancement of TCE binding to microsomal proteins. These results suggest that the binding is via an epoxide or other related electrophilic species. Similar results have been obtained by Uehleke and Poplawski-Tabarelli (1977). Mice were injected intraperitoneally with solution of ^{14}C-labeled TCE. Microsomes contained the highest number of irreversibly bound radioactivity. The concentration declined after 6 hours.

The information cited above suggests that the metabolites of TCE covalently bind with microsomal proteins and the binding can be increased/decreased by utilizing the enzyme inducer and inhibitors. Covalent protein binding of metabolites of xenobiotics had been used as a tool that allow us to detect whether reactive and possibly hazardous, metabolites are formed. In addition, interaction with nucleic acids moieties has to be examined.

DiRenzo and his coworkers (1982) studied in vitro covalent binding of a series of ^{14}C-labeled aliphatic halides to calf

Table VII-1

MICROSOMAL BIOACTIVATION AND COVALENT BINDING OF ALIPHATIC HALIDES TO CALF THYMUS DNA

Aliphatic halides[a]	Binding to DNA[b]
1,2 Dibromoethane	0.52±0.14(6)
Bromotrichloromethane	0.51±0.18(6)
Chloroform	0.46±0.13(6)
Carbon tetrachloride	0.39±0.08(6)
Trichloroethylene	0.36±0.14(7)
1,1,2-Trechloroethane	0.35±0.07(7)
Dichloromethane	0.11±0.05(5)
Halothane	0.08±0.01(6)
1,2-Dichloroethane	0.06±0.02(6)
1,1,1-Trichloroethane	0.05±0.01(3)

a ^{14}C-labeled aliphatic halides (1 mM) were incubated with hepatic microsomes. Carbon tetrachloride, bromotrichloromethane and halothane were incubated under an N_2 atomosphere while all other incubations were under an O_2 atmosphere for reasons as stated in MATERIALS AND METHODS.

b nmol bound/mg DNA/h. Values are the mean ± standard deviation for the number of experiments in parentheses.

Source: DiRenzo et al. 1982

thymus DNA following bioactivation by hepatic microsomes isolated from phenobarbital-treated rats. Six compounds--1,2,-dibromoethane, bromotrichloromethane, trichloroethylene, carbon tetrachloride, chloroform and 1,1,2-trichloroethane were incubated for 60 minutes (time-period previously determined to produce maximal covalent binding). Halides to DNA adducts were isolated utilizing Sephadex LH-20 column chromatography. Table VII-1 gives comparative binding to DNA of the selected aliphatic halides.

It is noteworthy that the compounds containing bromine are readily bioactivated and bound to DNA to a greater extent than the related chlorine-containing compounds in this series. This is illustrated by the binding to DNA of 1,2-dibromoethane (0.52±0.14) and 1,2-dichloroethane (0.06±0.02). Also those aliphatic halides that had the highest levels of covalent binding are those most frequently shown to be carcinogenic in laboratory animals.

Banerjee and Van Duuren (1978) carried out studies on the in vitro covalent binding of trichloroethylene to salmon sperm DNA, in the presence of microsomal preparation from $B_6C_3F_1$ hybrid mice. TCE metabolite-DNA adduct was purified by precipitation/reprecipitation technique with solvents. It was checked for protein and RNA contamination. TCE-DNA binding was dependent on the concentration of microsomal protein. Amount of binding of TCE to DNA in the presence of microsomes from male mice was higher than those from female mice. This correlates with the NCI cancer bioassay on trichloroethylene. The binding to DNA was enhanced by the in vivo pretreatment of the animals with phenobarbital.

In vivo TCE-DNA binding researches were performed by Stott and his coworkers. Male $B_6C_3F_1$ mice were dosed with 1,200 mg/kg ^{14}C-TCE by gavage in corn oil. The animals were

sacrificed 5 hours later by decapitation. Livers were frozen and processed for DNA isolation and purification. Three out of four animals had a maximum estimate of the average DNA level of 0.62 ± 0.42 alkylations/10^6 nucleotides. The authors suggested an epigenetic mechanism of tumor formation in the $B6C_3F1$ mouse because of the so-called low maximum estimation of alkylation. This conclusion appears to be far reaching based on a single experiment where only a single dose was given and only four animal were used. In addition their estimate of alkylation with higher standard deviation does not instill confidence in the mind of the reviewer.

In order to establish a correlation of covalent binding and hepatotoxicity, Allemand et al. (1978) demonstated that intraperitoneal administration of TCE (1,460 mg/kg) to rats resulted in raised SGPT levels, without detectable histologic lesion of the liver. Phenobarbital pretreatment of the animals increased hepatic cytochrome P-450, in vitro formation of the chemically reactive metabolite of TCE, the amount of metabolite bound in vivo, and the hepatotoxicity of a (1,460 mg/kg) dose of TCE. The inhibition of TCE metabolism with $CoCl_2$ decreased the hepatic cytochrome P-450, the in vitro formation rate of the chemically reactive metabolite

of TCE, and the hepatotoxicity of a 1 ml/kg dose of TCE. In an inhalation experiment, Carlson (1974) observed enhancement of TCE hepatotoxicity in male rats pretreated with phenobarbital and 3-methylcholanthrene. Indices of hepatotoxicity were serum isocitrate dehydrogenase, SGPT, SGOT and hepatic glucose-6-phosphatase; while TCE exposure levels ranged from 10,400 ppm to 6,900 ppm, lasting for a 2-hour periods. Moslen et al. (1977) also exposed male rats, after pretreatment with five different inducers of hepatic mixed function oxidases, to 1% (10,000 ppm) TCE for 2 hours. The magnitude of induction of cytochrome P-450 correlated with the extent of TCE-induced liver injury measured by serum transaminases level (r=0.95), with prolongation of anesthesia recovery time (r=0.95), and with enhanced urinary excretion of trichlorinated metabolites (r=0.88).

Factors other than enzyme induction could also influence the hepatotoxicity of trichloroethylene. For example, influences include changes in the redox state of the hepatocytes or depletion of co-factors required for specific metabolic steps. Cornish and Adefunin (1966) reported increased hepatotoxicity of rats pretreated with ethanol. An explanation for observed interaction of ethanol and trichloroethanol is the availability for NAD and NADPH--the co-factors required for the metabolism of trichloroethylene--at the step involving

biotransformation of chloral hydrate. The concentration of glutathione, an endogenous compound responsible for varied types of metabolic reaction in mammalian systems has been affected by the administration of trichloroethylene to the animals. After TCE administration to normal rats, hepatic glutathione was decreased. This was not true when the animals were pretreated with the chemicals which inhibit metabolism, suggesting that glutathione depletion was related to trichloroethylene metabolism. Also, in vitro addition of glutathione to the incubation mixture decreased the amount of trichloroethylene metabolite bound to microsomal proteins. Earlier it had been reported that tissue binding of TCE metabolite was related to hepatotoxicity.

Salvolainen (1977) reviewed some aspects of the mechanisms by which industrial solvents produced neurotoxic effects. Neurotoxic action may be described as responses that are related to nervous system function, to structure, or to both. The acute effects appear to be derived from the direct interaction of solvents on nerve cell membranes, whereas the development of chronic effect depends more on the metabolic effects of the individual chemical. To elicit anesthesia in surgical operations may be considered an example of the former effect. The majority of such effects are probably reversible.

It appears that for anesthesia, TCE would fall in the category of chemicals which interfere with nerve cell membrane. For chronic effect, metabolic changes have been cited for the neurotoxic effects of many chemicals. Specific effects on neuronal metabolisms and functions due to the exposure to TCE have not been examined.

Summary and Conclusions

1. Evidence has been generated that it is the metabolite of TCE rather TCE which is responsible for the hepatotoxic and potential carcinogenic response.

2. A metabolite of TCE covalently binds with the macromolecules including DNA.

3. It appears that TCE may fall in the category of chemicals which interfere with nerve cell membrane for its anesthetic response.

VIII. RISK ASSESSMENT

The National Academy of Sciences (NAS, 1977) made an assessment of human cancer risk associated with TCE in drinking water. The risk assessment was based upon the results of a carcinogenesis bioassay experiment with animals (NCI, 1976). In this study, highly significant differences in the incidence of hepatocellular carcinomas were found between treated and controlled mice of both sexes.

The available sets of dose-response data were individually considered according to the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low-dose level. These estimates are of lifetime human risks and have been corrected for species conversion on the dose/surface area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water/day containing Q ppb of the compound of interest. For example, a risk of 1×10^{-6} Q implies a lifetime probability of 2×10^{-5} of cancer if 2 liters/day were consumed and the concentration of the carcinogen was 10 ppb (i.e., Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million

people this translates into 4,400 excess lifetime deaths from cancer or 62.8/year. Since several data sets is typically available the range of the low-dose risk estimates are reported. For TCE at a concentration of 1 ug/liter (Q=1) the estimated risk for man would be $0.36\text{-}1.1\text{x}10^{-7}$ Q. The upper 95% confidence estimate of risk at the same concentration is $0.55\text{-}1.6\text{x}10^{-7}$.

It should be emphasized that these extrapolations are based on a number of unverifiable assumptions: extrapolation from high exposure to low exposure in mice, on the basis of a multi-stage mathematical model; extrapolation from mouse to man, on the basis of the surface-area rule; and extrapolation from gavage exposure to oral exposure assumed equal. These estimated human risks should be taken as crude estimates at best.

The CAG, using an "improved" multi-stage model has determined that 27 ug/l at 2 liters/day over a lifetime would result in an excess cancer risk estimate of 10^{-5} at the 95% confidence limit.

The National Academy of Sciences (NAS) and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water by mathematical

extrapolation from high-dose animal studies. Using the risk estimates generated by the NAS (1977-1979) where the multi-stage model was utilized, that range of trichloroethylene concentrations were computed that would nominally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption at the stated exposure level. From the NAS model it is estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a trichloroethylene concentration of 450 ug/l, 45 ug/l or 4.5 ug/l would increase the risk of one excess cancer per 10,000; 100,000 or 1,000,000 people exposed, respectively. Using the revised CAG approach and thus the "improved" multi-stage model, it can be estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a trichloroethylene concentration of 280 ug/l, 28 ug/l, or 2.8 ug/l would increase the risk of one excess cancer per 10,000; 100,000 or 1,000,000 people exposed, respectively. The numerical differences observed after utilizing the NAS and the CAG risk estimates are partly due to the fact that the dose extrapolation model used by the two groups is similar but not identical. The NAS has used the multi-stage model whereas the CAG has used the "improved" version of the multi-stage model recently discussed by Crump (U.S. EPA, 1980). In addition, the selection of the data and other parameters in each model will also result in some differences in risk assessments.

Table VIII-1

Drinking Water Concentrations And Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)*		
	CAG (95% confidence limit)	NAS (95% confidence limit)	NAS (point estimate)
10^{-4}	280	450	I400-450
10^{-5}	28	45	140-45
10^{-6}	2.8	4.5	14-4.5

*Assume 2 liters of water are consumed per day.

IX. Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70\text{ kg})}{(\text{Uncertainty factor})(2\text{ liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" or a "minimal-effect-level" is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exist valid experimental results on ingestion by humans, an uncertainty factor of 100 if there exist valid results in chronic or long-

term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if only limited data are available.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group has used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the incremental excess cancer rate that would be projected at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer risk rates also can be estimated using other models such as the one-hit model, the model, the logit model and the probit model. Current understanding of the biological mechanisms involved in cancer do not allow for choosing among the models. The estimates of incremental risks associated with exposure to low doses of potential carcinogens can differ by several orders of magnitude when these models are applied. The linear, non-threshold multi-stage model often gives one of the highest risk estimates per dose and thus would usually be the one most consistent with a regulatory philosophy which would avoid underestimating potential risk.

The scientific data base, which is used to support the estimating of risk rate levels as well as other scientific

endeavors, has an inherent uncertainty. In addition, in many areas, there exists only limited knowledge concerning the health effects of contaminants at levels found in drinking water. Thus, the dose-response data gathered at high levels of exposure are used for extrapolation to estimate responses at levels of exposure nearer to the range in which a st ndard might be set. In most cases, data exist only for ani uncertainty exists when the data are extrapolated to humans. When estimating risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and target organ of the test animals used in the experiment, as well as the exposure mode and dosing rates. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible additive, synergistic or antagonistic interactions.

Trichloroethylene studies which provide dos adverse health effects in humans are not available. Therefore, estimations based upon the best scientific judgments in experimental animals are required to quantify toxicological effects (QTE) with respect to concentrations in drinking water. With this objective in mind, this section analyses the data taking into consideration interspecies variation, observed adverse health effects (both carcinogenic and non-carcinogenic) and dosages.

A. Non-Carcinogenic Effects

Among the acute and chronic adverse effects due to TCE exposure, hepatotoxicity appear to be of most significance. All the animal species which have been studied, respond to the hepatotoxic effects of TCE - intensity of response dependent upon the dose and the duration of exposure. There are reports concerning the nephrotoxic effects of trichloroethylene. Central nervous system and cardiotoxic effects are observed at very high concentrations.

Several inhalation studies, after single or multiple exposures have provided observations on hepatotoxic effects. Kylin et al. (1962) compared the hepatotoxicity of chloroform, trichloroethylene and tetrachloroethylene. Mice were given TCE by inhalation for a single 4-hour time-period. The animals were sacrificed on the third day; the livers were analyzed by histological examination and by acetone-hexane extraction for fat. In addition, activity of serum ornithine carbamyl transferase was determined. Trichloroethylene at a concentration level of 6,400 ppm produced no significant damage to the liver. In this study, trichloroethylene was the least hepatotoxic, whereas chloroform was the most. Similar results were obtained by Plaa et al. (1958) and Gehring (1968) when animals were exposed to halogenated hydrocarbon solvents by subcutaneous injection and by inhalation. The results of these workers indicated that the halogenated hydrocarbon solvents rank in the order of their decreasing capacity to cause liver dysfunction: carbon tetrachloride, chloroform, 1,1,2-trichloroethane,

tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane.

Multiple inhalation exposure studies have been reported utilizing mice, rats and dogs. Seifter (1944) observed degeneration of liver parenchyma cells in dogs that were exposed either to 750 ppm TCE 8 hours/day, 6 days/week for 3 weeks or 500 to 750 ppm TCE 6 hours/day, 5 days/week for 8 weeks. Slight fatty infiltration of the liver of mice was detected by Kylin et al. (1965). These workers exposed female albino mice to 1,600 ppm TCE by inhalation for 4 hours daily, six days a week, over periods of one, two, four and eight weeks. The increase in liver fat content was detectable after one week's exposure and subsequently the liver fat showed no further increase. In terms of fatty degeneration of liver, the authors noticed that tetrachloroethylene was approximately 1/10 times less toxic than trichloroethylene. Male Wistar II rats inhaling 55 ppm TCE for 14 weeks, exhibited elevated liver weights but did not cause pathological changes measured by histopathological examinations, liver function tests, renal function tests and blood glucose (Kimmerle and Eben, 1973). Four animal species - rabbits, guinea pigs, rats and monkeys were exposed seven hours daily, 5 days a week, 100 to 3,000 ppm TCE vapors for approximately up to six months by Adams et al. (1951). Rats exposed to 300 - 3,000 ppm TCE for a period of 36 days (total of 27 exposures) showed an increase in liver and kidney weights. However, histopathological examination of the tissues failed

to reveal any abnormality in male rats, but some female rats showed fat vacuoles in the cytoplasm of the liver. Rats exposed to 200 ppm TCE for 205 days (total exposures 151) showed no significant abnormality from the controls. The authors concluded that the maximum concentrations without adverse effects were as follows: monkey, 400 ppm; rat and rabbit, 200 ppm; guinea pig, 100 ppm.

Because of the effects of TCE on the nervous system, it has been used as a general anesthetic agent. Studies performed as early as 1944, give information concerning the blood concentration of TCE for lethal as well as anesthetic effects. Dogs, rabbits, guinea pigs and cats were administered TCE by inhalation and blood levels were determined at death and anesthesia stages. Lethal blood TCE concentration in dogs were found to be 100-110 mg/100 ml blood. At the anesthetic stage, TCE blood levels were 24 - 37, 23 - 28, 14 - 18, 25 - 32 mg/100 ml blood for dogs, rabbits, guinea pigs and cats, respectively. As with the liver, guinea pigs appear to be the most sensitive species among the studied experimental animals with respect to the anesthetic response. The blood-brain ratio at anesthetic dosages were approximately 1:2 for both guinea pigs and dogs (Kulkarni, 1944).

Hisptopathological changes in neural tissues have been observed on acute and long-term exposure of animals to TCE. A single exposure of dogs to 30,000 ppm TCE in air resulted in death within 20 minutes. No obvious changes were found in the nervous

system. In a longer-term experiment, the animals were subjected to TCE concentration ranging from 500 - 3,000 ppm for periods varying 2 - 8 hours daily, often for 5 days weekly. The total exposure period was between 60 - 162 hours. The exposures appear to selectively destroy the Purkinje layer of the cerebellum. The cerebral hemispheres showed mild changes -- scattered cortical neurons became swollen or pyknotic and the white matter of the myelin developed a mild focal swelling (Baker, 1958). Bartonicek and Brun (1970) injected TCE intramusculary in female rabbits and observed moderate neurological changes in the exposed animals. The dosage regimen included subacute exposure for 29 days, injected animals with 2.47 g/kg body weight three times a week. For chronic exposure experiment, the animals were injected intramuscularly for 41 to 247 days with 1.62 g/kg week. The rabbits were sacrificed at different times during the test and the brains examined histologically and histochemically for any pathological change. Round cell infiltration around blood vessels and in the parenchyma occurred in all animals of the subacute and in one of the chronic experiments but not in the controls. Disappearance of Purkinje cells and basket cells was definitely shown only in the chronic experiment.

Grandjean (1960) exposed male rats to 200 and 800 ppm TCE vapors for 4 to 11 weeks. The rats were subjected to a single 3-hour TCE exposure just before testing. After the exposure, trained rats responding to signals, climbed up a rope to reach

a feeding through where they found a small dextrose pellet as a reward. The results indicated that the increase in the number of spontaneous climbs after exposure to the solvent is significant in comparison with the control tests. The observed effect was not dose-dependent. The authors concluded that TCE in doses studied modified the psychological equilibrium of rats by increasing excitability. The author in the 1963 report described the effect of TCE vapors on the swimming performance and on the motor activity of rats. The animals were exposed for six hours and swimming tests were performed 5 - 15 minutes later. At 400 ppm, TCE retarded only the rats swimming with an additional load in a manner barely significant while 800 ppm adversely affected the performance, both with load and without, in a significant manner. One hour after termination of exposure, no significant changes in the swimming times were observed.

Reports on the accidental ingestion of TCE are available. A single oral dose of 7.6 g in a 4 1/2 year old child produced toxic effects. Assuming a 20 kg body of weight of the child, the estimated dose is approximately 380 mg/kg. In another incident, an adult who ingested 21 g of trichloroethylene exhibited symptoms such as vomiting, abdominal pain, inebriation, transient unconsciousness and myocardial infarction. In the second case, the dose is estimated at 300 mg/kg. Therefore, the lowest toxic dose in humans is 300-380 mg/kg.

Occupational exposures give some information with regard to exposure and obvert adverse health effects. However, these data do not provide precise exposure levels and are cofounded by the fact that the workers are also exposed concurrently to other chemicals. Also, it is not possible to associate adverse health effects with the chemical(s) with certainty. In an electroplating plant, when the exposure was between 627-2093 mg/m^3 for 2-3 weeks, the workers complained of headaches, muscle and joint pains, nausea, vomiting, loss of appetite, depression, dizziness and narcosis. The workers had liver damage as indicated by cholesterol flocculation test and hyperglobinemia.

Epidemiological evidence cannot be related to the exposure levels with confidence, however, exposure of workers to trichloroethylene and its association with observed health effects - fatigue, dizziness, alochol intolerance, conduction of disturbance of heart muscle, nervous system disorders, increase in plasma Y -globulin and decrease in albumin concentation, is worth mentioning. Some worker had albumin and elevated urobilinogen in urine. These studies cannot be used for determining the quantification of toxicological effects (QTE).

B. Quantification of Non-Carcinogenic Effects

Similarities in bioeffects, across species - humans, dogs, rabbits, guinea pigs, rats and mice, as a result of

TCE exposure either by inhalation, intramuscular injection or gavage have effects on the central nervous system, liver and the heart. TCE also has been shown to be carcinogenic in mice in two studies. Because of the special nature of the carcinogenic effect, it is discussed separately in this section.

The central nervous system and the liver of the mammalian system appear to be the sensitive endpoints with respect to the adverse health effects. There are limited data concerning the dosage, duration of exposure and the effects on the central nervous system. There is only one study in which human volunteers were exposed to 600 mg/m^3 TCE for two 4-hr. periods. In this study psychophysiological changes were noted in human volunteers. This study cannot be used for recommending a longer-term exposure or QTE.

Liver toxicity should be used as an end point, for est. QTE for TCE in drinking water. TCE has been shown to damage liver of humans as indicated by cholesterol flocculation test and hyperglobinemia. The exposure related to this effect was between 627-2093 mg/m^3 for 2-3 weeks. The exposure in mg/kg/day can be estimated as:

$$\frac{627 \times 10 \times 0.3}{70} = 26.87 \text{ mg/kg}$$

627 = lowest estimated exposure dose in mg/m_3

10 = cubic meter of air-TCE mixture inhaled

0.3 = assumed fraction of TCE retained in the body after inhalation

70 = average body weight of an adult human

Rats exposed to 300 mg/m^3 (55 ppm), five days a week for 14 weeks, had elevated liver weights. Assuming the lung-whole body weight ratios for humans (adults) and rats (adults) to be roughly equivalent, the total dose of trichloroethylene to humans can be estimated. The calculations are:

$$\frac{(300\ mg/m^3)\ 8\ m^3/day\ (5)(0.30)}{(7)} = 514\ mg/day$$

Where: 55 ppm = 300 mg/m^3 minimum effect level

8 m^3 = air inhaled during the experiment

5/7 = fraction converting from 5 to 7-day exposure

0.30 = absorption rate

Estimated dosages which adversely affect the liver of humans are 26.87 - 89.7 mg/kg for an exposure period of 2-3 weeks. Two - three weeks exposure is too short a period to estimate an ADI for humans. Furthermore, this was a very crude estimate and the studies were not well controlled. The estimate of 7.34 mg/kg (513.8 mg for a 70 kg adult) as an adverse health effect dose from the rat study appear to be a reasonable level for the calculation of an ADI.

If 7.34 mg/kg dose is accepted as a minimum effect dose, an uncertainty factor of 1,000 can be applied to calculate an ADI. The calculation is:

$$ADI = \frac{7.34\ mg/kg \times 70\ kg}{1000} = 0.514\ mg/day$$

The ADI of TCE using non-carcinogenic data and assuming 100 percent exposure from drinking water is 0.514 mg/day. It should be appropriately reduced if there is also TCE exposure from other sources such as food and air. In case, 100 percent exposure is assumed from drinking, then an adjusted ADI can be calculated as:

$$\text{Adjusted ADI} = \frac{0.514 \text{ mg}}{2 \text{ l}} = 0.257 \text{ mg/l}$$

C. Carcinogenic Effects

Bacterial mutagenesis systems are most commonly used as a screening technique to determine the mutagenic and carcinogenic potential of chemicals. Trichloroethylene was found mutagenic in Salmonella typhimurium strain and the E. coli K 12 strain, utilizing liver microsomes for activation (Greim et al. 1975; 1977). Bartsch et al. (1979) used S-9 fractions from liver specimens for activation instead of microsomes for mutagenesis test. The authors reported trichloroethylene as marginally mutagenic. Waskell (1978) reported trichloroethylene nonmutagenic in Ames test system with activation. The negative response obtained by later research cannot be explained at the present time.

Sacchromyces cerevisiae (yeast), and Fisher rat embryo, have also been used to study mutagenic response. After activation with liver microsomal fractions, trichloroethylene

was mutagenic in strains of yeast such as sacchromyces cervevisiae strains D_4, D_7 and XV185-14C (Bronzetti et al. 1978, Shahin and Von Borstel 1977). Price et al. (1978) tested TCE for in vitro cell transforming potential in a Fisher rat embryo system (F1706). The transformed cells grew in a semisolid agar and produced undifferentiated fibrosarcomas when inoculated into new born Fisher rats.

The National Cancer Institute (NCI) (1976) reported that TCE induced cancer in mice. TCE was administered by oral gavage five times per week for 78 weeks. The time weighted average daily doses were 1,169 and 2,339 mg/kg for male mice and 869 and 1,739 mg/kg for female mice. These tests were conducted using industrial grade (99% pure) TCE on Osborne-Mendel rats and B6C3F1 mice. A complete necropsy and microsc[illegible]aluation were conducted on all the animals (except 7 who died at unscheduled times out of the original 480).

No significant difference was noted in neoplasms between experimental and control groups of rats. However, in both male and female mice, the higher dose induced primary malignant tumors in the liver. For males, 26 of 50 mice who received the low dosage and 31 of the 48 mice who received the high dosage developed hapatocellular carcinomas while only 1 out of 20 of the controls showed neoplasms. In female mice, 4 of

the 50 receiving the low dosage and 11 out of 47 receiving the high dosage developed neoplasms as compared to 0 out of 20 of the controls.

In the NCI study cited above, the test chemical, trichloroethylene, was later found to contain epichlorohydrin - a carcinogen. Therefore, NCI repeated the bioassay with epichlorohydrin-free trichloroethylene. Rats (F344/N) and mice (B6C3F1) of both sexes were used. Trichloroethylene was mixed with corn oil and administered by gavage five times per week for 103 weeks. Rats received dosages of 500 and 1,000 mg/kg. These dose levels were lower than the initial doses used in the earlier bioassay in Osborne-Mendel rats (650 and 1,300 mg/kg for both sexes). As with the rats, the dosage levels used in the mice were lower than in the earlier study. The dose selected for the study in mice was 1,000 mg/kg for both sexes.

Trichloroethylene was not found to be carcinogenic for female F344/N rats. The experiment with male rats was considered inadequate because these rats received dose levels of trichloroethylene which exceeded the maximum tolerated dose. Trichloroethylene was carcinogenic for both sexes of B6C3F1 mice, producing hepatocellular carcinomas in males and females.

D. Quantification of Carcinogenic Effects:

To assist the regulators in making decision for the Control of Chemical Carcionogens in the environment, several scientists have attempted to estimate excess cancer risk on exposure from carcinogens. With respect to contamination of water with carcinogens, the National Academy of Sciences and EPA's Carcinogen Assessment Group (CAG) calculated additional cancer risk estimates.

Using the revised CAG approach and thus the "improved" multi-stage model, it can be estimated that water with TCE concentrations of 280 ug/l, 28 ug/l or 2.8 ug/l would increase the risk of one excess cancer per 10,000; 100,000 or 1,000,000 people exposed, respectively. These estimates were from the NCI bioassay data utilizing TCE contaminated with epichlorohydrin. Since then, NCI-bioassay utilizing epichlorohydrin free TCE has become available, the data form this bioassay has been reviewed and evaluated for carcinogenicity. Epichlorohydrin-free TCE has again been reported to be carcinogenic in mice.

E. QTE Development

Several organizations have attempted to derive acceptable levels of TCE in water. These values are given in Table IX-1. The National Academy of Sciences (1977) estimated excess

cancer risk due to the exposure of humans to TCE in drinking water. They used a multistage model for their calculations. Cancer risk estimate at the upper 95 percent confidence level for 1 ug/l TCE was 0.55×10^{-7}. This translated into a concentration of 45 ug/l for a risk of 10^{-5}. The estimates reported by the EPA's Office of Water Regulation and Standards for an identical risk is 27 ug/l. These calculations take into consideration the average amount of fish consumed daily by an individual. The differences in the two estimates may be attributed to the different mathematical model used, the assumption made for these calculations, such as the consumption of fish by an individual and the animal species used, such as the rat or mouse. The World Health Organization published a tentative guideline level of ug/l. This was based on the NCI mouse data utilizing a linear multistage extrapolation model. It is noteworthy that these risk estimates are made utilizing the total exposure from drinking water. The risk would be proportionally increased if the exposure from air and food is taken into consideration.

Table IX-1. Recommended Concentrations of TCE in Drinking Water

Organization	Non-Carcinogenic Endpoint	Carcinogenic Endpoint
The National Academy of Sciences (1977)	-	-
The National Academy of Sciences (1980)	105 mg/l for 1-day 15 mg/l for 10-day	-
U.S. EPA (OWRS)	6.77 mg/l for lifetime	27 ug/l
U.S. EPA (ODW, HA's)	2 mg/l - 1-day 0.2 mg/l - 10-day 0.080 mg/l for Longer-term	-
World Health Organization		30 ug/l

The Academy (1980) also calculated levels of TCE for a short-term exposure. In these estimations, the carcinogenic potential of TCE was not taken into consideration. They estimated concentrations for one-day and seven-day exposures as 105 mg/l and 15 mg/l, respectively . Their calculations were based on the rough approximation of a toxic dose in an accidental exposure case; it was not a controlled experiment where the subjects were exposed to several dose levels and the no effect dose level was not established. EPA's Office of Water Regulation and Standards established a level of 6.77 mg/l, estimated from TLV of 100 ppm and an average daily consumption 6.5 gm fish by an individual. It is worth mentioning that TLV's are established for healthy adult workers, mostly males and are not recommended for the general public where the population consists of healthy as well as sick subjects of both sexes. They also calculated an alternate level utilizing Van Duuren's study, where a single dose of 2.38 mg/kg/day was used. This study was for a short duration and should not be used for estimating a lifetime acceptable level.

The Office of Drinking Water issued a Health Advisory (formerly called SNARL) in 1977. This Health Advisory estimated negligible risk levels of 1-day, 10-day and longer-term as 2 mg/l, 0.2 mg/l and 0.080 mg/l, respectively. Since then, more data have become available, therefore, these levels

should be evaluated and revised, if necessary. It should be remembered that these health advisories were established for transient exposures, they do not take cancer risk estimate into consideration, and do not incorporate the exposure of humans to TCE from sources such as food and air.

Use of a two year feeding study, in at least two experimental animals, one of them being a rodent, would be the best means of calculating an ADI. Since these data are not available, an attempt has been made and an ADI of 0.514 mg/day has been calculated from a 3-month inhalation study in rats.

Since, it is assumed that humans consume about two liters of water per day, the adjusted ADI, would be:

$$\text{Adjusted ADI} = \frac{0.514 \text{ mg}}{2 \text{ l}} = 0.257 \text{ mg/l}$$

The carcinogenic potential of TCE was not taken into consideration in the above calculations for the ADI, however, this aspect of adverse health effects should not be ignored. There is limited evidence concerning the carcinogenicity of TCE.

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