AMBIENT WATER QUALITY CRITERIA FOR

TRICHLOROETHYLENES

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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Aquatic Life Toxicology

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CRITERIA DOCUMENT

TRICHLOROETHYLENE

CRITERIA

Aquatic Life

The available data for trichloroethylene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 45,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of trichloroethylene to sensitive freshwater aquatic life but adverse behavioral effects occur to one species at concentrations as low as 21,900 µg/l.

The available data for trichloroethylene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of trichloroethylene to sensitive saltwater aquatic life.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of trichloroethylene through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 27 µg/l, 2.7 µg/l, and 0.27 µg/l, respectively.

TABLE OF CONTENTS

	Page
Criteria Summary	
Introduction	A-1
Aquatic Life Toxicology	B-1
Introduction	B-1
Effects	B-1
Acute Toxicity	B-1
Chronic Toxicity	B-2
Plant Effects	B-2
Residues	B-2
Miscellaneous	B-3
Summary	B-3
Criteria	B-3
References	B-9
Mammalian Toxicology and Human Health Effects	C-1
Exposure	C-1
Ingestion from Water	C-1
Ingestion from Food	C-1
Inhalation	C-3
Dermal	C-4
Pharmacokinetics	C-4
Absorption	C-4
Distribution	C-5
Metabolism	C-8
Excretion	C-12
Effects	C-13
Acute, Subacute, and Chronic Toxicity	C-13
Synergism and/or Antagonism	C-19
Teratogenicity	C-21
Mutagenicity	C-21
Carcinogenicity	C-23
Criterion Formulation	C-27
Existing Guidelines and Standards	C-27
Basis and Derivation of Criterion	C-27
References	C-33
Appendix	C-47

If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 807 μg/l, 80.7 μg/l, and 8.07 μg/l, respectively.

INTRODUCTION

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

TCE has a molecular weight of 131.4; a water solubility of 1,000 μg/ml; a vapor pressure of 77 mm Hg and a melting point of 83°C (Patty, 1963). Its relative chemical stability, non-flammability, volatility and poor water solubility make TCE a very useful solvent.

Annual production of TCE in the United States approximates 234,000 metric tons (40 FR 48907). The volatilization of TCE during production and use is the major source of environmental levels of this compound. TCE has been detected in air, in food, and in human tissues (Pearson and McConnell, 1975). Its detection in rivers, municipal water supplies, the sea, and aquatic organisms indicate that TCE is widely distributed in the aquatic environment (McConnell, et al. 1975; Pearson and McConnell, 1975; U.S. EPA, 1978).

TCE is not expected to persist in the environment because of its rapid photooxidation in air, its low water solubility and its volatility (Pearson and McConnell, 1975; Dillings, et al. 1976; Patty, 1963).

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Aquatic Life Toxicology*

INTRODUCTION

No data on the effects of trichloroethylene on freshwater aquatic life were published prior to 1978, and consequently the data base is quite limited.

There are few data on the effects of trichloroethylene on saltwater organisms. There was a 50 percent decrease in ^{14}C uptake by the alga *Phaeodactylum tricornutum* at a concentration of 8,000 µg/l (Pearson and McConnell, 1975). Borthwick (1977) exposed sheepshead minnows and grass shrimp to 20,000 and 2,000 µg/l, respectively, and observed erratic swimming, uncontrolled movement, and loss of equilibrium after several minutes. No other data for saltwater organisms were found.

EFFECTS

Acute Toxicity

The 48-hour EC_{50} value for *Daphnia magna* and trichloroethylene is 85,200 µg/l (Table 1). When comparisons were made (Canton and Adema, 1978) among three laboratories, the 50 percent effect concentrations for *Daphnia magna* ranged from 41,000 to 100,000 µg/l. Within one laboratory, *Daphnia pulex* was also tested to determine any difference in sensitivity, and the results were 39,000 and 51,000 µg/l indicating no difference in sensitivity between species.

Alexander, et al. (1978) tested fathead minnows in flow-through tests with measured concentrations and in static tests without measuring the expo-

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

sure concentrations. The LC_{50} values were 40,700 and 66,800 µg/l, respectively. The bluegill has also been tested in static tests with unmeasured concentrations (U.S. EPA, 1978), and the 96-hour LC_{50} value is 44,700 µg/l.

The data on acute static tests with the bluegill under comparable conditions (U.S. EPA, 1978) in this and other criteria documents on structurally related chemicals show a correlation between toxicity and degree of chlorination. The 96-hour LC_{50} values for this species are 73,900 and 135,000 µg/l for 1,1- and 1,2-dichloroethylene, respectively, 44,700 µg/l for trichloroethylene, and 12,900 µg/l for tetrachloroethylene. These results indicate an increase in the lethal effect on bluegills with an increase in chlorine content. The correlation of toxicity for *Daphnia magna* is not as clear. The 48-hour LC_{50} values are 79,000, 85,200, and 17,700 µg/l for 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene, respectively (U.S. EPA, 1978).

Chronic Toxicity

No chronic tests have been conducted with any freshwater or saltwater species.

Plant Effects

Pearson and McConnell (1975) exposed the saltwater alga, *Phaeodactylum tricornutum*, to trichloroethylene. There was a 50 percent decrease in ^{14}C uptake at a concentration of 8,000 µg/l (Table 2).

Residues

Bioconcentration by bluegill was studied (U.S. EPA, 1978) using radiolabeled trichloroethylene, and after 14 days the bioconcentration factor was 17 (Table 3). The half-life of this compound in tissues was less than one day. Such bioconcentration and biological half-life data suggest no residue problem will occur at exposure concentrations that are not directly toxic to aquatic life.

Miscellaneous

After 96 hours loss of equilibrium was exhibited by 50 percent of fathead minnows exposed to trichloroethylene at a concentration of 21,900 µg/l (Table 4). This effect occurred at a lower concentration than the lethal effects discussed previously (Table 1).

Grass shrimp and the sheepshead minnow demonstrated erratic swimming, uncontrolled movement, and loss of equilibrium after several minutes of exposure to 2,000 and 20,000 µg/l of trichloroethylene, respectively (Table 4).

Summary

Two freshwater cladocerans, *Daphnia magna* and *Daphnia pulex*, have been exposed to trichloroethylene, and the species acute values are 64,000 and 45,000 µg/l, respectively. These species are of similar sensitivity as the fathead minnow and the bluegill (96-hour LC_{50} values from 40,700 to 66,800 µg/l). When exposed to a lower concentration, 21,900 µg/l, there was a loss of equilibrium by the fathead minnow. The bioconcentration factor for the bluegill was 17 with a tissue half-life of less than one day.

Of the saltwater species tested, there were signs of erratic swimming, uncontrolled movement, and loss of equilibrium after several minutes of exposure to 2,000 µg/l by the grass shrimp and 20,000 µg/l by the sheepshead minnow. There was also a 50 percent decrease in ^{14}C uptake by a saltwater alga at 8,000 µg/l trichloroethylene.

CRITERIA

The available data for trichloroethylene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 45,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of

trichloroethylene to sensitive freshwater aquatic life, but adverse behavioral effects occur to one species at concentrations as low as 21,900 µg/l.

The available data for trichloroethylene indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2,000 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of trichloroethylene to sensitive saltwater aquatic life.

Table 1. Acute values for trichloroethylene

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	85,200	--	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	100,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia magna*	S, U	94,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia magna*	S, U	41,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia magna*	S, U	43,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia magna*	S, U	55,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia magna*	S, U	56,000	64,000	Canton & Adema, 1978
Cladoceran, *Daphnia pulex*	S, U	51,000	--	Canton & Adema, 1978
Cladoceran, *Daphnia pulex*	S, U	39,000	45,000	Canton & Adema, 1978
Fathead minnow, *Pimephales promelas*	FT, M	40,700	--	Alexander, et al. 1978
Fathead minnow, *Pimephales promelas*	S, U	66,800	40,700	Alexander, et al. 1978
Bluegill, *Lepomis macrochirus*	S, U	44,700	44,700	U.S. EPA, 1978

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Plant values for trichloroethylene (Pearson & McConnell, 1975

Species	Effect	Result (µg/l)
	FRESHWATER SPECIES	
Alga, *Phaeodactylum tricornutum*	50% decrease in uptake of ^{14}C during photosynthesis	8,000

Table 3. Residues for trichloroethylene (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	17	14

Table 4. Other data for trichloroethylene

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Fathead minnow, *Pimephales promelas*	96 hrs	Loss of equilibrium EC50	21,900	Alexander, et al. 1978
		SALTWATER SPECIES		
Grass shrimp, *Palaemonetes pugio*	96 hrs	*	2,000	Borthwick, 1977
Sheepshead minnow, *Cyprinodon variegatus*	96 hrs	*	20,000	Borthwick, 1977

* Intoxication for both fish and shrimp characterized by erratic swimming, uncontrolled movement, and loss of equilibrium after several minutes of exposure.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The National Organics Monitoring Survey observed trichloroethylene (TCE) in 4 of 112 drinking waters at a mean concentration of 11 μg/l in March-April 1976, in 28 of 113 cities averaging 2.1 μg/l in May-July 1976, and 19 of 105 cities averaging 1.3 μg/l in November 1976 - January 1977 (U.S. EPA, 1978a). TCE in waters may occur as a result of direct contamination or from atmospheric contamination by rainfall (Pearson and McConnell, 1975). TCE may also be formed during the chlorination of water ,National Academy of Sciences (NAS), 1977; Bellar, et al. 1974..

Ingestion from Food

There is little information concerning the occurrence of TCE in foodstuffs. Because of its high partition coefficient (195:1) in an octanol-water system, TCE is expected to bioaccumulate in fatty tissue. This has been borne out with a test exposure of bluegill fish which show a bioconcentration factor of 17 for TCE relative to the water in the controlled test environment (U.S. EPA, 1978b). In England, TCE has been observed at concentrations up to 10 μg/kg in meats, and up to 5 μg/kg in fruits, vegetables, and beverages (McConnell, et al. 1975). Packets of tea were found to contain 60 μg TCE/kg. Little TCE would be expected in other foodstuffs except in the case where TCE is used as a solvent for food extractions (Fishbein, 1976). Current maximum allowable concentrations of TCE in these foods are 10 mg/kg in instant coffee, 25 mg/kg in ground coffee, and 30 mg/kg in spice extracts (21 CFR 121:1041).

Some manufacturers are now using methylene chloride rather than TCE for decaffeinating coffee (Waters, 1977). It is unlikely that significant exposures in the general population would be encountered by these sources because of the high volatility of TCE.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady state bioconcentration factor of 17 was obtained for trichloroethylene using bluegills containing about one percent lipids (U.S. EPA, 1978b). An adjustment factor of 3.0/4.8 = 0.695 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is

the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for trichloroethylene, and the edible portion of all aquatic organisms consumed by Americans, is calculated to be 17 x 0.625 = 10.6.

Inhalation

By far the most serious exposures of humans to TCE are confined to a relatively small industrial population (Fishbein, 1976). Currently the Threshold Limit Value (TLV)* adopted for TCE by the American Conference of Governmental Industrial Hygienists is 535 mg/m^3 (100 ppm) (ACGIH, 1977). Assuming a 10 m^3 tidal volume for an 8-hour day would result in a daily exposure of 5,350 mg/day during the work week, which would greatly exceed that derived from food and water exposures under ordinary circumstances. Other inhalation exposures would be associated with the use of products containing TCE, such as cleaning fluids (Waters, et al. 1977). There are insufficient data to make a quantitative assessment of exposure from such products. The hazards of such exposure would more often be acute because of their sporadic rather than long-term use as in the industrial setting.

*"Threshold limit values adopted for TCE by the American Conference of Governmental Industrial Hygienists refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Because of wide variations in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a small percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness." (ACGIH, 1977).

A problem encountered with the use of TCE as an anesthetic (Defalque, 1961) is the formation of breakdown products with high degrees of toxicity, such as phosgene and dichloroacetylene (Goodman and Gilman, 1966). Likewise, similar problems may occur in certain industrial circumstances where the liquid or vapor may come into contact with hot surfaces or be exposed to ultraviolet radiation (as from inert gas metal arc welding) (Rinzema, 1971). The occurrence of such compounds complicates epidemiological assessments of TCE effects in the workplace.

Dermal

Stewart and Dodd (1964) conducted controlled human studies which demonstrated rapid absorption of TCE through intact human skin. They concluded, however, that skin exposure is insignificant relative to inhalation exposure and that, during normal industrial use, there is little likelihood that toxic amounts of TCE will be absorbed through the skin. It seems reasonable to conclude that dermal absorption could make little additional contribution to that obtained through either inhalation or ingestion.

PHARMACOKINETICS

Absorption

TCE is readily absorbed by all routes of exposure. This would be predicted upon the basis of its physical and chemical properties (Goldstein, et al. 1974). Most human data concerning TCE absorption has been obtained with inhalation as the route of exposure because of interest in the compound as an industrial toxicant and its use as an anesthetic. Stewart, et al. (1962) reported TCE concentrations of 4.5 mg/l to 7 mg/l of blood within two hours of exposing

volunteers to a time-weighted average concentration of 1,420 mg/m^3 (range: 856-2,140 mg/m^3). Concentrations did not rise further with time, implying a rapid approach to steady-state with inhalation exposures. Retention of inhaled TCE has been estimated to approximately 36 percent by Nomiyama and Nomiyama (1971). Monster, et al. (1976) presents a range of 28 to 74 percent as compiled from several reports.

Absorption of TCE following ingestion has not been studied in humans. In rats, 72 to 85 percent and 10 to 20 percent of the total orally administered dose could be accounted for in expired air and urine, respectively, with less than 0.5 percent appearing in the feces (Daniel, 1963). This indicates that at least 80 percent (and probably more) of ingested TCE is systemically absorbed.

Stewart and Dodd (1964) detected up to 2.7 mg/m^3 TCE in alveolar air following immersion of an individual's thumb in TCE for 30 minutes. Although the data are insufficient to calculate rate of absorption through the skin, they demonstrate rapid absorption of TCE through intact human skin.

Distribution

The distribution patterns of TCE in the body approximate those that would be expected on the basis of its chemical and physical properties (Goldstein, et al. 1974). Based on its partition coefficient of 195 to 1 in an octanol/water system (log P = 2.29), TCE is expected to bioaccumulate slightly in fatty tissue. The distribution of TCE in various tissues as compared to fat, for both man (McConnell, et al. 1975) and animals (Fabre and Truhaut, 1952) are given in Tables 1 and 2, respectively. In guinea pigs nearly

TABLE 1

Concentration of TCE in Human Tissues at Autopsy*

Subject	Age/Sex	Tissues	Concentration (ug/kg wet tissue)
A	76/F	Body fat	32
		Kidney	<1
		Liver	5
		Brain	1
B	76/F	Body fat	2
		Kidney	3
		Liver	2
		Brain	<1
C	82/F	Body fat	1.4
		Liver	3.2
D	48/M	Body fat	6.4
		Liver	3.5
E	65/M	Body fat	3.4
		Liver	5.2
F	75/M	Body fat	14.1
		Liver	5.8
G	66/M	Body fat	4.6
H	74/F	Body fat	4.9

*Source: McConnell, et al. 1975

TABLE 2

Distribution of TCE in Guinea Pigs*

	Concentration (mg/100 g fresh tissue)			
Organ	TCE[1]	TCE[2]	TCE[3]	TCE[4]
Adrenals	-	3.4	2.2	3.8
Blood	1.3	1.0	0.5	0.8
Brain	0.5	0.7	0.9	1.0
Fat	3.1	3.5	3.9	3.8
Kidney	2.2	0.8	1.4	1.8
Liver	0.8	0.5	1.0	0.6
Lungs	0.8	1.2	0.7	0.8
Muscle	-	0.5	0.2	0.2
Ovaries	-	2.3	2.3	-
Spleen	1.7	1.9	1.3	0.9
Urine	-	3.5	3.1	2.6

*Source: Fabre and Truhaut, 1952

[1] Inhalation of 9 mg/l, 4 hr/day for 5 days; total 20 hr.
[2] Inhalation of 6 mg/l, 4.5 hr/day for 13 days; total 58.5 hr.
[3] Inhalation of 6 mg/l, 5 hr/day for 19 days; total 95 hr.
[4] Inhalation of 7 mg/l, 5 hr/day for 23 days; total 115 hr.

equivalent concentrations are observed in the adrenals and fat; ovaries tend to accumulate about 50 percent; and other tissues about 25 percent of the TCE concentration observed in fat (Table 2).

Laham (1970) demonstrated transplacental diffusion of TCE in humans. The ratio of fetal blood concentrations to maternal blood concentrations varied between 0.52 and 1.90.

Metabolism

The metabolism of TCE appears to be central to its long-term deleterious effects. In a qualitative sense, metabolism of TCE appears similar across species (Ikeda and Ohtsuji, 1972; Kimmerle and Eben, 1973a,b). The principal products of TCE metabolism measured in urine are trichloroacetaldehyde, trichloroethanol, and conjugated derivatives (glucuronides) of trichloroethanol. The metabolite trichloroethanol has been suggested as being responsible for long-term CNS effects of TCE inhalation (Ertle, et al. 1972). In terms of reported carcinogenic and mutagenic effects of TCE, intermediary metabolites rather than the final products of the pathway are of paramount importance. Daniel (1963) suggested the pathway presented in Figure 1 for TCE metabolism.

The essential feature of this pathway is the formation of a reactive epoxide, trichloroethylene oxide, which can alkylate nucleic acids and proteins (Van Duuren and Banerjee, 1976; Bolt and Filser, 1977). Such covalent binding can be increased with epoxide hydrase inhibition (Van Duuren and Banerjee, 1976). As can be seen, the formation of trichloroacetaldehyde (Byington and Leibman, 1965) requires rearrangement of chlorine atoms (Henschler, 1977).

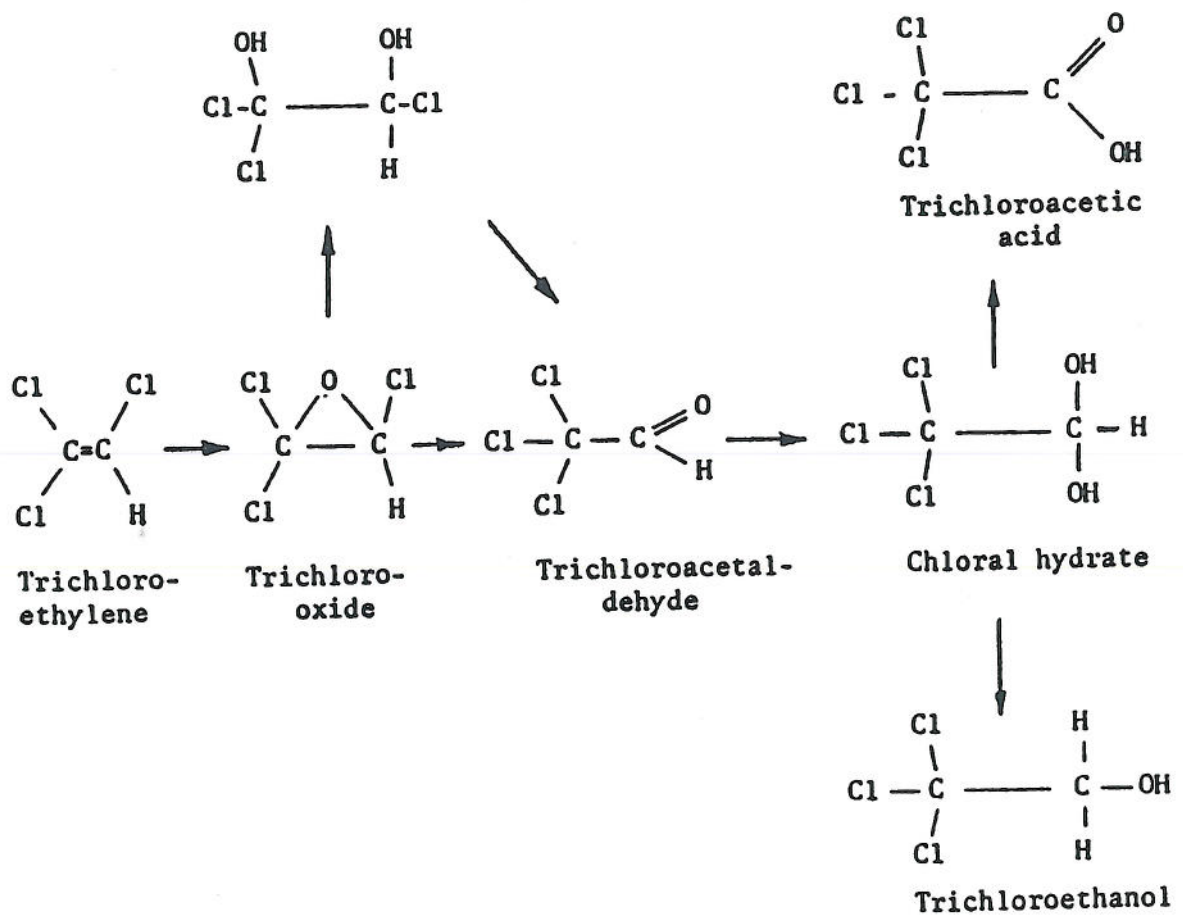

FIGURE 1

TCE Metabolism*

*Source: Daniel, 1963

The measurement of specific activities of trichloroacetic acid and trichloroethanol following oral administration to rats of radiolabeled TCE indicates that this rearrangement is intramolecular and not an exchange with the body chloride pool (Daniel, 1963). The importance of this observation is that it is not observed with thermal rearrangements in vitro (Greim, et al. 1975). Although urinary excretion of trichloroethanol precedes excretion of trichloroacetic acid following exposure, it is clear that this is not a precursor-product relationship since trichloroethanol is poorly converted to trichloroacetic acid in vivo (Daniel, 1963). Rather, the earlier and more extensive excretion of trichloroethanol appears to result from a more rapid conversion of trichloroacetaldehyde to trichloroethanol than the conversion of trichloroacetaldehyde to trichloroacetic acid (Ikeda and Imamura, 1973).

There is one report indicating that the pattern of metabolism of TCE in humans differs according to sex (Nomiyama and Nomiyama, 1971). Within the first 24 hours of exposure to 1,345-2,044 mg/m^3 in air, females tend to excrete more trichloroacetic acid and less trichloroethanol than males. Similarly, the ratio between trichloroethylene exposure and urinary trichloroacetic acid excretion appears to decrease with age (Grandjean, et al. 1955). If the toxicity of TCE is dependent upon its metabolism, these data would suggest the possibility of age and sex differences in susceptibility to the adverse effects of TCE.

Phenobarbital administration to rats or hamsters in vivo increases the oxidation of TCE. This results in an increase in the conversion of trichloroethylene to trichloroacetaldehyde (Ikeda

and Imamura, 1973). No differences were observed in the conversion of trichloroacetaldehyde to trichloroacetic acid or trichloroethanol. Despite induction of microsomal enzymes, conversion of TCE to trichloroacetaldehyde appears to remain as the rate limiting step. As predicted by the increased activity of alcohol dehydrogenase (Friedman and Cooper, 1960), the total trichloroethanol excretion is increased to a greater extent than trichloroacetic acid excretion by phenobarbital pretreatment (Leibman and McAllister, 1967). It is notable that oxidation of trichloroethylene is reduced effectively by the alcohol dehydrogenase inhibitor tetraethyl-thiuram disulfide (Disulfiram) (Bartonicek and Teisinger, 1962). Muller, et al. (1975) observed blood levels of TCE in volunteers inhaling TCE and concurrently ingesting ethanol to be 2.5 times higher than in the absence of ethanol; the TCE level in brain can be expected to exhibit an equivalent increase. These authors suggest that this accumulation of TCE (postulated to result from complete depression by ethanol of TCE oxidation) may be responsible for the ethanol intolerance observed in workers exposed to TCE. On the other hand, Ertle, et al. (1972) believe formation and accumulation of trichloroethanol to be responsible for the "psycho-organic syndrome" encountered during occupational exposure to TCE. Trichloroethanol is said to be at least three times more potent than TCE on a variety of measures of central nervous system activity (Mikiskova and Mikiska, 1966). Ethanol has been shown to increase the rate of reduction of chloral hydrate to trichloroethanol in humans (Sellers, et al. 1971) and in experimental animals (Gessner, 1973; Kaplan, et al. 1969), thus an alternative explanation to that of Muller, et al.

(1975) is offered for TCE-ethanol interactions. If trichloroethanol is the agent responsible for chronic central nervous system toxicity, inducers of microsomal enzymes in general might be expected to have a synergistic effect on the toxicity of TCE. The study of the effect of microsomal induction on hepatotoxicity has not yielded consistent results across laboratories (Cornish, et al. 1973; Carlson, 1974; Moslen, et al. 1977a). The differences in these results appear to be attributable to the different modes of administration of TCE. Inhalation of one percent (v/v) in air resulted in increased hepatotoxicity subsequent to phenobarbital pretreatment, whereas the effects of intraperitoneal injections of up to 2 ml TCE/kg were not enhanced by such pretreatment. These results may be complicated by the fact that high doses of TCE deactivate microsomal enzyme systems (Moslen, et al. 1977a).

Excretion

The biological half-life of TCE and its metabolites has been examined in humans and experimental animals. In the rat (male, SPF-Wistar II), concentrations of TCE in expired air were undetectable eight hours after inhalation of TCE at concentrations of up to 330 ppm (Kimmerle and Eben, 1973a). After administration by stomach tube of ^{36}Cl-labeled TCE to Wistar rats, 72 to 85 percent of the radioactivity (presumably primarily TCE) was recovered in the expired air with a half-life of five hours (Daniel, 1963). In humans, inhaled TCE is rapidly absorbed from the lungs, with 28 to 74 percent being retained and metabolized in the body (Monster, et al. 1976). Four hours after acute exposure to approximately 215 mg/m^3, TCE was undetectable in the blood. On the other hand, tri-

depressant activities of TCE. They are of little value in assessing the possibility of longer term cumulative and perhaps irreversible effects on nervous system function which have been suggested by epidemiological studies (Grandjean, et al. 1955; Nomiyama and Nomiyama, 1977). They do suggest, however, that the TLV for TCE (535 mg/m^3) has been established at a level very close to the threshold for the acute effects of TCE on healthy adult male volunteers.

In an epidemiological study, Grandjean, et al. (1955) obtained evidence of increased nervous system disorders in occupational exposures to the compound of 5 to 15 years duration; concentrations measured at the time of the study averaged below the TLV. Nomiyama and Nomiyama (1977) also report headaches in workers exposed to TCE concentrations as low as 144 mg/m^3. Bardodej and Vyskoch (1956) reported insomnia, tremors, severe neurasthenic syndromes coupled with anxiety states, and progressive bradycardia following occupational exposure to levels of TCE ranging from 160 to 3,400 mg/m^3. Disturbances of the nervous system were reported to continue for up to at least one year after final exposure. Such studies have inherent problems in relating effects directly to TCE exposure because historical data is lacking and the possible compound contaminants or breakdown products are not known. Questions raised by these data have not been adequately addressed in controlled studies in humans or experimental animals.

TCE also carries some abuse potential, documented by cases of deliberate and repetitive inhalation (James, 1963; Ikeda and Imamura, 1973). In occupational settings, this abuse has resulted in

inability to sleep on off-days without inhalation of TCE (Bardodej and Vyskoch, 1956). TCE abuse has been associated with hepatorenal toxicity (Clearfield, 1970). Death following massive acute inhalation exposure is most commonly due to respiratory and cardiac failure (Smith, 1966).

Studies of effects of TCE on the nervous system of experimental animals have been extremely limited, and are confined to behavioral and histopathological studies. Behavioral studies have generally confirmed that the CNS depressant activity of TCE observed in man occurs in rats following roughly equivalent exposures (Khorvat and Formanek, 1959; Goldberg, et al. 1964a,b). CNS effects are reversible in rats following three to four week exposures to an average concentration of 670 mg/m^3 TCE for four hours per day, five days per week (Goldberg, et al. 1964b). Bartonicek and Brun (1970) demonstrated the loss of Purkinje cells with associated basket cells in the cerebellum, and other less specific damage to the telencephalic cortex, basal ganglia and brain stem nuclei in rabbits after intramuscular injections of TCE at a level of 4.38 g/animal, three times a week for four weeks. Similar alterations had been described by Bernardi, et al. (1956) in rabbits exposed by inhalation to 9,530 mg/m^3 TCE for 20 to 30 days, and by Baker (1958) in dogs exposed to 1,600 to 2,700 mg/m^3 TCE. Evidence of such permanent damage has been reported only with high doses for relatively short periods of time. As mentioned above, the long-term, low dose effects of TCE on the central nervous system have not been well evaluated.

chloroethanol, a major metabolite, persisted in the blood for several hours. TCE and its metabolites are excreted in exhaled air, urine, sweat, feces, and saliva (Kimmerle and Eben, 1973). TCE is lost from the body with a half-time of about 1.5 hours (Stewart, et al. 1962). Trichloroacetic acid, trichloroethanol and the glucuronide of trichloroethanol are excreted more slowly. The biological half-life measured in urine of humans has ranged from 12 to 50 hours for trichloroethanol and from 36 to 73 hours for trichloroacetic acid (Ikeda and Imamura, 1973; Ertle, et al. 1972). Excretion of trichloroethanol and its glucuronide increase linearly with exposure to TCE. However, the rate of excretion of trichloroacetic acid increases linearly with inhalation exposures up to 268 mg/m^3 but tends to level out with higher exposures in humans (Ikeda and Imamura, 1973). These data in humans are consistent with kinetics of conversions of trichloroacetaldehyde to trichloroethanol and trichloroacetic acid in rats (Ikeda, et al. 1970).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Classically, TCE is known as a central nervous system depressant. Trichloroethylene has been used in medicine as a general anesthetic (Defalque, 1961), but this use has declined because of impurities formed when TCE comes into contact with soda lime used as a carbon dioxide absorbent in respiratory equipment used in surgery. Dichloroethylene, one of the compounds thus formed, produces cranial nerve palsies (Goodman and Gilman, 1966).

Although the clinical picture is predominated by the direct CNS depression produced by high exposures to TCE, there is evidence

of longer term CNS effects resulting from TCE exposure (Grandjean, et al. 1955). There is some justification for suspecting that these effects may arise from metabolites of TCE. Chloral hydrate and trichloroethanol are metabolites known to affect the nervous system (Ertle, et al. 1972). Since chloral hydrate does not ordinarily accumulate with TCE exposures (Leibman and McAllister, 1967; Cole, et al. 1975) and because trichloroethanol produces marked central nervous system effects (Cabana and Gessner, 1970; Kriegl-stein and Stock, 1973), the latter compound has been implicated as being responsible for the longer term CNS effects of TCE.

Psychomotor function and subjective responses to TCE have been studied in short-term, controlled human clinical studies. Stewart, et al. (1970) reported mild fatigue and sleepiness in normal adults after four to five days of exposure to 1,070 mg/m^3 for seven hours a day. Stopps and McLaughlin (1976) observed a progressive decline in psychomotor function of one adult male following exposure to concentrations of TCE of 1,070 mg/m^3 and higher for a period of less than three hours. In a larger study involving six male students exposed to two 4-hour exposures of TCE in one day, at an average concentration of 590 mg/m^3, Salvini, et al. (1971) demonstrated a statistically significant decrease in performance ability. Nomiyama and Nomiyama (1977) reported headaches in healthy male students exposed to TCE at 433 mg/m^3 for four hours a day for six days, but were unable to demonstrate effects on a flicker fusion test or on two point discrimination even at 1,070 mg/m^3 TCE. These studies, however, are of such short duration that they are measuring primarily the threshold for the general central nervous system

Prolonged occupational exposures to TCE have been associated with impairment of peripheral nervous system function. Persistent neuritis (Bardodej and Vyskoch, 1956), and temporary loss of tactile sense and paralysis of the fingers after direct contact with the solvent (McBirney, 1954) have been reported.

Use of TCE as an anesthetic has been associated with toxicity to a number of other organ systems. This literature has been reviewed by Defalque (1961). Cardiac arrhythmias including bradycardia, auricular and ventricular premature contractions, and ventricular extrasystoles have been reported. The dose-response relationships for these effects have not been established in man or experimental animals.

Fatal hepatic failure has been observed following use of TCE as an anesthetic. This effect generally has been observed in patients with complicating conditions such as malnutrition, toxemias, and burns, or those who had received transfusions (Defalque, 1961). Liver failure in experimental animals is marked by generalized binding of TCE metabolites to proteins and nucleic acids (Bolt and Filser, 1977). In contrast to vinyl chloride, binding of TCE metabolites appears to involve binding to free amino groups as well as to sulfhydryl groups. Binding of TCE metabolites and its hepatotoxic effects have been reported to increase with induction of microsomal mixed function oxidases (MFO) and treatment with 1,2-epoxy-3,3,3-trichloropropane, an inhibitor of epoxide hydrase. These findings are somewhat complicated by the fact that liver necrosis and reduction in liver glutathione were not acutely produced by inhaled TCE without pretreatment with phenobarbital

(Adams, et al. 1951; Moslen, et al. 1977b). Glutathione conjugates have not been identified as metabolites of TCE, although they have been suggested (Reynolds and Moslen, 1977). Glutathione acts to protect against oxidative damage to tissues (DeBruin, 1976). This makes it difficult to rationalize TCE hepatotoxicity resulting simply from increased rates of metabolism, since a scavenging role for glutathione cannot be invoked as a protective mechanism as it has been for chloroform (Docks and Krishna, 1976). It is possible that the decreased glutathione represents increased peroxidative activity with combined phenobarbital and TCE treatment (Ullrich, 1975). On the other hand, increased serum glutamate-oxaloacetate transaminase activity (also indicative of hepatotoxicity) may be induced by injected TCE, but the effect is not enhanced by phenobarbital pretreatment (Cornish, et al. 1973). Despite these reports which used high doses in experimental animals and described toxicity in humans exposed to anesthetic doses of TCE, liver damage in the industrial setting appears to be rare (Bardodej and Vyskoch, 1956). Hepatotoxic defects have been difficult to produce in experimental animals given acute subanesthetic doses for up to eight weeks (Kylin, et al. 1963). Even longer duration exposures at levels up to 17,000 mg/m^3 have failed to produce more than a low incidence of fatty infiltration of the liver (Kylin, et al. 1965). However, hepatic damage was observed in cases of repeated abuse of TCE (Huff, 1971).

Renal failure has been an uncommon problem with TCE anesthesia (Defalque, 1961). Although depressed kidney function can be documented with TCE exposure in experimental animals, it requires very

high doses (Klaasen and Plaa, 1967), and on a relative basis TCE is a much less potent renal toxin than chloroform or carbon tetrachloride. Renal damage has been reported in fatal cases involving TCE abuse (Huff, 1971).

Industrial use of TCE is often associated with dermatological problems (Bauer and Rabens, 1974). Most often this is a result of direct skin contact with the concentrated solvent and is probably limited to those effects secondary to solvent action. No such effects have been reported for exposures to dilute aqueous solutions of TCE.

TCE, along with a number of other low molecular weight chlorinated compounds, greatly increases bile duct-pancreatic fluid flow in rats (Hamada and Peterson, 1977). The fluid is considerably altered in protein and in ionic composition. The physiological significance of this alteration is presently unknown.

Synergism and/or Antagonism

Long-term toxicity of TCE appears to depend largely on its metabolic products. Consequently, other chemicals which enhance or inhibit steps in the metabolism of TCE will act to either increase or decrease its toxicity. Many drugs, e.g., phenobarbital, and environmental chemicals, e.g., PCB, induce the mixed function oxidase system. These compounds have been observed to act synergistically with TCE to produce liver damage (Carlson, 1974; Moslen, et al. 1977b; Reynolds and Moslen, 1977). Rats exposed to 37,000, 42,000, and 56,000 mg/m^3 TCE vapor, respectively, for two hours showed elevated activities of serum glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and isocitrate dehydrogenase.

Hepatotoxicity, as indicated by increased levels of these hepatic enzymes in the serum, was greatly enhanced by pretreatment with the metabolic inducers phenobarbital and 3-methylchlolanthrene (Carlson, 1974). The latter finding suggests that a metabolite of TCE contributes to its toxicity. Metabolism of TCE shares some common enzymatic steps with the metabolism of ethanol. While TCE inhibits oxidation of ethanol, ethanol appears to enhance formation of trichloroethanol from TCE (Gessner, 1973; Cabana and Gessner, 1970). Enhanced toxicity of TCE and its metabolic products has been observed with ethanol ingestion in both man (Bardodej and Vyskoch, 1956; Seage and Burns, 1971) and experimental animals (Cornish and Adefuin, 1966; Ferguson and Vernon, 1970; Gessner and Cabana, 1970).

TCE has also been reported to sensitize the myocardium to arrhythmias induced by epinephrine (Dhuner, et al. 1957). This has been observed following accidental ingestion of TCE and has proven fatal in some cases (Defalque, 1961). Since chloral hydrate-associated arrhythmias may also involve adrenergic stimulation, TCE sensitization may result from metabolites of TCE rather than from TCE itself (DiGiovanni, 1969).

The central nervous system depressant activity of TCE could possibly be additive with the effects of other central nervous system depressants and generally antagonistic towards stimulants (Defalque, 1961). However, the latter would be primarily symptomatic antagonists having little relationship to underlying toxicity of the compound, particularly long-term toxicity.

Chloral hydrate has been reported to enhance the anticoagulant effects of warfarin (Koch-Weser and Sellers, 1971) and bishydroxycoumarin (Beliles and Foster, 1974). The potentiation is apparently associated with a displacement of the anticoagulants from plasma albumin by trichloroacetic acid (Sellers and Koch-Weser, 1970), as evidenced by a shortened warfarin half-life. Many other drugs bind to albumin and may be displaced by trichloroacetic acid resulting in a potentiation of their usual pharmacological properties (Ertle, et al. 1972). As pointed out earlier, trichloroacetic acid is a metabolite of TCE. Consequently, TCE exposures may have the potential of synergizing the effects of anticoagulant drugs.

Teratogenicity

Trichloroethylene has not been shown to be a teratogen. Exposure of mice and rats to 1600 mg/m TCE on days 6 through 15 of gestation for seven hours a day did not produce teratogenic effects in mice or rats (Schwetz, et al. 1975). Although not statistically significant, there was evidence of hemorrhages in the cerebral ventricles (2/12 litters) and cases of undescended testicles (2/12 litters) observed in the offspring of TCE-treated mice. These effects were observed seldomly or not at all in the other experimental groups (1/90 otherwise treated or control litters for hemorrhage in cerebral ventricles, 0/90 for undescended testicles). This appears to be the only teratogenesis study conducted with TCE.

Mutagenicity

TCE has been reported to possess mutagenic activity in a number of bacterial strains. In many mutagenicity tests, however, technical grade TCE, in which epichlorohydrin and epoxybutane were

present, was used. Epichlorohydrin and epoxybutane have been shown to be mutagenic in microorganisms. Greim, et al. (1975) demonstrated reverse mutations in E. coli K12 at a concentration of 3.3 mM (434,000 µg/l) TCE in the incubation media in the presence of phenobarbital-induced mouse liver microsomes. The highest mutation frequency (2.32 times spontaneous mutation rate) was seen in the arg^+ back mutation system. Simmon, et al (1977) found that in the presence of Arochlor 1254® induced-Sprague Dawley rat liver microsomes, or $B6C3F_1$ mouse liver microsomes, 6 mM to 22 mM (789,091 µg/l to 2,893,333 µg/l) TCE exposure in a dessicator increased the S. typhimurium (TA100) revertant rate. Similar observations have been made in the yeast Saccharomyces cerevisiae (Strain XV 185-14C) in the presence of mouse liver microsomal mixture. Concentrations of 10 µl/ml and 20 µl/ml (14.5 g/l to 29 g/l) significantly increased the frequency of homoserine, histidine, and lysine revertants over those of control levels after one to four hours of exposure (Shahin and von Barstel, 1977). TCE has been uniformly negative in mutagenicity testing in the absence of metabolic activation (Simmon, et al. 1977; Greim, et al. 1945; Shahin and von Barstel, 1977). Henschler (1977) and his associates have closely associated the mutagenic activity of the chlorinated ethylenes with unsymmetrical chlorine substitution that renders the respective epoxides unstable, e.g., vinyl chloride, 1,1-dichloroethylene and trichloroethylene. There is some question whether TCE is mutagenic. On chemical analysis, technical grade TCE was found to contain epichlorohydrin and epoxybutane, two compounds that Henschler, et al. (1977) observed to be more potent mutagens than TCE in S. typhi-

murium (TA100). Pure TCE was weakly mutagenic. These investigators concluded that the mutagenic activity formerly attributable to TCE probably was due in part to mutagenic contaminants, found in some samples of TCE.

Carcinogenicity

Trichloroethylene has been shown to induce transformation in a highly sensitive *in vitro* Fischer rat embryo cell system (F1706) that is used for identifying carcinogens. At a concentration of 1 M, TCE induced transformation of rat embryo cells as characterized by the appearance of progressively growing foci of cells lacking contact inhibition and by the growth of macroscopic foci when inoculated in semi-solid agar. The transformed cells grew as undifferentiated fibrosarcomas at the site of inoculation in 100 percent of newborn Fischer rats between 27 and 68 days post-inoculation (Price, et al. 1978).

The National Cancer Institute (NCI, 1976) observed an increased incidence of hepatocellular carcinoma in mice (strain $B6C3F_1$) treated with TCE. The time weighted doses administered for five days/week for 78 weeks were 1,169 and 2,339 mg/kg for males and 869 and 1,739 mg/kg for females. Similar experiments in Osborne-Mendel rats failed to increase the incidence of tumors in this species. However, the rats also responded poorly to the positive control carbon tetrachloride, indicating that the $B6C3F_1$ mouse is a much more sensitive test animal to induction of carcinomas by chlorinated compounds. The data obtained from mice are summarized in Table 3. In addition, some evidence of metastasis of hepatocellular carcinomas to the lung was observed in both low and high dose male mice (4/50 and 3/48, respectively).

TABLE 3

Incidence of Hepatocellular Carcinoma in TCE-treated $B6C3F_1$ Mice*

	Males	Females
Control	1/20	0/20
Low dose	26/50	4/50
High dose	31/48	11/47

*Source: NCI, 1976

Three other long-term bioassays testing the carcinogenicity of trichloroethylene have been conducted. An inhalation study by Bio-Test, Inc., yielded positive results in $B6C3F_1$ mice, but not rats (Bell, et al. 1978). An inhalation study by Maltoni (1979) in rats yielded negative results. A series of experiments involving both skin painting and oral exposure in ICR/Ha Swiss mice by Van Duuren, et al. (1979) yielded negative results. Thus positive carcinogenic results have only been seen in $B6C3F_1$ mice in two studies.

Furthermore, it has been pointed out that TCE used in the NCI and Bio-Test bioassays (1976) contained traces of monofunctional alkylating agents, epichlorohydrin and epoxibutane as stabilizers (Henschler, et al. 1977; Bell, et al. 1978). The mutagenic potency of these compounds in Salmonella TA100 was of sufficient magnitude to suggest that they might account for the observed carcinogenicity of TCE. However, the results of these bioassays have been accepted for the purpose of this document because the grade of TCE used in these studies is representative of that used industrially.

Only one systematic study relating trichloroethylene exposure and the incidence of human cancer was found in the available literature (Axelson, et al. 1978). Workers were segregated on the basis of urinary trichloroacetic acid concentrations, which would indicate time-weighted exposures to TCE of either more or less than 160 mg/m^3, and also on the basis of more or less than ten years exposure duration. A total of 518 men were included in the study, but only eight fell into the latter category. In no category was any excess cancer mortality observed. However, the authors note that "only a very strong effect of TCE with regard to liver carci-

nogenicity would have been detectable with the size of this study" and conclude that, although the cancer risk to man cannot be ruled out, exposure to low levels of TCE probably does not present a very serious and general cancer hazard.

CRITERION FORMULATION

Existing Guidelines and Standards

Trichloroethylene has been regulated primarily from the industrial health standpoint. Concentrations allowed in the working environment vary widely in different countries (Table 4). Because of use of TCE in decaffeinating coffee and the extraction of spice oleoresins, the Food and Drug Administration (FDA) has limited concentrations of TCE that may be allowed in the final product. These limits are 10 mg/kg in instant coffee, 25 mg/kg in ground coffee, and 30 mg/kg in spice extracts (21 CFR 121:1041).

The presently established ACGIH TLV listed in Table 11 (in the ACGIH document), has been established entirely on the basis of short-term exposures of healthy male volunteers. This level has not taken into account the possibility of potential synergists present in the general environment or the possibility of sensitive populations (ACGIH, 1977). It has not yet incorporated consideration of TCE carcinogenicity indicated by recent NCI data (1976). As can be seen in Table 4, industrial hygiene standards established by European countries are less than one-half that allowed in the U.S.

Basis and Derivation of Criterion

No quantitative animal or human data exist that may be used to refine the ACGIH estimate of noncarcinogenic risks from exposure to TCE. Sensitive populations undoubtedly exist, as documented by interactions of TCE toxicity with ethanol. However, no quantitative data exist on which to weigh such factors. Calculation of an acceptable concentration for water quality criteria from the TLV on

TABLE 4

Industrial Hygiene Standards for Trichloroethylene in Various Countries*

Country	mg/m^3	Calculated Allowable Daily Exposure mg/day
USA	535	3,821
Sweden	160	1,143
Czechoslovakia	250	1,786
Federal Republic of Germany	260	1,857
German Democratic Republic	250	1,768
USSR	1	7

*Source: Fishbein, 1976

the basis proposed by Stokinger and Woodward (1958) is illustrated as follows:

$$\frac{535\ mg/m^3 \times 50\ m^3/week \times 0.36^*}{7\ days/week \times 100^{**}} = 14\ mg/day$$

*Coefficient of respiratory absorption vs. absorption via ingestion.

**Safety factor for sensitive populations.

Assuming a 2 liter daily consumption of water and a safety factor of 100 for sensitive populations, and the consumption of 6.5 grams of fish which has a bioconcentration factor of 10.6, concentrations of TCE in drinking water would be limited to 6.77 mg/l on this basis.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Trichloroethylene is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of trichloroethylene in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases, and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of trichloroethylene corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5}

for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams fish and shellfish. (2)	0.27 µg/l	2.7 µg/l	27 µg/l
Consumption of fish and shellfish only.	8.07 µg/l	80.7 µg/l	807 µg/l

(1) Calculated by applying a linearized multistage model, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document, to the animal bioassay data presented in the Appendix and in Table 3. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 3 percent of the trichloroethylene exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 10.6-fold. The remaining 97 percent of trichloroethylene exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of trichloroethylene, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding trichloroethylene concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding trichloroethylene concentrations. Because data indicating other sources of trichloroethylene exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

As discussed in the Carcinogenicity section, several uncertainties have been alluded to which may affect the evaluation of TCE as a carcinogen; namely: a) the contamination of the TCE used in the NCI bioassay, and b) the negative results in several bioassays. For comparison purposes as suggested by public comments, a protective level based on a toxic endpoint has been calculated. This protective level should be derived using data from the NCI bioassay or Van Duuren, et al. (1979) since these studies provide the best chronic data available. Two specific responses were observed in the NCI study for rats: 1) dose related decreased survival over time, and 2) chronic nephropathy (both doses). Although the decreased survival in rats was not substantial, it was

statistically significant in females at the low dose. Consequently, this exposure level may be regarded as a frank-effect-level (FEL) rather than the lowest-observable-adverse-effect-level (LOAEL) and, strictly speaking, cannot be used to derive a criterion. The Van Duuren, et al. (1979) study tested only one dose of TCE (2.38 mg/kg/d) and no effects were noted. This no-observable-effect-level (NOEL) can be used with appropriate safety factors to derive a protective level. Thus,

$$\frac{2.38 \text{ mg/kg/d} \times 70 \text{ kg}}{100} = 1.666 \text{ mg/d},$$

where 70 kg is the assumed body weight of a man and 100 represents the safety factor according to National Academy of Sciences recommendations (i.e., scanty results in humans with valid results from chronic animal bioassays). A protective ambient water level is calculated as follows:

$$C = \frac{1.666 \text{ mg/d}}{2 \text{ l/d} + 0.0065 \text{ kg/d} \times 10.6 \text{ l/kg}},$$

$$= 0.806 \text{ mg/l, or}$$

$$806 \ \mu\text{g/l},$$

where 2 l/d and 0.0065 kg/d is the average daily water (in liters) and fish (in kilograms) consumption for humans and 10.6 l/kg is the BCF for TCE.

It must be noted, however, as the Carcinogen Assessment Group has outlined in the Appendix, that the cancer based criterion is to be used in the case of TCE. Until the ongoing bioassay is published the recommended criterion based on the presently available NCI bioassay (NCI, 1976) is 27 ug/l for the 10^{-5} risk level.

The expected publications of studies by Maltoni and the NCI by the end of 1981 should resolve these uncertainties. At that time, the criterion for TCE will be reevaluated.

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APPENDIX

Derivation of Criterion for Trichloroethylene

The NCI bioassay tested female and male $B6C3F_1$ mice with trichloroethylene at various concentrtions in the diet. Both sexes were found to develop significant incidences of hepatocellular carcinoma in dose-related fashion. The incidences of heptocellular carcinoma in male mice are listed below and are used in the derivation of a water quality criterion for trichloroethylene. The parameters of the extrapolation model are:

Dose (mg/kg/day)	Incidence (No. responding/No. tested)
0	1/20
835	26/50
1,671	31/48

le = 546 days
Le = 630 days
L = 630 days

w = 0.034 kg
R = 10.6 l/kg

With these parameters the carcinogenic potency factor for humans, q_1*, is 1.26×10^{-2} $(mg/kg/day)^{-1}$. The result is that the water concentration should be less than 27 µg/l in order to keep the individual lifetime risk below 10^{-5}.

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