

**NTP REPORT ON CARCINOGENS BACKGROUND  
DOCUMENT for TRICHLOROETHYLENE**

**FINAL  
MARCH 1999**

Prepared for

the October 30-31, 1997,  
Meeting of the Report on Carcinogens Subcommittee  
of the NTP Board of Scientific Counselors

Prepared by

Integrated Laboratory Systems  
Post Office Box 13501  
Research Triangle Park, North Carolina 27709  
NIEHS Contract No. N01-ES-25346

# TABLE OF CONTENTS

<b>NTP Report on Carcinogens Listing for Trichloroethylene.....</b>	<b>1</b>
<b>Listing Criteria from the Report on Carcinogens, Eighth Edition.....</b>	<b>3</b>
<b>1.0 CHEMICAL PROPERTIES.....</b>	<b>4</b>
<b>1.1 Chemical Identification.....</b>	<b>4</b>
<b>1.2 Physical-Chemical Properties .....</b>	<b>5</b>
<b>1.3 Packaging and Shipping.....</b>	<b>5</b>
<b>2.0 HUMAN EXPOSURE .....</b>	<b>5</b>
<b>2.1 Use .....</b>	<b>5</b>
<b>2.2 Production .....</b>	<b>6</b>
<b>2.3 Exposure .....</b>	<b>6</b>
<b>2.3.1 Environmental Exposure.....</b>	<b>6</b>
<b>2.3.1.1 Air.....</b>	<b>6</b>
<b>2.3.1.2 Water.....</b>	<b>7</b>
<b>2.3.1.3 Soil .....</b>	<b>7</b>
<b>2.3.1.4 Consumer Products .....</b>	<b>7</b>
<b>2.3.1.5 Food .....</b>	<b>7</b>
<b>2.3.2 Occupational Exposure.....</b>	<b>7</b>
<b>Table 2-1 NIOSH National Occupational Exposure Survey</b>	
<b>(NOES 1980-1983)*: By Industry.....</b>	<b>8</b>
<b>2.4 Regulations and Criteria.....</b>	<b>9</b>
<b>3.0 HUMAN STUDIES .....</b>	<b>22</b>
<b>Table 3-1 Post IARC (1995) Human Studies .....</b>	<b>25</b>
<b>4.0 EXPERIMENTAL CARCINOGENESIS .....</b>	<b>26</b>
<b>5.0 GENOTOXICITY.....</b>	<b>26</b>
<b>5.1 Summary of IARC (1995) Genotoxicity Studies .....</b>	<b>26</b>
<b>5.2 Genotoxicity Studies Published Post IARC (1995) .....</b>	<b>27</b>
<b>Table 5-1 Summary of Recent Trichloroethylene Genotoxicity</b>	
<b>Studies.....</b>	<b>28</b>

<b>6.0 OTHER RELEVANT DATA.....</b>	<b>29</b>
<b>6.1 Absorption, Distribution, Metabolism, and Excretion .....</b>	<b>29</b>
<b>6.1.1 Absorption and Distribution .....</b>	<b>29</b>
<b>6.1.2 Metabolism and Excretion .....</b>	<b>29</b>
<b>Figure 6-1 Proposed Metabolism of TCE in Rats .....</b>	<b>30</b>
<b>Table 6-1 Metabolites of TCE by Species.....</b>	<b>33</b>
<b>6.2 Pharmacokinetics.....</b>	<b>34</b>
<b>6.3 Structure-Activity Relationships.....</b>	<b>34</b>
<b>6.3.1 Chlorinated Alkanes and Alkenes .....</b>	<b>34</b>
<b>6.3.2 Structural Analogues .....</b>	<b>35</b>
<b>6.3.2.1 Vinyl Chloride .....</b>	<b>35</b>
<b>6.3.2.2 Vinylidene Chloride.....</b>	<b>35</b>
<b>6.3.2.3 Tetrachloroethylene.....</b>	<b>36</b>
<b>6.3.3 Metabolites .....</b>	<b>37</b>
<b>6.3.3.1 Dichloroacetic Acid and Trichloroacetic Acid.....</b>	<b>37</b>
<b>6.3.3.2 Chloral Hydrate .....</b>	<b>38</b>
<b>6.3.3.3 Dichlorovinylcysteine .....</b>	<b>38</b>
<b>6.4 Immune Suppression .....</b>	<b>39</b>
<b>6.5 Molecular Changes in Human Tumors.....</b>	<b>39</b>
<b>7.0 MECHANISMS OF CARCINOGENESIS .....</b>	<b>40</b>
<b>7.1 Liver Cancer .....</b>	<b>40</b>
<b>7.2 Lung Cancer.....</b>	<b>40</b>
<b>7.3 Kidney Cancer .....</b>	<b>41</b>
<b>7.4 Structural Analogues.....</b>	<b>42</b>
<b>8.0 REFERENCES.....</b>	<b>43</b>
<b>APPENDIX A - Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 63 (Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals), Trichloroethylene, pp. 75-158 (1995).....</b>	<b>A-1</b>
<b>APPENDIX B - Excerpts from the 1990 NTP Technical Report Toxicology and Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) [CAS No. 79-01-6] in F344/N Rats and B6C3F1 Mice (Gavage Studies), pp. 7-8, 34-39, 46-51 .....</b>	<b>B-1</b>

**APPENDIX C - Description of Online Searches for Trichloroethylene ..... C-1**

**APPENDIX D - Report on Carcinogens (RoC), 9<sup>th</sup> Edition**

**Review Summary ..... D-1**

## NTP Report on Carcinogens Listing For Trichloroethylene

### Carcinogenicity

Trichloroethylene (TCE) is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans.

Epidemiological data are limited for evaluating the carcinogenicity of trichloroethylene in humans. Studies have suggested that occupational exposure to TCE causes cancer of the liver and biliary tract, and also non-Hodgkin's lymphoma (IARC, 1995e). Another study has indicated that occupational exposure to TCE has been associated with cancer of the kidneys (Henschler et al., 1995a,b; Brüning et al., 1997). Results of three cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected (RR = 1.8), and a moderately elevated risk for non-Hodgkin's lymphoma (IARC, 1995e). Further, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated ground water deserves mention (IARC, 1995e). For a cohort of cardboard workers exposed almost exclusively to high levels of TCE, the standardized incidence ratio for kidney cancer was 7.97 (95% CI = 2.59-18.59) (Henschler et al., 1995a).

The findings in humans are predated and supported by evidence in experimental animals. Target site concordance for TCE-induced tumors is consistent between humans and rodents. In mice, TCE causes increases in benign and malignant tumors of the liver (NCI, 1976; Maltoni et al., 1988; cited by IARC, 1995e; NTP 243, 1990), increases in tumors of the lung (Maltoni et al., 1988; cited by IARC, 1995e), and lymphomas (Henschler et al., 1980). In rats, TCE induces cancers of the kidney (Maltoni et al., 1988; cited by IARC, 1995e; NTP 273, 1988; NTP 243, 1990), interstitial cell tumors of the testis (Maltoni et al., 1988; cited by IARC, 1995e; NTP 273, 1988), and possibly leukemias (Maltoni et al., 1988; cited by IARC, 1995e).

### Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Mechanistically, renal cell carcinomas (RCCs) from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the von Hippel-Landau (VHL) tumor suppressor gene, a gene that has been associated with renal cell carcinomas (Brüning et al., 1997). RCC tissues from all 23 TCE-exposed persons [mainly from Henschler et al. (1995a) cohort] analyzed thus far showed aberrations of the VHL gene, with 30% having aberrations in exon 1, 44% in exon 2, and 26% in exon 3. By comparison to TCE-unexposed RCC patients, VHL mutation frequencies of 33-55% were found in different cohorts, with about 24% affecting exon 2.

There is biological plausibility of the kidney tumors observed and TCE exposures because (1) site and histopathological characteristics of the tumors observed in patients and in experimental animals are identical (Vamvakas et al., 1993); (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant et al., 1986; cited by IARC, 1995e and Bernauer et al., 1996); (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE are identical in humans and in experimental animals (Birner et al., 1993; cited by IARC, 1995e and Clewell et al., 1995); and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner et al.,

1993; cited by IARC, 1995e and Clewell et al., 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

Rodents exposed to TCE typically exhibit dose-related cytomegaly of the kidneys, the lesion often being more severe in males, with none or few being found in male or female vehicle-control mice or rats. Toxic nephropathy commonly occurs in the solvent-exposed rodents, likewise being more frequent and more severe than seen in controls. In humans, substantially more cases of tubule cell damage were found among renal cell carcinoma patients who had been exposed to high levels of TCE over many years than among RCC patients who had not been exposed to TCE (Henschler et al., 1995a).

Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchanges in peripheral lymphocytes of workers exposed to trichloroethylene were considered inconclusive. In rodents, TCE did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange, or unscheduled DNA synthesis, whereas an increase in micronuclei and DNA single-strand breaks/alkaline labile sites was observed. TCE did not induce gene mutations in human cells. In mammalian cells *in vitro*, TCE induced cell transformation, sister chromatid exchange, and gene mutations, but not chromosome aberrations (IARC, 1995e).

### **Listing Criteria from the Report on Carcinogens, Eighth Edition**

*Known To Be A Human Carcinogen:*

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

*Reasonably Anticipated To Be A Human Carcinogen:*

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

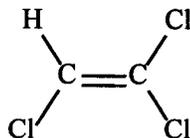
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

## 1.0 CHEMICAL PROPERTIES

Trichloroethylene  
[79-01-6]



### 1.1 Chemical Identification

Trichloroethylene (C<sub>2</sub>HCl<sub>3</sub>, mol. wt. = 131.39) is also called:

Ethene, trichloro- (9CI)	Flock flip	Trichloran
Ethylene, trichloro- (8CI)	Fluate	Trichloren
Acetylene trichloride	Gemalgene	Trichlorethylene
Algylen	Germalgen	Trichloroethene
Anamenth	Germalgene	1,1,2-Trichloroethene
Benzinol	Lanadin	1,12-Trichloroethylene
Blacosolv	Lethurin	1,2,2-Trichloroethylene
Blancosolv	Narcogen	Trichloroethylene (CAN)
Cecolene	Narkogen	Tri-clene
Chlorilen	Narkosoid	Trielene
1-Chloro-2,2-dichloroethylene	Nialk	Trielin
Chlorylea	Perm-a-chlor	Trieline
Chlorylen	Perm-a-clor	Triklone
Chorylen	Petzinol	Trilen
Circosolv	Philex	Trilene
Drawhaspol	TCE	Triline
Densinfluat	Threthylen	Trimar
1,1-Dichloro-2-chloroethylene	Threthylene	Triol
Dow-Tri	Trethylen	Tri-Plus
Dukeron	Trethylene	Vestrol
Ethynyl trichloride	Tri	Vitran
Ethylene trichloride	Triad	Vitran
Ethylene, 1,1,2-trichloro-	Trial	Vestrosol
Fleck-Flip	Triasol	

Trichloroethylene (TCE) has a UN shipping number of UN1710 and RCRA waste number of U228.

## 1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless, unless dyed blue	HSDB (1997)
Physical State	Liquid	HSDB (1997)
Melting Point, °C	-84.8	Budavari (1996)
Boiling Point, °C	86.9	Budavari (1996)
Critical Pressure, atm	49.7	HSDB (1997)
Critical Temperature, °C	271	HSDB (1997)
Specific Gravity (liquid) at 20 °C/4 °C	1.4642	Budavari (1996)
Odor	Ethereal odor, sweet chloroform-like odor	HSDB (1997)
Odor Threshold:		
Water	10 mg/L	Verschueren (1983; cited by HSDB, 1997)
Air	21.4 ppm (115 mg/m <sup>3</sup> )	Fazzalari (1978; cited by HSDB, 1997)
Solubility:		
Water at 25 °C	0.11 g/100 g	PPG Industries, Inc. (1997)
Organic Solvents	Soluble in chloroform, acetone, alcohol, and diethyl ether	HSDB (1997)
Vapor density at 87 °C and 760 mmHg, g/L	4.45	PPG Industries, Inc. (1997)
Vapor pressure at 0 °C	19.9 mm Hg	HSDB (1997)
Vapor pressure at 20 °C	57.8 mm Hg	HSDB (1997)

Upon combustion TCE produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, TCE decomposes by forming hydrochloric acid (HSDB, 1997).

### 1.3 Packaging and Shipping

TCE is generally shipped in 55-gal drums, tank trucks, or single compartment tank cars, with a capacity of 10,000 and 20,000 gal. PPG Industries, Inc., ships from its Louisiana plant and terminals located in New Jersey, Illinois, and California (PPG Industries, Inc., 1997).

## 2.0 HUMAN EXPOSURE

### 2.1 Use

TCE is used mainly as a degreaser for metal parts (CMR, 1983; cited by Gist and Burg, 1995). Five main industrial groups use TCE in vapor or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries (IARC, 1995e). TCE can be used as an extraction solvent and a chemical intermediate and as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (ATSDR, 1995).

## **2.2 Production**

IARC (1995e) reported that two companies in the United States produced TCE ca. 1992 with a combined annual capacity of 160,000 tons (145,000 metric tons or Mg). The SRI *Directory of Chemical Producers, United States* listed only one producer (SRI, 1996).

## **2.3 Exposure**

### **2.3.1 Environmental Exposure**

ATSDR is developing information on potential public exposure to TCE and possible long-term health consequences in a subregistry to the National Exposure Registry for hazardous waste sites. The TCE subregistry includes 3 sites in Michigan, 4 sites in Indiana, 6 sites in Illinois, and 1 site each in Pennsylvania and Arizona. Environmental and tissue data will serve as the basis for estimating exposure (Gist et al., 1994).

#### **2.3.1.1 Air**

Air is the primary route of potential environmental exposure to TCE. Most of the TCE emissions into the atmosphere are from vapor degreasing operations. Mean TCE background levels in air range from 0.03 parts per billion (ppb) ( $0.16 \mu\text{g}/\text{m}^3$ ) in rural areas to 0.46 ppb ( $2.5 \mu\text{g}/\text{m}^3$ ) for urban and suburban areas. Areas near emission sources have up to 1.2 ppb ( $6.4 \mu\text{g}/\text{m}^3$ ) TCE in the air (ASTDR, 1995).

The Toxic Chemical Release Inventory for 1995 (TRI95, 1997) contains reports on environmental releases of TCE from 717 U.S. facilities. Of these, 591 reported releases to the atmosphere of more than 2000 lb (0.9072 Mg). Among the 591 facilities, 132 released individually 2000 to 10,000 lb (0.9072 to 4.536 Mg); 328 released between 10,000 and 50,000 lb (4.536 to 22.68 Mg); 114 released between 50,000 and 200,000 lb (22.680 to 90.718 Mg); and 17 released greater than 200,000 lb ( $>90.718$  Mg) each. The total amount of TCE released in 1995 by the 717 facilities was 25,484,235 lb (11,559 Mg), while the 17 greatest emitters together released 6.1 million lb (2770.4 Mg). The greatest releases were generally from metalworking facilities, with 3 sites each reporting under Standard Industrial Classification (SIC) codes 3317 (steel pipe and tubes) and 3714 (motor vehicle parts and accessories). Other facilities (1 each) reported under SICs 3089 (plastics and plastic products, not elsewhere classified), 3671 (electron tubes), and 3721 (aircraft).

TCE is one of the volatile organic compounds (VOCs) measured in the U.S. EPA's large-scale Total Exposure Assessment Methodology (TEAM) studies (Wallace et al., 1996). In studies in the United States (Maryland, New Jersey, and California) in the 1980s (1981-1987), determination of TCE exposure via personal air monitors carried by 750 persons for two consecutive 12-hour periods revealed TCE median personal air concentrations of 0.3 to  $3.0 \mu\text{g}/\text{m}^3$ . Breath samples taken in the evenings after several hours at home from 50 to 350 persons in two New Jersey cities in 1981-1983 and 75 persons in two California towns in 1984 had 0.1 to  $0.9 \mu\text{g TCE}/\text{m}^3$  (median personal air concentrations of  $1.7\text{-}3.0 \mu\text{g}/\text{m}^3$ ). However, in 1984 and 1987, TCE was not detected in the breath of 140 persons in Los Angeles, CA (personal air levels were  $0.3\text{-}1.2 \mu\text{g}/\text{m}^3$ ), nor in 1987 in 75 persons in Baltimore, MD (personal air levels were  $1.1 \mu\text{g TCE}/\text{m}^3$ ).

### 2.3.1.2 Water

Industrial discharges of wastewater streams are the primary release of TCE into aquatic systems. TRI95 (1997) includes data from 28 facilities that had each released more than 10 lb (4.5 kg) TCE to water in 1995. Five facilities each released 250 to 280 lb (114 to 127 kg). The total release of TCE to water was 1477 lb (0.670 Mg). Four of the five facilities were metalworking plants; one was a plant that produced TCE as a by-product and for onsite use and processing. TCE background levels in large bodies of water range from 0.001 to 0.007 ppb ( $\mu\text{g/L}$ ), while values reported for rainwater and snow are 0.0008 to 0.039 ppb ( $\mu\text{g/L}$ ) TCE (Gist and Burg, 1995). In the U.S. EPA's Contract Laboratory Program Statistical Database, TCE was found in approximately 3% of surface water samples and 19% of ground water samples at a geometric mean surface water concentration of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and a geometric mean groundwater concentration of 27.3 ppb (individual sample values ranged from <0.1 to  $\leq 27300$  ppb) (U.S. Environmental Protection Agency, 1989; cited by IARC, 1995e).

### 2.3.1.3 Soil

The total releases of TCE to land and underground injection wells in 1995 were 3577 lb (1.622 Mg) and 550 lb (0.249 Mg, respectively) (TRI95, 1997).

### 2.3.1.4 Consumer Products

TCE is present in typewriter correction fluids, paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg, 1995). Former uses of TCE as an extraction solvent for cosmetics and drug products and as a dry cleaning agent have been discontinued (IARC, 1995).

### 2.3.1.5 Food

TCE has been found in a variety of foods with the highest levels being found in meats, 12-16 ppb (0.09-0.12  $\mu\text{mol/kg}$ ), and U.S. margarine, 440-3,600 ppb (3.35-27.4  $\mu\text{mol/kg}$ ) (ATSDR, 1995). TCE had been used as an extraction solvent for natural fats and oils, spices, hops, and caffeine (from coffee), but FDA banned these uses in 1977 (IARC, 1995e).

## 2.3.2 Occupational Exposure

According to the U.S. National Institute for Occupational Safety and Health (NIOSH, 1990), 401,373 employees in 23,225 plants in the United States during 1980-1983 were potentially exposed to TCE (**Table 2-1**).

**Table 2-1. NIOSH National Occupational Exposure Survey (NOES 1980-1983)\*: By Industry**

Industry	Number of Plants	Number of Employees	Number of Female Employees
Agricultural Services	339	1695	1695
General Building Contractors	661	5463	3106
Heavy Construction Contractors	65	5420	5306
Special trade Contractors	834	1879	1287
Food and Kindred Products	190	2062	604
Tobacco Manufactures	43	517	
Textile Mill Products	214	26846	21509
Apparel and Other Textile Products	207	1226	1188
Lumber and Wood Products	505	4932	1189
Furniture and Fixtures	184	1352	
Paper and Allied Products	167	4331	1846
Printing and Publishing	2372	26317	10227
Chemicals and Allied Products	236	10277	3151
Petroleum and Coal Products	256	2020	
Rubber and Misc. Plastic Products	862	15772	2381
Leather and Leather Products	33	65	
Stone, Clay, and Glass Products	275	1494	1341
Primary Metal Industries	379	5047	417
Fabricated Metal Products	2196	49046	30065
Machinery, Except Electrical	1871	22210	2786
Electric and Electronic Equipment	1197	97000	47714
Transportation Equipment	207	9305	559
Instruments and Related Products	984	16293	5032
Miscellaneous Manufacturing Industries	803	6261	2938
Railroad Transportation	22	262	
Trucking and Warehousing	989	5852	5072
Transportation by Air	481	15216	3782
Communication	603	8776	1802
Electric, Gas, and Sanitary Services	117	4336	429
Whole trade- Durable Goods	960	3735	2260
Whole trade - Nondurable Goods	352	704	
Personal Services	277	1044	70
Business Services	716	12973	3475
Auto Repair, Services, and Garages	1295	11197	4861
Miscellaneous Repair Services	406	812	
Health Services	569	11302	9059
Museums, Botanical, Zoological Gardens	82	1643	164
TOTAL	23225	401373	175316

\* NIOSH (1990)

## 2.4 Regulations and Criteria

FDA regulations govern the presence of TCE in color additives, bottled water, food as extraction solvent residues and as indirect additives as migrants from adhesives, etc., used in food packaging.

The OSHA Permissible Exposure Limit (PEL) for time-weighted average (TWA) exposure in a 40-hour work week to TCE in workroom air is 100 ppm (537 mg/m<sup>3</sup>) with a ceiling value of 200 ppm (1070 mg/m<sup>3</sup>) (29 CFR 1910.1000, 1996 [CHEMLIST, 1997]). NIOSH considers TCE to be a potential occupational carcinogen, recommending that exposure be limited to the lowest feasible concentration. NIOSH recommends a REL (Recommended Exposure Level) of 2 ppm (11 mg/m<sup>3</sup>) during use of TCE as an anesthetic and a 10-hour TWA of 25 ppm (130 mg/m<sup>3</sup>) during all other exposures (Ludwig, 1994). The Threshold Limit Value (TLV) recommended by ACGIH is 50 ppm (269 mg/m<sup>3</sup>); the Short-Term Exposure Limit or Ceiling recommended is 100 ppm (537 mg/m<sup>3</sup>). ACGIH (1996) classified TCE as A5 (*Not Suspected as a Human Carcinogen*).

EPA regulates TCE as a Hazardous Air Pollutant under the Clean Air Act (CAA) 1990 Amendments and as a Volatile Organic Compound (VOC) subject to emission standards under the CAA Section 111 (40 CFR Part 60, 1995) (CHEMLIST, 1997).

Under the Safe Drinking Water Act, the Maximum Contaminant Level (MCL) for community and nontransient, noncommunity water systems is set at 0.005 mg/L (40 CFR Part 141, 1996) (CHEMLIST, 1997). The World Health Organization (WHO, 1993) recommended a provisional guideline value for TCE in drinking water of 0.070 mg/L. Based on a 1985 study by Buben and O'Flaherty, WHO (1993) calculated a total daily intake (TDI) of 0.0238 mg/kg bw by applying an uncertainty factor of 3000 to the study's LOAEL (lowest observable adverse effect level) of 100 mg/kg bw/day when mice were exposed for 5 days/week for 6 weeks. The observed adverse effects were minor effects in relative liver weight. Ten percent of the TDI was allocated to drinking water to derive the provisional guideline value of 70 µg/L.

TCE is regulated under RCRA as a Halogenated Organic Compound (HOC) and under the Land Disposal Restrictions. Under the latter, hazardous wastes that contain total concentrations of HOCs of at least 1000 mg/L (liquids) or 1000 mg/kg (nonliquids) are prohibited from land disposal. Under 40 CFR 268.40 and 268.48, treatment standards are given for wastewater and nonwastewater extract concentrations, or the applicable Technology Code (40 CFR 268.42) is given (CHEMLIST, 1997).

TCE is regulated under Sections 110 and 313 of the Superfund Amendment Reauthorization Act (SARA). Priority data needs established under Section 110 include exposure levels in humans living near hazardous waste sites and other populations and epidemiological studies on health effects, including carcinogenicity. Under EPCRA Section 313 (Community Right-to-Know and the Toxic Chemical Release Inventory [TRI], 40 CFR Part 372 Subpart D, 1992), TCE is one of the 19 substances for which the de minimus for reporting changes from 1.0 percent to 0.1 percent. Under TRI, since 1989, manufacturers of at least 25,000 lb/yr (11,350 kg/yr) and other handlers of at least 10,000 lb/yr (4,540 kg/lb) must report releases of TCE to any environmental medium. Under 40 CFR Part 302 Table 302.4, TCE is on the CERCLA List of Hazardous Substances with an RQ for reporting releases of 100 lb (45.4 kg) or more (CHEMLIST, 1997).

TCE is regulated under the Clean Water Act (CWA) Sections 301, 307, and 311 (40 CFR Part 423, 1996; 40 CFR Parts 116 and 117, 1996). TCE is a priority pollutant in final discharges resulting from steam electric power generation. It is designated a hazardous substance if discharged to navigable waters. The Reportable Quantity (RQ) for notification is 100 lb (45.4 kg) (CHEMLIST, 1997).

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 48 FR 48335, 10/18/83.</p> <p>40 CFR 60.480 ff.—Subpart B—Standards of Performance for Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry.</p> <p>40 CFR 60.660 ff.—Subpart NNN—Standards of Performance for Volatile Organic Compound (VOC) Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Distillation Operations. Promulgated: 55 FR 26942, 06/29/90.</p> <p>40 CFR 60.700 ff.—Subpart RRR—Standards of Performance for Volatile Organic Compounds Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Reactor Processes. Promulgated: 58 FR 45962, 08/31/93.</p>	<p>The provisions of this part apply to the owner/operator of any stationary source which contains an affected facility (a stationary source with an apparatus to which a standard is applicable).</p> <p>Each owner or operator of facilities producing trichloroethylene as an intermediate or final product must demonstrate compliance with the provisions of this subpart.</p> <p>Affects distillation units not discharging their vent steams into a recovery system, or a combination of two or more distillation units and a common recovery system into which their vent steams are discharged, which uses, contains, or produces trichloroethylene. Specific standards, monitoring, and recordkeeping requirements apply.</p> <p>Affects reactor units not discharging their vent steams into a recovery system, or a combination of two or more reactor units and a common recovery system into which their vent steams are discharged, which use, contain or produce trichloroethylene. Specific standards, monitoring, and recordkeeping requirements apply.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Codes: 42 U.S.C. 7401, 7412, 7414, 7416, 7601.</p> <p>40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Codes: 42 U.S.C. 7401 et seq.</p> <p>40 CFR 63.100 ff.—Subpart F—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry. Promulgated: 59 FR 19454, 04/22/94.</p> <p>40 CFR 63.110 ff.—Subpart G—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry for Process Vents. Promulgated: 59 FR 19468, 4/22/94.</p>	<p>This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants, and applies to the owner or operator of any stationary source for which a standard is prescribed under this part. As of 50 FR 52422, 12/23/95, trichloroethylene was listed because of the serious health effects, including cancer, from ambient air exposure.</p> <p>Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.</p> <p>This subpart applies to chemical manufacturing process units that manufacture trichloroethylene and are located at a plant site that is a major source as defined in section 112(a) of the CAA. Owners and operators of sources subject to this subpart shall comply with the requirements of subparts G and H of this part.</p> <p>The provisions of this subpart apply to all process vents, storage vessels, transfer racks, and wastewater streams within a source subject to subpart F of this part. Emission standard: Emissions of trichloroethylene shall be controlled to the level represented by a given equation (see 40 CFR 63.112[a]). Specific process vent and methods and procedures provisions apply.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 63.460 ff.—Subpart T— National Emission Standards for Halogenated Solvent Cleaning. Promulgated: 59 FR 61805, 12/2/94.</p> <p>40 CFR 63.680 ff.—Subpart DD— Applicability and designation of affected sources. Promulgated: 61 FR 34158, 07/01/96.</p> <p>40 CFR 63.800 ff.—Subpart JJ— National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/7/95.</p> <p>40 CFR 116—PART 116— DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/1978. U.S. Codes: 33 U.S.C. 1251 et seq.</p> <p>40 CFR 117—PART 117— DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated 44 FR 50776, 08/29/79. U.S. Codes: FWPCA 311(b)(2)(A) and 501(a) as amended by the CWA of 1977.</p>	<p>Individual batch vapor, in-line vapor, in- line cold, and batch cold solvent cleaning machines that use trichloroethylene alone or in a mixture with other HAPs listed in a total concentration greater than 5%. Specific batch cold cleaning, vapor, in-line, and alternative standards and monitoring and recordkeeping requirements apply.</p> <p>The provisions of this subpart apply to plant sites at which a major source of trichloroethylene emissions occurs as defined in 40 CFR 63.2, or at which is located one or more operations that receives offsite materials as specified in 40 CFR 63.680(b).</p> <p>The provisions of this subpart apply to each facility that is engaged in the manufacture of wood furniture or wood furniture components and that is a major source as defined in 40 CFR 63.2. Trichloroethylene is excluded from use in cleaning and washoff solvents.</p> <p>This regulation designates trichloroethylene as a hazardous substance under section 311(b)(2)(a) of the FWPCA. The regulation applies to discharge of the substances identified in table 116.4 to surface waters.</p> <p>Discharges to water of amounts equal to or greater than the RQ must be reported to EPA. Reportable quantity (RQ) for environmental releases of trichloroethylene to water is 100 lb (45.4 kg).</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 132—PART 132—WATER QUALITY GUIDANCE FOR THE GREAT LAKES SYSTEM. Promulgated: 60 FR 15387, 03/23/95. U.S. Codes: 33 U.S.C. 1251 et seq.</p> <p>40 CFR 141—PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Codes: Public Health Service Act sections 1413-1416, 1445, and 1450 as amended by 1974 SDWA. U.S.C. 300.</p> <p>40 CFR 141 ff.—Subpart D—Reporting, Public Notification and Recordkeeping. Promulgated: 60 FR 33932, 06/29/95.</p> <p>40 CFR 141.50 ff.—Subpart F—Maximum Contaminant Level Goals. Promulgated: 50 FR 46901, 11/13/85, and others.</p> <p>40 CFR 141.60 ff.—Subpart G—National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels. Promulgated: 52 FR 25716, 07/08/87.</p> <p>40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 06/26/88.</p>	<p>Water criteria for protection of human health is provided. For drinking water the limit is 0.29 g TCE/L and for nondrinking water, the limit is 0.037 g/L.</p> <p>To protect a safe drinking water supply, community and non-transient, non-community water systems must monitor for certain compounds listed.</p> <p>EPA has set forth an enforceable drinking water standard to limit trichloroethylene levels at 0.005 ppm to reduce the risk of cancer or other adverse health effects which have been observed in laboratories.</p> <p>MCLG in primary drinking water is zero for trichloroethylene.</p> <p>Maximum contaminant levels apply to community water systems and non-transient, non-community water systems based on the best available technology treatment techniques. The MCL for trichloroethylene is 0.002 mg/L.</p> <p>Trichloroethylene is identified as a hazardous waste to be restricted from EPA Class I hazardous waste injection wells.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 257—PART 257—CRITERIA FOR CLASSIFICATION OF SOLID WASTE DISPOSAL FACILITIES AND PRACTICES. Promulgated: 56 FR 51016 10/9/91. U.S. Codes: 42 U.S.C. 6907(a)(3) and 6944(a); 33 U.S.C. 1345(d).</p> <p>40 CFR 258—PART 258—CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Codes: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a) and 6949a(c).</p> <p>40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTES. Appendix VIII—Basis for Listing Hazardous Waste. Promulgated: 45 FR 33119, 05/19/80; 53 FR 13388, 04/22/88. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938.</p> <p>40 CFR 264—PART 264—STANDARDS FOR OWNERS AND OPERATORS OF HAZARDOUS WASTE TREATMENT, STORAGE, AND DISPOSAL FACILITIES, Appendix IX. List (Phase 1) of Hazardous Constituents for Ground-Water Monitoring. Promulgated: 45 FR 33221, 05/19/80. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6924, and 6925.</p>	<p>Maximum trichloroethylene contaminant level in groundwater for solid waste disposal facilities is 0.005 mg/L. Reportable quantity of trichloroethylene is 100 lb (45.4 kg). Label, packaging, and shipping codes are also listed in the Hazardous Materials Table.</p> <p>The provisions of this part establish minimum national criteria under RCRA, as amended, for all MSWLF units and under the CWA, as amended, for MSWLF that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment. Maximum contaminant level for trichloroethylene is 0.005 mg/L.</p> <p>Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities. For trichloroethylene, the regulatory level is 0.5 mg/L; its hazardous waste number D040.</p> <p>The provisions of this part establish minimum national standards which define the acceptable management of hazardous waste, and apply to owners and operators of all facilities which treat, store, or dispose of hazardous waste; exceptions do exist. Trichloroethylene has a Practical Quantitation Limit (PQL) of 1 µg/L.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 266—PART 266— STANDARDS FOR THE MANAGEMENT OF SPECIFIC HAZARDOUS WASTES AND SPECIFIC TYPES OF HAZARDOUS WASTE MANAGEMENT FACILITIES. Promulgated: 50 FR 666, 1/4/85. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6924, and 6934.</p> <p>40 CFR 266.100 ff.—Subpart H— Hazardous Waste Burned in Boilers and Industrial Furnaces. Promulgated: 56 FR 7208, 02/21/91.</p> <p>40 CFR 302—PART 302— DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.</p> <p>40 CFR 302.4—Sec. 302.4 Designation of hazardous substances. Superfund (CERCLA, SARA) reportable quantity (RQ) is 100 lb (45.4 kg).</p>	<p>Standards to control emissions are promulgated for generators, transporters, and users of materials used in a manner that constitutes disposal. Affected compounds are listed in 40 CFR 266.40.</p> <p>Hazardous waste burned or processed in a boiler or industrial furnaces are regulated by this subsection to limit release into the environment. Maximum concentration limit for trichloroethylene for residues is 0.005 mg/kg. Maximum Allowable Wastewater Concentration is 6.6 ppm. Maximum Allowable Concentration for trichloroethylene in solid waste is 0.05 ppm.</p> <p>This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.</p> <p>EPA designated as hazardous those substances that when released into the environment may present substantial danger to the public health or welfare or the environment. Notification of EPA is required if the RQ is released to the environment.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Codes: 42 U.S.C. 11013, 11028.</p> <p>40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74, as amended at 47 FR 24537, 06/04/82. U.S. Codes: 33 U.S.C. 1251 et seq.</p> <p>40 CFR 413—PART 413—ELECTROPLATING POINT SOURCE CATEGORY. Promulgated: 46 FR 9467, 01/28/81. U.S. Codes: 33 U.S.C. 1251 et seq., as amended by the CWA of 1977 (Public Law 95-217).</p> <p>40 CFR 414—PART 414—ORGANIC CHEMICALS, PLASTICS, AND SYNTHETIC FIBERS. Promulgated: 52 FR 42568, 11/5/87. U.S. Codes: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361.</p>	<p>This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards. As of 1/1/87, trichloroethylene was listed under the specific toxic chemical listings.</p> <p>The provisions of this part set forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699. Trichloroethylene is listed as a toxic pollutant.</p> <p>Regulates discharge of waste streams from several categories of industrial processes that involve electroplating or electroless plating. The concentration limit of trichloroethylene is 0.01 mg/L.</p> <p>EPA gives pretreatment standards for existing sources (PSES) for metals and organics in effluents from several manufacturing categories. Limitations represent the degree of effluent reduction attainable by application of Best Available Technology (BAT).</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 414.91 ff.—Subpart I—Direct Discharge Point Sources That Use End-of-Pipe Biological Treatment.	Effluent limitation for trichloroethylene maximum concentrations for any one day is 54 µg/L, for any monthly average is 21 µg/L.
	40 CFR 414.101 ff.—Subpart J—Direct Discharge Point Sources That Do Not Use End-of-Pipe Biological Treatment	Effluent limitation for trichloroethylene maximum concentrations for any one day is 69 µg/L, for any monthly average is 26 µg/L.
	40 CFR 414.110 ff.—Subpart K—Indirect Discharge Point Sources.	Effluent limitation for trichloroethylene maximum concentrations for any one day is 69 µg/L, for any monthly average is 26 µg/L.
	40 CFR 423—PART 423—STEAM ELECTRIC POWER GENERATING POINT SOURCE CATEGORY. Promulgated: 47 FR 52304, 11/19/82. U.S. Codes: 33 U.S.C. 1311; 1314(b), (c), (e), and (g); 1316(b) and (c); 1317 (b) and (c); and 1361.	The provisions of this part apply to trichloroethylene discharges resulting from the operation of a generating unit by an establishment generating electricity for distribution and sale, which results from a process utilizing fossil-type or nuclear fuel in conjunction with a thermal cycle that uses the steam water system as the thermodynamic medium.
	40 CFR 433—PART 433— METAL FINISHING POINT SOURCE CATEGORY. Promulgated: 48 FR 32485, 07/15/83. U.S. Codes: 33 U.S.C. 1311, 1314(b) (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	The provisions of this subpart apply to plants which discharge trichloroethylene while performing any of the following six metal finishing operations on any basis material: Electroplating, Electroless Plating, Anodizing, Coating (chromating, phosphating, and coloring), Chemical Etching and Milling, and Printed Circuit Board Manufacture.

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
E P A	<p>40 CFR 464—PART 464—METAL MOLDING AND CASTING POINT SOURCE CATEGORY. Promulgated: 50 FR 45247, 10/30/85. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.</p> <p>40 CFR 467—PART 467—ALUMINUM FORMING POINT SOURCE CATEGORY. Promulgated: 48 FR 49149, 10/24/83. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.</p> <p>40 CFR 468—PART 468—COPPER FORMING POINT SOURCE CATEGORY. Promulgated: 48 FR 36957,08/15/83. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), and 1361.</p> <p>40 CFR 469—PART 469—ELECTRICAL AND ELECTRONIC COMPONENTS POINT SOURCE CATEGORY. Promulgated: 48 FR 15394, 04/08/83. U.S. Codes: 33 U.S.C. 1311, 1314, 1316, 1317, 1318, and 1361.</p>	<p>The provisions of subparts A through D apply to metal molding and casting facilities that discharge or may discharge trichloroethylene to waters of the U.S. or that introduce trichloroethylene into a POTW.</p> <p>This part applies to any aluminum forming facility which discharges or may discharge trichloroethylene to U.S. waters or which introduces or may introduce trichloroethylene into a POTW.</p> <p>The provisions of this part apply to discharges or trichloroethylene resulting from the manufacture of formed copper and copper alloy products.</p> <p>The provisions of subparts B through D are applicable to discharges of trichloroethylene resulting from the manufacture of electronic crystals, cathode ray tubes, and luminescent materials.</p>
F D A	<p>21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643 03/22/77. S. Code: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e</p> <p>21 CFR 73.30—Sec. 73.30 Annatto extract.</p>	<p>This part lists color additives that are exempt from certification in foods, drugs, cosmetics, and medical devices.</p> <p>Trichloroethylene may be safely used in the color additive Annatto extract, including pigments precipitated therefrom.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
F D A	<p>21 CFR 103—PART 103—QUALITY STANDARDS FOR FOODS WITH NO IDENTITY STANDARDS. Promulgated: 42 FR 14325 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 343, 348, 349, 371, 379e.</p> <p>21 CFR 103.35—Sec. 103.35 Bottled Water. Promulgated: 60 FR 57123 11/13/95 [Sec. 103.35 was removed 6/13/96.] U.S. Code: 21 U.S.C. 321, 341, 343, 3348, 349, 371, 379e.</p> <p>21 CFR 165.110 ff—Subpart B—Requirements for Specific Standardized Beverages—Bottled water. Promulgated: 60 FR 57124 11/13/95. U.S. Code: 21 U.S.C. 321, 341, 343, 343A, 348, 349, 371, 379e.</p> <p>21 CFR 172—PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14491 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 342, 348, 371, 379e.</p> <p>21 CFR 172.560—Sec. 172.560 Modified hop extract.</p> <p>21 CFR 173—PART 173—SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14526 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348.</p>	<p>The label of a food is required to state its quality based on, but not limited to, levels of microorganisms and such physical characteristics as turbidity, color, flavor, and odor.</p> <p>The allowable level for volatile organic chemical (VOC) trichloroethylene in bottled water is 0.005 mg/L.</p> <p>The regulations in subparts A and B govern the labeling and effective chemical substance limits for specific standardized beverages. The allowable level for volatile organic chemical (VOC) trichloroethylene in bottled water is 0.005 mg/L.</p> <p>The regulations in subparts A through I govern the amount of food additives allowed for human consumption.</p> <p>The residues of the modified hop extract, manufactured from hops by initial extraction and fractionation, may not contain more than 150 ppm trichloroethylene.</p> <p>The subparts A through D govern which polymer substances, polymer adjuvants for food treatments, enzyme preparations, microorganisms, solvents, lubricants, release agents, and related substances may be used in food for human consumption.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
F D A	<p>21 CFR 173.290—Sec. 173.290 Trichloroethylene.</p> <p>21 CFR 175— PART 175—INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS. Promulgated: 42 FR 14534 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.</p> <p>21 CFR 175.105— Sec. 175.105 Adhesives.</p>	<p>Tolerances are established for residues of trichloroethylene resulting from its use as a solvent in the manufacture of foods: 25 ppm in decaffeinated ground coffee, 10 ppm in decaffeinated soluble (instant) coffee extract, and 30 ppm in spice oleoresins.</p> <p>The subparts A through C deal with components of adhesives and of coatings that may migrate into food from packaging.</p> <p>Trichloroethylene may be safely used in adhesives intended for use as components of articles intended for use in packaging, transporting, or holding food.</p>
N I O S H	<p>1/78. Special Occupational Hazard review of Trichloroethylene. DHEW Pub. No. (NIOSH) 78-130, NTIS No. PB8-1226987.</p> <p>3/77. Criteria for a Recommended Standard....Occupational Exposure to Waste Anesthetic Gases and Vapors. Pub. No. 77-140, NTIS No. PB274 238.</p> <p>6/6/75. Current Intelligence Bulletin #2—Trichloroethylene (TCE). In: NIOSH Current Intelligence Bulletin Reprints-Bulletins 1 through 18 (1975-1977). Pub. No. 78-127, NTIS No. PB83-105080.</p>	<p>NIOSH recommends that trichloroethylene be treated as a potential occupational carcinogen. Summary of NIOSH recommendation: recommended exposure limit—25 ppm TWA; 2 ppm ceiling limit (1 hr) as a waste anesthetic gas.</p>

REGULATIONS<sup>a</sup>

	Regulatory Action	Effect of Regulation/Other Comments
<p>N I O S H</p>	<p>1973. Criteria for a Recommended Standard...Occupational Exposure to Trichloroethylene. DHEW (NIOSH) Pub. No. 73-11025, NTIS No. PB 222 222.</p> <p>29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74. U.S. Code: 29 U.S.C. 653, 655, and 657.</p> <p>29 CFR 1910—Subpart Z—Toxic and Hazardous Substances.</p> <p>29 CFR 1910.1000—Sec. 1910.1000 Air contaminants. Promulgated: 58 FR 40191, 07/27/93. U.S. Code: also includes 5 U.S.C. 553.</p> <p>20 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FE 8577, 02/09/79; 44 FR 20940, 04/06/79. U.S. Code: 29 U.S.C. 653, 655, and 657.</p> <p>29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.</p> <p>29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts and mists. Promulgated: 61 FR 9249, 9250 03/07/96. U.S. Code: 40 U.S.C. 333; 29 U.S.C. 653, 655, and 657.</p>	<p>PEL <math>\leq</math>100 ppm (546 mg/m<sup>3</sup>) 8-hr TWA. Ceiling 2000 ppm (1090 mg/m<sup>3</sup>)</p> <p>PEL <math>\leq</math>100 ppm (546 mg/m<sup>3</sup>) 8-hr TWA.</p>

<sup>a</sup>The regulations in this table have been updated through 62 Federal Register 37448, July 11, 1997.

### 3.0 HUMAN STUDIES

Case reports, descriptive studies, case-control studies, cohort studies, and environmental drinking-water studies reported through 1995 are reviewed in IARC (1995e, pp. 95-104; see Appendix A). Weiss (1996) reviewed essentially the same literature with the addition of one cohort study that had not been published in the open literature. The case-control studies reviewed included those for liver, malignant lymphoma, Hodgkin's disease, renal-cell carcinoma, cancer of the colon, brain tumors, childhood brain tumors, childhood leukemia, and tumors at multiple sites. Most of these studies did not provide relative risk estimates for exposure to only TCE; rather these studies defined occupational exposure or the occupational exposure of the parent using a broad solvent group of which TCE was one of several solvents, or by job or industry title. The cohort studies were primarily of three occupational groups: TCE production workers including workers who had undergone biological monitoring (the reason for which is unknown), aircraft maintenance workers, and workers employed in miscellaneous manufacturing industries. TCE exposure of these cohorts occurred during its use as a metal degreaser. Most workers studied in these cohorts, generally, had low-level TCE exposure, although a small number of those studied may have had high-level peak exposure to TCE. IARC placed greatest weight on the conclusions of three cohort studies (Spirtas et al., 1991; Axelson et al., 1994; and Anttila et al., 1995; all cited by IARC 1995e). These studies were considered particularly relevant for the epidemiologic evaluation of TCE since they contained the better exposure measures, and each study had a sufficiently long follow-up period. Additionally, IARC combined results from these studies in an attempt to examine consistency of results across studies. Based on these three most informative studies, IARC noted a consistently elevated risk for cancer of the liver and biliary tract, with a statistically significant elevated risk for liver and biliary tract cancer with 23 observed cases and 12.87 expected cases (RR = 1.79; 95% Confidence Interval [CI] 1.13-2.68) (all three studies combined), and a modestly elevated risk for non-Hodgkin's lymphoma with 27 cases observed and 18.9 expected (RR = 1.42; 95% CI 0.94-2.09). IARC, additionally, noted a marginally increased risk for non-Hodgkin's lymphoma and exposure to TCE-contaminated ground water in two studies. In each study, statistically significant risks were not consistently seen across all subgroups. Based on their review, IARC concluded that there was limited evidence for the carcinogenicity of TCE in humans. Weiss (1996), evaluating the same body of literature, considered the evidence for a causal association quite limited owing to the small increases in site-specific cancer risks and to the few observed numbers of site-specific cancers.

One retrospective cohort study reviewed prior to publication by IARC (1995e) has been the focus of continued discussion within the scientific community. Henschler et al. (1995a) compared the incidence of renal cancer among 169 male workers (of 183 identified workers) in a German cardboard factory exposed for at least one year (between 1956 and 1975) to TCE, with that for a comparison group of 190 unexposed male workers in the same factory. The follow-up period averaged 34 years and the incidence of cancer among workers was compared to the expected cancer rates using two registries (Denmark and the former German Democratic Republic [GDR]). TCE was the primary organic solvent used for cleaning and degreasing, while other agents that were occasionally used were of negligible quantity. Direct exposure measurements were unavailable [although Brüning et al. (1996) were able to give some qualitative classifications]; workers were classified as exposed or not exposed based on working in three locations. Potentially high levels of TCE exposure may have been encountered by

workers. In the cardboard-machine area, TCE was kept in open barrels and used biweekly to soak rags for cleaning machinery. Workers reported leaving often for fresh air and experiencing drowsiness, headaches, and a sweet taste in the mouth. In two other areas, the locksmith's area and the electrical workshop, TCE was also kept in open barrels, and metal parts were dipped into open baths of TCE for degreasing. No protective measures were used; workers manually dipped the metal parts without using gloves, then set them out to dry in the work area, and then returned the used TCE to the open barrel. In addition, they used TCE to clean floors, work clothes, and their hands.

By the study's closing date of December 31, 1992, five exposed workers and no control workers had been diagnosed with kidney cancer, primarily renal cell carcinoma. Four of the renal cell tumors originated in the tubule epithelia. Additionally, by mid-1993, two more exposed workers were diagnosed with kidney cancer. Three of the seven workers who developed cancer had worked in the cardboard-machine area, one in the locksmith's area, and three in the electrical workshop. The SIR (standardized incidence ratio) was 7.97 (95% CI = 2.59-18.59) based on the Danish rates and 9.66 (CI = 3.14-22.55) based on the GDR rates. By the end of 1992, 50 exposed workers had died, as had 52 control workers. Of the 50 exposed workers who died (SMR = 0.79), 15 died from malignant neoplasms (SMR = 1.01); two of these died from renal cancer (SMR = 3.28, 95% CI, 0.40-12). Of the 52 control workers who died (SMR = 1.03), 15 died from malignant neoplasms (SMR = 1.16), none of which was renal cancer. Time between exposure and diagnosis of renal cancer was 18 years or more. There was no significant difference between the groups in body mass index, blood pressure, diuretic intake, smoking habits, and drinking habits. These factors were not used directly in the analysis to confirm the lack of confounding.

In humans, substantially more cases of tubule cell damage were found among renal cell carcinoma patients who had been exposed to high levels of TCE over many years than among RCC patients who had not been exposed to TCE (Henschler et al., 1995a).

The study has been criticized on a number of grounds. IARC (1995e) noted that the study may have been initiated after the observation of a cluster. Swaen (1995) and Bloemen and Tomenson (1995) also noted the study was a cluster study, high exposures were speculative, physician and hospital records should not be compared with general population mortality rates, and a general inventory of cancer incidence was not performed. Weiss (1996) was also concerned about the possibility of increased disease surveillance because of a suspected cluster.

Henschler et al. (1995b) responded by stating that cluster studies have commonly been a mechanism for identifying human occupational carcinogens, and that epidemiological studies not initiated by a cluster have only occasionally identified human carcinogens successfully. They further replied that although exposure data were not obtainable, the factory's consumption of TCE was well documented and its operational processes were well described. Furthermore, they noted that the best morbidity records available were used and that the absence of increased kidney cancer in the other studies may have been related to the much lower TCE exposures experienced by these other cohorts.

In summary, the concerns raised about the Henschler et al. (1995a) study have generally limited its usefulness for assessing the causal evidence for the human carcinogenicity of TCE; however, the utility of this study may be to promote further research regarding the possible association between renal cell carcinoma incidence and TCE exposure.

A recent population based case-control study in Montreal (Fritschi and Siemiatycki, 1996) found a significantly increased risk of melanoma from occupational exposure to trichloroethylene (see **Table 3-1**). However, the association was based on a relatively small number of exposed subjects and there did not appear to be a difference in the exposure categories. The trichloroethylene analysis was part of a larger study that examined melanoma occurrence in relation to 85 individual substances in 13 occupations and 20 industries. The odds ratio (OR) estimate of the relative risk of melanoma, based on four exposure cases, was 3.4 (95% CI = 1.0-12.3) for the category of potentially substantial exposure to trichloroethylene. A similar OR of 3.4 (exposure cases = 4; 95% CI = 1.0-12.3) was found for the substantial exposure category.

Table 3-1 Post IARC (1995) Human Studies of Trichloroethylene

Design	Population Group	Exposure	Effect	Potential Confounders	Comments	Reference
case-control	<p>Cases: 103 men resident in Montreal, Canada, with histologically confirmed cutaneous melanoma, aged 35-70; response rate = 83%</p> <p>Controls: Two groups - 1) 533 cancer patients, excluding lung cancer 2) 533 population controls from electoral lists or random digit dialing; response rate = 71%</p>	<p><b>Evaluation:</b> semistructured probing interview for detailed information about all jobs of each subject throughout working life; chemists and industrial hygienists evaluated exposure to 294 substances, including trichloroethylene, by consideration of occurrence, exposure frequency, concentration of substance; assigned exposure categories</p> <p><b>Categories:</b> unexposed, insubstantial exposure, substantial exposure</p>	<p><b>Estimation:</b> analyzed exposures with four or more cases of melanoma; used unconditional logistic regression model, including three confounders (age, years of schooling, ethnicity), to derive odds ratios (OR) for melanoma risk for three exposure groups; pooled data from two control groups after confirmation of similar results from independent analyses</p> <p><b>OR (95% CI; no. cases) for melanoma risk:</b>                      3.8 (1.1-13.6; 4) for insubstantial exposure to trichloroethylene                      3.4 (1.0-12.3; 4) for substantial exposure to trichloroethylene                      3.6 (1.5-9.1; 8) for any exposure to trichloroethylene</p>	<p>age, ethnic origin, origin of parents, birthplace, residence for first 15 years, height, weight, years of schooling, annual income, recent hobbies; information from structured questionnaire</p> <p>no information obtained on adult exposure to sun</p>	<p>weakened by small number of cases</p>	<p>Fritschi and Siemiatycki (1996)</p>

Abbreviations: OR = odds ratio; CI = confidence interval

#### 4.0 EXPERIMENTAL CARCINOGENESIS

Experimental carcinogenicity studies conducted by NTP are reported in NTP (1988; 1990, pp. 34-51; see Appendix B). These and other studies conducted prior to 1995 are reviewed in IARC (1995e, pp. 105-109; see Appendix A). More recent experimental carcinogenicity studies were not located. Based on the studies conducted, IARC (1995e) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of TCE.

NTP (1988) conducted a two-year carcinogenicity study to evaluate for strain differences among rats (ACI, August, Marshall, Osborne-Mendel) in their sensitivity to TCE administered by gavage. NTP concluded that these studies were inadequate because of chemically induced toxicity, reduced survival, and deficiencies in study conduct. Despite these limitations, a significant increase in the incidence of renal tubule-cell adenoma occurred in male Osborne-Mendel rats and interstitial cell neoplasms of the testis were observed in Marshall rats.

Subsequently, NTP (1990) evaluated the carcinogenicity of epichlorohydrin-free TCE administered by gavage to B6C3F<sub>1</sub> mice and F344/N rats. TCE was carcinogenic in B6C3F<sub>1</sub> mice, inducing a significant increase in the incidence of hepatocellular carcinomas in males and females and hepatocellular adenomas in females. Although the experiment in male F344/N rats was considered inadequate for evaluating the carcinogenic activity of TCE, a significant increase in the incidence of renal tubule-cell neoplasms occurred in males. TCE was not carcinogenic in female rats.

IARC (1995e) noted that TCE, when tested by inhalation, induced in mice an increased incidence of lymphomas in NMRI mice, liver tumors in ICP mice, and lung tumors in ICR, Swiss, and B6C<sub>3</sub>F<sub>1</sub> mice. Maltoni et al. (1988; cited by IARC, 1995e) observed an increased incidence of interstitial-cell testicular tumors in Sprague-Dawley rats and noted that TCE possibly induces leukemias in rats.

Rodents exposed to TCE typically exhibit dose-related cytomegaly of the kidney, the lesion often being more severe in males, with none or few being found in male or female vehicle control mice or rats. Toxic nephropathy commonly occurs in the solvent-exposed rodents, likewise being more frequent and more severe than seen in controls.

#### 5.0 GENOTOXICITY

##### 5.1 Summary of IARC (1995) Genotoxicity Studies

Genotoxicity studies reported prior to 1995 are reviewed in IARC (1995e, pp. 122-133; see Appendix A). In general, TCE was negative for genetic activity in a broad range of bacterial, lower eukaryote, and *in vitro* and *in vivo* mammalian cell assays. It has been suggested that the positive response could be confounded by the use of impure TCE and/or the presence of potentially mutagenic stabilizers (Goeptar et al., 1995). The following is summarized from IARC (1995e).

In prokaryotes, pure TCE did not usually induce gene mutations or DNA damage, while preparations containing epoxide stabilizers were mutagenic. In lower eukaryotes, TCE was negative for the induction of gene conversion and reverse mutations in *Saccharomyces cerevisiae* (with and without metabolic activation), forward mutations in *Schizosaccharomyces pombe* (with and without metabolic activation), mitotic crossing over in *Aspergillus nidulans* (without metabolic activation), and sex-linked recessive lethal mutations in *Drosophila melanogaster* dosed via injection. TCE was positive for the induction of forward mutations in *A. nidulans*

(without metabolic activation) and equivocal for sex-linked recessive lethal mutations in *D. melanogaster* dosed via feed.

In *in vitro* studies using mammalian cells, TCE was negative for the induction of unscheduled DNA synthesis (UDS) in primary rat hepatocytes, gene mutations in human lymphoblastoid cells (with and without metabolic activation), chromosomal aberrations in Chinese hamster ovary (CHO) (with and without metabolic activation), and inhibition of intercellular communication in rat hepatocytes. In contrast, TCE was positive *in vitro* for covalent DNA binding to calf thymus and salmon sperm DNA (with metabolic activation only) and to the DNA of primary mouse and rat hepatocytes, sister chromatid exchanges (SCE) in CHO cells (with and without metabolic activation), gene mutations in mouse lymphoma cells (with metabolic activation only), inhibition of intercellular communication in primary mouse hepatocytes, and morphological transformation in rat embryo cells.

*In vivo*, TCE administered orally or by intraperitoneal (i.p.) injection was equivocal for covalent binding to the DNA of mouse and rat liver and negative for DNA of mouse spleen, pancreas, lung, testis, kidney, and brain. When administered orally and/or by inhalation, TCE was negative for the induction of UDS in mouse hepatocytes, SCE in mouse splenocytes and rat lymphocytes, dominant lethal mutations in mice, and chromosomal aberrations in mouse splenocytes and rat lymphocytes. TCE was negative for the induction of micronuclei in mouse bone marrow (when administered i.p.) or in mouse splenocytes, mouse spermatocytes, and rat lymphocytes (when administered by inhalation). It was negative and positive for DNA single-strand breaks/alkali labile sites in mouse liver (administered i.p. or orally) and positive for micronucleated polychromatic erythrocytes in mice treated orally and in rats treated by inhalation.

Several studies were conducted to evaluate for genotoxic effects in occupationally exposed humans. The frequency of sperm head abnormalities was not increased. In two studies evaluating the frequency of SCE in mitogen-stimulated lymphocytes, one reported no increase while a second study reported an increase among TCE-exposed smokers but not among nonsmokers. In two studies, a significant increase in chromosomal damage in mitogen-stimulated lymphocytes was detected.

## **5.2 Genotoxicity Studies Published Post IARC (1995)**

In addition to these *in vitro* and *in vivo* studies reviewed by IARC (1995e), TCE was reported as negative for mitotic recombination (as measured by the eye mosaic test) in *D. melanogaster* exposed to TCE via inhalation (Vogel and Nivard, 1993), negative for the induction of chromosomal aberrations in Chinese hamster lung cells (with and without metabolic activation) (Matsuoka et al., 1996), and negative for the induction of UDS in hepatocytes of B6C3F<sub>1</sub> mice (Miyagawa et al., 1995) treated orally. These studies are summarized in greater detail in **Table 5-1**.

TABLE 5-1. SUMMARY OF RECENT TRICHLOROETHYLENE GENOTOXICITY STUDIES

System	Biological Endpoints	Dose and Exposure	Duration	Findings	Comments	Reference	
<b>Lower Eukaryotes</b>							
<i>Drosophila melanogaster</i> strain C-1	mitotic recombination (eye mosaic assay)	n.a.	NG	280 to 4000 ppm via inhalation for 17 h	negative	Genetic principle involves loss of heterozygosity for the wild type, white eye color gene resulting from mitotic recombination between two X chromosomes.	Vogel and Nivard (1993)
<b>Mammalian Systems <i>in vitro</i></b>							
Chinese hamster lung cell line CHL/1us	chromosomal aberrations	-/+	NG	0.33, 0.66, and 1.31 mg/mL for 6, 24, and 48 h -S9 and 6 h +S9	negative/negative	No increase in chromosomal aberrations at any exposure period or S9 condition.	Matsuoka et al. (1996)
<b>Mammalian Systems <i>in vivo</i></b>							
B6C3F <sub>1</sub> mouse hepatocytes	unscheduled DNA synthesis (UDS)	n.a.	NG	600 and 1200 mg/kg (single gavage treatment)	negative	Hepatocytes were collected 24, 39, and 48 h after treatment and exposed to [ <sup>3</sup> H]thymidine for 4 h.	Miyagawa et al. (1995)

Abbreviations: n.a. = not applicable; NG = not given

## 6.0 OTHER RELEVANT DATA

### 6.1 Absorption, Distribution, Metabolism, and Excretion

#### 6.1.1 Absorption and Distribution

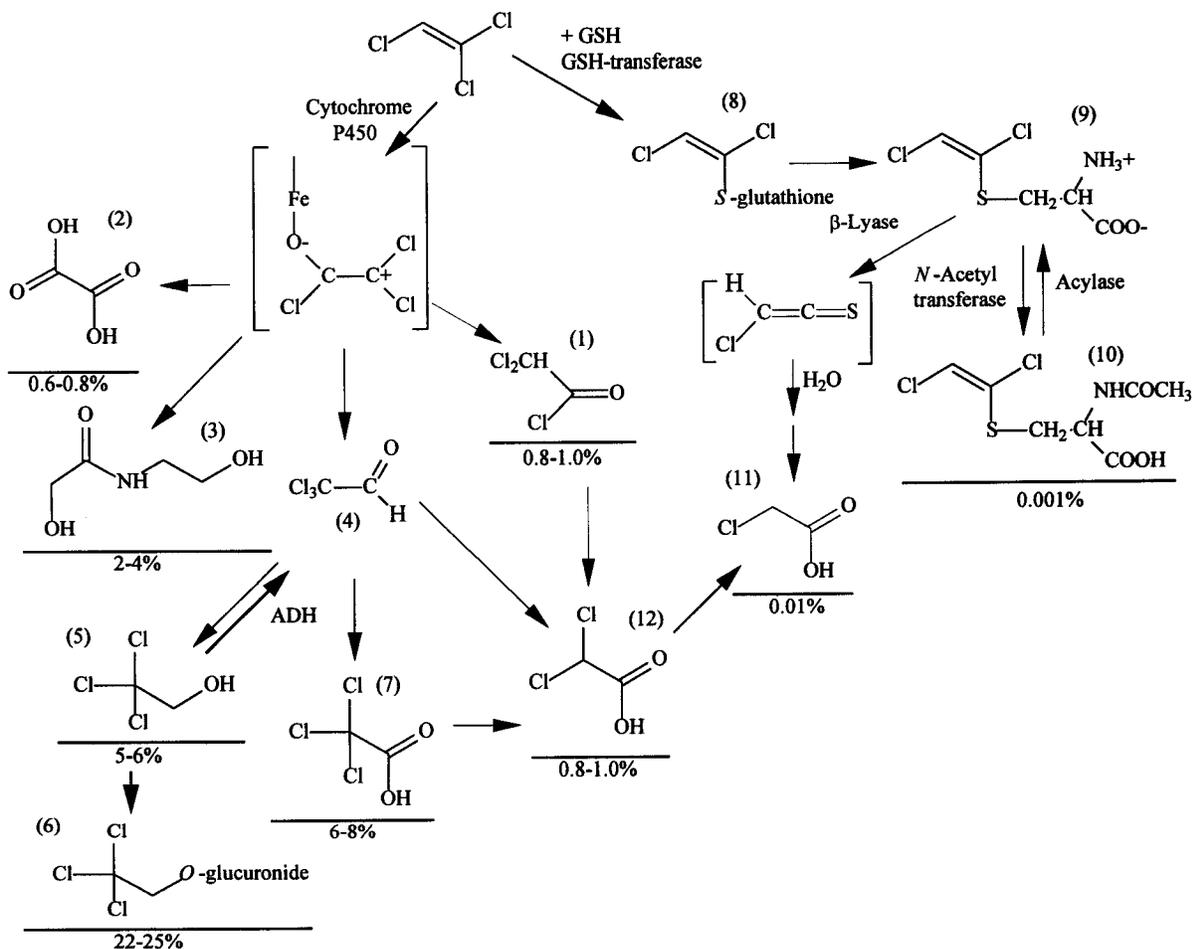
Studies in rats and mice have found rapid absorption of TCE through the lungs and from the gastrointestinal tract but negligible absorption through skin (IARC, 1995e). After 4 hours of exposure to 529 ppm (2840 mg/m<sup>3</sup>, 21.6 mmol/m<sup>3</sup>), male Fischer 344 rats had blood TCE concentrations of 35.5 µg/mL (0.27 µmol/mL), while females exposed to 600 ppm (3220 mg/m<sup>3</sup>, 24.5 mmol/m<sup>3</sup>) had blood TCE concentrations of 25.8 µg/mL (0.196 µmol/mL) (Fisher et al., 1991; cited by IARC, 1995e). Male and female B6C3F<sub>1</sub> mice were exposed for four hours to 110-748 ppm (591-4020 mg/m<sup>3</sup>, 4.50-30.6 mmol/m<sup>3</sup>) and 42-889 ppm (226-4780 mg/m<sup>3</sup>, 1.72-36.4 mmol/m<sup>3</sup>), respectively. The highest mean blood concentration seen for males was 7.3 µg/mL (0.056 µmol/mL) after exposure to 748 ppm (4020 mg/m<sup>3</sup>, 30.6 mmol/m<sup>3</sup>) while females reached a high of 6.3 µg/mL (0.048 µmol/mL) after exposure to 368 ppm (1980 mg/m<sup>3</sup>, 15.1 mmol/m<sup>3</sup>) (Fisher et al., 1991; cited by IARC, 1995e).

Mice given 280 mg/kg (2.13 mmol/kg) radiolabeled TCE in a 10-minute inhalation exposure were studied by whole body autoradiography (Bergman, 1983; cited by IARC, 1995e). TCE was found throughout the body in well-perfused organs; redistribution to adipose tissue occurred after 30 minutes. TCE is concentrated in lipophilic organs such as liver or brain due to an oil:water partition coefficient of 900:1 (Müller et al., 1975; Kilburn and Warshaw, 1993; both cited by Gist and Burg, 1995). Ovaries (Manson et al., 1984; cited by Gist and Burg, 1995) and spermatocytes (Land et al., 1979; cited by Gist and Burg, 1995) are other tissues in which TCE concentrates.

#### 6.1.2 Metabolism and Excretion

Rats and mice metabolize TCE via two different methods—oxidation by cytochrome P450 and conjugation with glutathione (Byington and Leibman, 1965; Leibman, 1965; Dekant et al., 1986, 1990; Commandeur and Vermeulen, 1990; Goepfert et al., 1995; all cited by Bernauer et al., 1996) (see **Figure 6-1**).

**Figure 6-1. Proposed Metabolism of TCE in Rats.** Underlined compounds are identified urinary metabolites (IARC, 1995e). (Figure modified from Dekant et al., 1984; Dekant, 1986; both cited by IARC, 1995e.) (1) dichloroacetyl chloride, (2) oxalic acid, (3) *N*-(hydroxyacetyl)aminoethanol, (4) chloral, (5) trichloroethanol, (6) trichloroethanol glucuronide, (7) trichloroacetic acid, (8) dichlorovinylglutathione, (9) *S*-1,2-dichlorovinylcysteine, (10) *S*-1,2-dichlorovinyl-*N*-acetylcysteine, (11) monochloroacetic acid, (12) dichloroacetic acid. Percentages were determined after an oral dose of 200 mg/kg.



More than 99% of urinary TCE metabolites stem from cytochrome P450-catalyzed reactions (Dekant et al., 1984; cited by IARC, 1995e). One such reaction is the oxidation of TCE to chloral, which may proceed through rearrangement of the putative epoxide intermediate 1,1,2-trichlorooxirane (Powell, 1945; Bonse et al., 1975; both cited by Vamvakas, 1993), or by rearrangement of a non-epoxide intermediate (Miller and Guengerich, 1982; cited by Vamvakas, 1993). Upon contact with aqueous solutions, chloral is rapidly converted to its hydrate (IARC, 1995a). Reduction of chloral hydrate yields trichloroethanol and trichloroethanol glucuronide while oxidation results in trichloroacetic acid (TCA) (Butler, 1949; Daniel, 1963; Kimmerle and Eben, 1973; all cited by IARC, 1995e). TCA glucuronide has been found in the urine of non-human primates treated with TCE by intramuscular injection (Müller et al., 1982; cited by IARC, 1995e). Dichloroacetic acid (DCA) may be formed by a rearrangement of the putative epoxide intermediate 1,1,2-trichlorooxirane and subsequent hydrolysis (Hathway, 1980; cited by IARC, 1995e) or by biotransformation of chloral hydrate or TCA (Larson and Bull, 1992b; cited by IARC, 1995e). Oxalic acid may be formed by oxidation of DCA (Larson and Bull, 1992b; cited by IARC, 1995e) or by cleavage, either enzymatic or non-enzymatic, of 1,1,2-trichlorooxirane followed by spontaneous elimination of two equivalents of hydrochloric acid, reaction with water, and oxidation (Dekant et al., 1984; cited by IARC, 1995e). *N*-Hydroxyaminoacetyethanol is thought to be formed by the reaction of TCE oxidized intermediates with aminoethanol or phosphatidylethanol with subsequent hydrolysis of the acylated lipid (Dekant et al., 1984; cited by IARC, 1995e). There are significant quantitative differences between rats and mice in the metabolism of TCE to TCA and DCA (Green, 1990). TCE metabolism in the mouse is linear over a wide range of dose levels, while metabolism becomes saturated in the rat at relatively low dose levels.

In the less common of the two metabolic pathways, TCE is conjugated to glutathione. The result is dichlorovinylglutathione (DCVG), which can be converted to *S*-1,2-dichlorovinylcysteine (DCVC). DCVC can then follow one of two paths, forming either monochloroacetic acid or *N*-acetyldichlorovinylcysteine, which has been found to be excreted in a dose-dependent manner after experimental exposure of rats and human volunteers to TCE (Bernauer et al., 1996).

Most TCE metabolites found in experimental animals have also been found in humans (see **Table 6-1**) and there is no evidence that the metabolism of TCE in animals differs from human metabolism (IARC, 1995e). Based on *in vitro* metabolism studies with 23 human hepatic microsomal samples, Lipscomb et al. (1997) concluded that CYP2E1 was predominantly responsible for the microsomal-mediated metabolism of TCE. Furthermore, the lack of uniformity among these samples in their capacity to metabolize TCE suggested to these investigators that subpopulations of individuals may exist with increased susceptibility to TCE.

After TCE is absorbed from the gastrointestinal (GI) tract, first-pass elimination by the liver and lungs play a major role in clearing TCE. When male Sprague-Dawley rats were injected with 0.17 mg/kg (1.3  $\mu\text{mol/kg}$ ) TCE in a 5% aqueous Alkamuls emulsion, the liver eliminated 10-fold more drug than did the lungs on the first pass (Lee et al., 1996). As the dose increased beyond 1 to 2 mg/kg (8 to 15  $\mu\text{mol/kg}$ ), hepatic first-pass elimination diminished. In human subjects exposed by inhalation for three hours to TCE at concentrations up to 315 ppm (1690  $\text{mg/m}^3$ , 12.9  $\text{mmol/m}^3$ ), metabolism was not saturated (Ikeda, 1977; Nomiyama and Nomiyama, 1977; both cited by Lee et al., 1996). This finding led the authors to hypothesize

that a single pass through the liver is sufficient to completely remove TCE from the blood. Based on these data, Lee et al. (1996) concluded that since metabolism should not be saturated by the daily doses of TCE to which humans are exposed, first-pass elimination should remove a substantial portion of the TCE from the blood before it reaches extra-hepatic organs.

A substantial delay between elimination of TCE from blood and appearance of the metabolite TCA in blood was reported by Templin et al. (1993; cited by Stenner et al., 1997). Stenner et al. (1997) performed a study to determine if enterohepatic recirculation of trichloroethanol and TCA could explain the TCA concentrations seen in blood following administration of TCE. Male F344 rats with and without intact enterohepatic recirculation were given intravenous doses of 100 mg/kg (0.669 mmol/kg) trichloroethanol. The results demonstrated that roughly 36% of the trichloroethanol and 76% of the TCA in systemic blood was due to enterohepatic recirculation. Urinary excretion of TCA was decreased by 80% in rats lacking enterohepatic recirculation following intravenous administration of trichloroethanol (Stenner et al., 1997). Using these as well as previous findings, the authors concluded that enterohepatic recirculation can account for the delay seen prior to the appearance of TCA in the blood after administration of oral doses of TCE.

TCE metabolites are excreted primarily in the urine; however, up to 30% can be eliminated by excretion in the bile (Gist and Burg, 1995). The major metabolites found in urine in humans are trichloroethanol, trichloroethanol glucuronide, and TCA (Cole et al., 1975; cited by IARC, 1995e).

**Table 6-1. Metabolites of TCE by Species**

Metabolite <sup>a</sup>	Reference
<b>Rat</b>	
<i>N</i> -acetyl- <i>S</i> -(1,2-dichlorovinyl)- <i>L</i> -cysteine (10)	Dekant et al. (1986); Commandeur and Vermeulen (1990); Dekant et al. (1990); all cited by IARC (1995e)
<i>N</i> -acetyl- <i>S</i> -(2,2-dichlorovinyl)- <i>L</i> -cysteine (isomer of 10)	Dekant et al. (1986); Commandeur & Vermeulen (1990); Dekant et al. (1990); all cited by IARC (1995e)
chloroacetic acid (11)	Green and Prout (1985; cited by IARC, 1995e)
dichloroacetic acid (12)	IARC (1995e)
<i>N</i> -(hydroxyacetyl)aminoethanol (3)	IARC (1995e)
oxalic acid (2)	IARC (1995e)
trichloroacetic acid (7)	Kimmerle and Eben (1973; cited by IARC, 1995e)
trichloroethanol (5)	Kimmerle and Eben (1973; cited by IARC, 1995e)
trichloroethanol glucuronide (6)	IARC (1995e)
<b>Chimpanzees, Baboons, and Rhesus Monkeys</b>	
trichloroacetic acid glucuronide (formed from 7)	Müller et al. (1982; cited by IARC, 1995e)
<b>Human</b>	
<i>N</i> -acetyl- <i>S</i> -(1,2-dichlorovinyl)- <i>L</i> -cysteine (10)	Birner et al. (1993; cited by IARC, 1995e); Bernauer et al. (1996)
<i>N</i> -acetyl- <i>S</i> -(2,2-dichlorovinyl)- <i>L</i> -cysteine (isomer of 10)	Birner et al. (1993; cited by IARC, 1995e); Bernauer et al. (1996)
chloral hydrate (formed from 4)	Cole et al. (1975; cited by IARC, 1995e)
<i>N</i> -(hydroxyacetyl)aminoethanol (3)	Dekant et al. (1984; cited by IARC, 1995e)
oxalic acid (2)	Dekant et al. (1984; cited by IARC, 1995e)
trichloroacetic acid (7)	Cole et al. (1975; cited by IARC, 1995e)
trichloroethanol (5)	Cole et al. (1975; cited by IARC, 1995e)
trichloroethanol glucuronide (6)	Cole et al. (1975; cited by IARC, 1995e)

<sup>a</sup>Numbers in parentheses correspond to the numbers in Figure 6-1.

## 6.2 Pharmacokinetics

The maximum metabolic rate ( $V_{\max}$ ) for TCE in rats is 100.6  $\mu\text{g}/\text{min}$  (0.77  $\mu\text{mol}/\text{min}$ ) with a Michaelis constant ( $k_m$ ) of 5.05  $\mu\text{g}/\text{mL}$  (0.038  $\mu\text{mol}/\text{mL}$ ). Absorption by organs occurs with the following organ-to-blood partition coefficients: GI tract, 1.35; liver, 2.17; spleen 0.63 (Varkonyi et al., 1995).

Another study calculated the  $V_{\max}$  in humans to be 215.0 mg/hr (1.636 mmol/hr) based on the  $V_{\max}$  found in rats using the allometric relationship (Human  $V_{\max}$ ) = (Rat  $V_{\max}$ ) [70/(Rat wt., kg)]<sup>0.7</sup> (Gargas et al., 1986; cited by Rappaport, 1993). Of the absorbed dose of TCE, 0.75 is the fraction metabolized ( $F_M$ ) as obtained from estimated human clearance rates (Sato and Nakajima, 1987; cited by Rappaport, 1993). Using these two values, Rappaport (1993) calculated that 178.3 mg/m<sup>3</sup> (1,357 mmol/m<sup>3</sup>) is the highest mean TCE concentration to which a person can be exposed while maintaining linear kinetics. This is slightly lower than the occupational threshold limit value of 269.0 mg/m<sup>3</sup> (50 ppm; 2.047 mmol/m<sup>3</sup>) (ACGIH, 1996).

The urine of humans exposed to varying levels of TCE was examined for the presence of TCE metabolites (Bernauer et al., 1996). After inhalation of 160 ppm, excretion of the mercapturate metabolites, *N*-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-*L*-cysteine, seemed to become saturated while excretion of oxidatively formed metabolites increased linearly. Elimination of mercapturates in humans exhibited a biphasic nature in addition to a slow rate of elimination compared to the oxidatively formed metabolites. When five male volunteers were exposed to 70 ppm (380 mg/m<sup>3</sup>, 2.9 mmol/m<sup>3</sup>) TCE for 4 hours per day over a 5-day period, trichloroethanol concentrations in urine rose rapidly, then stabilized, and remained high for the duration of the 5 days (Monster et al., 1979; cited by IARC, 1995e). Urinary excretion of TCA continued to rise until the end of exposure. The major metabolites of TCE are cleared from humans at very different rates. TCA is slowly eliminated in urine with a half-life of about 52 hours, but trichloroethanol and trichloroethanol glucuronide are eliminated rapidly with half-lives of about 10 hours (Müller et al., 1972, 1974; cited by IARC, 1995e). The difference is even more marked in rats; high levels of TCA are present in the blood for up to 30 hours in contrast to trichloroethanol and chloral hydrate, which are cleared from the blood with a half-life of 1 to 2 hours (Kimmerle and Eben, 1973; cited by IARC, 1995e).

## 6.3 Structure-Activity Relationships

### 6.3.1 Chlorinated Alkanes and Alkenes

A knowledge-based SAR approach (MULTICASE) was used to examine the structural basis for, among other things, the induction of aneuploidy by chlorinated alkanes and alkenes in *A. nidulans* (Rosenkranz and Klopman, 1996). Data on induction of aneuploidy by 35 chlorinated alkanes or alkenes came from Crebelli et al. (1992; cited by Rosenkranz and Klopman, 1996). Compounds inducing aneuploidy were found to have significantly higher water solubilities (1.157 vs. 0.764 [sic],  $p = 0.02$ ) and significantly lower log P (octanol: water partition coefficient) values (1.988 vs. 2.424,  $p = 0.009$ ) than inactive compounds. Nine structural fragments were found to correlate with the ability to induce aneuploidy in 11 of 12 chemicals. One of these fragments is found in TCE: Cl-CH=C-Cl.

### 6.3.2 Structural Analogues

Structural analogues of TCE include vinyl chloride (chloroethylene), vinylidene chloride (1,1-dichloroethylene), and 1,1,2,2-tetrachloroethylene (perchloroethylene).

#### 6.3.2.1 Vinyl Chloride

Based on human epidemiological studies and case reports, and rodent carcinogenicity data, IARC (1979) concluded that there was sufficient evidence for the carcinogenicity of vinyl chloride to humans and experimental animals, respectively. IARC (1987a) reaffirmed vinyl chloride's evaluation as a human carcinogen, citing several additional epidemiological studies and case reports. Occupational exposure to vinyl chloride is associated with increased risks for angiosarcoma of the liver, hepatocellular carcinoma, brain and lung tumors, and malignancy of the hematopoietic and lymphatic system. Some studies indicated a possibility of increased risk of gastric and gastrointestinal cancer (other than liver) (IARC, 1987). Green (1990) noted that workers in vinyl chloride manufacturing also experienced increases in tumors of the skin and thyroid, although a causal relationship was not established. One study indicated excessive fetal mortality among wives of workers exposed to vinyl chloride, and several others reported increased rates of birth defects in children whose parents lived in communities with vinyl chloride-poly(vinyl chloride) or other chemical processing facilities (IARC, 1979).

Vinyl chloride has been extensively tested in rats, hamsters, and mice via inhalation exposure and oral, subcutaneous, and i.p. administration. Oral administration or inhalation of vinyl chloride induced Zymbal's gland tumors in rats and hamsters, nephroblastomas in rats, forestomach papillomas and melanomas in hamsters, and pulmonary and mammary gland tumors in mice (IARC, 1979, 1987a). In all three species, exposure to vinyl chloride induced hemangiosarcoma of the liver (IARC, 1979, 1987a; Green, 1990). Vinyl chloride was carcinogenic in rats exposed prenatally (IARC, 1979).

Green (1990) observed that vinyl chloride's wide range of effects in many species was characteristic of a genotoxic carcinogen. As reviewed in IARC (1979), vinyl chloride induced unscheduled DNA synthesis (UDS) in primary rat hepatocytes, gene mutation in cultured Chinese hamster lung cells, gene conversion in yeast, and DNA damage and mutation in bacteria. It also induced sex-linked recessive lethals in *D. melanogaster* and was mutagenic in plants and *S. pombe* (but not other fungi). In rodents exposed *in vivo*, vinyl chloride induced chromosomal aberrations, SCE, and micronuclei in bone marrow cells, and alkylated DNA in tissues of mice and rats. Workers exposed to vinyl chloride vapor showed induction of chromosomal aberrations in peripheral blood lymphocytes. Two additional studies of exposed workers indicated negative results for sister chromatid exchanges (SCE), while one study indicated a weakly positive response. Green (1990) suggested that vinyl chloride's carcinogenic activity results from its metabolism by microsomal mixed-function oxidases to chloro-oxirane (chloroethylene oxide) and chloroacetaldehyde, two mutagenic metabolites, and concludes that vinyl chloride is a classical genotoxin causing cancer by somatic mutation.

#### 6.3.2.2 Vinylidene Chloride

IARC (1987b) concluded that vinylidene chloride was not classifiable as a human carcinogen because of inadequate evidence and also considered the evidence for its carcinogenicity to animals to be limited. There were no data available on its genetic and related effects in humans. Green (1990) stated that the question of vinylidene chloride's carcinogenicity

has never been resolved, although as the closest analogue of the well established carcinogen vinyl chloride, it might be expected to be carcinogenic.

Experimental carcinogenicity has been tested via inhalation and oral administration in mice and rats, via topical application and subcutaneous administration to mice, and via inhalation in hamsters (IARC, 1987b). Oral administration produced negative results in mice and rats. Inhalation produced no treatment-related neoplasms in rats and hamsters; in mice, however, males showed a treatment-related increase in the incidence of kidney adenocarcinomas, females showed an increase in the incidence of mammary carcinomas, and both males and females showed an increase in pulmonary adenomas. Mice given several subcutaneous administrations showed no tumors at injection sites. Maltoni et al. (1984a,b; cited by Green, 1990) found severe nephrotoxicity in Swiss mice exposed to high doses, and tumors in only 2 of 18 surviving mice. Male Swiss mice were more susceptible to nephrotoxic effects than were other mouse strains, rats, and hamsters. Green (1990) suggests that kidney damage in Swiss mice may facilitate expression of the weak genotoxic potential of vinylidene chloride's metabolites.

As reviewed by IARC (1987b), vinylidene chloride was mutagenic in plant cells and bacteria and induced mutation and gene conversion in yeast. Although it was not mutagenic or clastogenic in cultured Chinese hamster lung cells, it did induce UDS in primary rat hepatocytes. *In vivo*, vinylidene chloride did not induce dominant lethal mutations in mice or rats, or chromosomal aberrations in bone marrow cells of rats, but did induce UDS in treated mice.

#### 6.3.2.3 Tetrachloroethylene

IARC (1995c) has evaluated tetrachloroethylene as probably carcinogenic to humans, based on limited evidence in humans and sufficient evidence in experimental animals. In epidemiological studies, occupational exposure to tetrachloroethylene presented increased risk for esophageal cancer, non-Hodgkin's lymphoma, and cervical cancer. In experimental carcinogenicity studies, mice given tetrachloroethylene by gavage showed an increased incidence of hepatocellular carcinomas (IARC, 1995c). Mice exposed to high doses by inhalation showed exposure-related increases in hepatocellular adenomas and carcinomas (NTP, 1986). Rats exposed to high doses by inhalation showed a dose-related increase of mononuclear-cell leukemia; also observed but not statistically significant was an increase in the incidence of renal tubule-cell adenomas and adenocarcinomas in male rats (NTP, 1986). In a study by Anna et al. (1994; cited by IARC [1995e]), the liver tumors induced in mice treated chronically with tetrachloroethylene for up to 76 weeks exhibited a decreased frequency of H-*ras* mutations and an increased frequency of K-*ras* mutations compared to liver tumors from concurrent and historical control animals.

Tetrachloroethylene is generally negative in most genetic toxicology assays (IARC, 1995c). Tetrachloroethylene was not active in the SOS chromotest with *Escherichia coli* and was not mutagenic to bacteria in the absence of metabolic activation. Purified tetrachloroethylene was not mutagenic in *S. typhimurium* or *E. coli* in the presence of rat liver S9. However, purified tetrachloroethylene was mutagenic in *S. typhimurium* TA100 in the presence of rat liver glutathione S-transferase, glutathione, and kidney microsomes (Vamvakas et al, 1989; cited by IARC, 1995c). In stationary-phase yeast, it did not induce gene conversion, mitotic recombination, or reverse mutations, while conflicting data were obtained for cells in logarithmic growth. Tetrachloroethylene was negative for the induction of sex-linked recessive lethal mutations in *D. melanogaster*, unscheduled DNA synthesis in rat primary hepatocytes,

chromosomal aberrations or SCE in cultured Chinese hamster lung cells (with and without metabolic activation), and for mutations in mouse lymphoma cells (with and without metabolic activation). However, DNA binding of radioactively labeled tetrachloroethylene to calf thymus DNA *in vitro* in the presence of metabolic activation, and to DNA and proteins of mouse and rat liver, kidney, and stomach *in vivo* have been reported. It was also reported positive for cell transformation in Fischer rat embryo cells but not in mouse BALB/c-3T3 cells. In *in vivo* studies, the frequency of gene conversion and reverse mutations was not increased in a host-mediated assay using yeast recovered from the liver, lungs, and kidneys of mice treated with tetrachloroethylene. A significant increase in DNA damage (strand breaks/alkali-labile sites) in mouse liver and kidney, but not lung, was detected after treatment.

IARC (1995c) noted two studies of workers occupationally exposed to tetrachloroethylene in which small increases of peripheral lymphocytes showing numerical chromosome abnormalities (Ikeda et al., 1980; cited by IARC, 1995c), and SCE frequency in subjects who smoked (Seiji et al, 1990; cited by IARC, 1995c). In both studies, the possible confounding effects of smoking were not controlled.

### 6.3.3 Metabolites

#### 6.3.3.1 Dichloroacetic Acid and Trichloroacetic Acid

IARC (1995b) concluded that the evidence for the carcinogenicity of DCA was inadequate for humans and limited for experimental animals. In four studies, oral administration of pH-neutralized DCA to male B6C3F<sub>1</sub> mice resulted in an increased incidence of hepatocellular adenomas and carcinomas. Expression of *c-myc* and *c-H-ras* was increased by approximately 3-fold and 4-fold, respectively, in hepatic carcinomas sampled from DCA-treated mice. Although the frequency of mutations at codon 61 of *H-ras* was not significantly different between liver tumors in DCA-treated and control mice, the spectra of these mutations showed a significant increase in CTA and a corresponding decrease in AAA.

The genetic toxicity of DCA in prokaryotic or animal cells is inconsistent IARC (1995b). In *S. typhimurium*, DCA did not induce differential toxicity in DNA-repair-deficient strains but was mutagenic. DCA did not induce  $\lambda$  prophage in *E. coli*, nor did it induce DNA strand breaks in cultured human CCRF-CEM cells, without metabolic activation, or in mouse or rat hepatic cells. *In vivo*, DCA administered acutely induced DNA strand breaks in liver cells of rats and mice in one laboratory, while another laboratory using higher doses reported the absence of DNA strand breakage in rat and mouse hepatic cells after single or repeated dosing, or in epithelial cells from mouse spleen, stomach, and duodenum after a single dose.

IARC (1995d) concluded that there is inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of TCA. TCA induced a significant increase in the incidence of hepatocellular adenomas and carcinomas in two B6C3F<sub>1</sub> male mouse drinking water studies (IARC, 1995d). Expression of *c-myc* and *c-H-ras* was increased by approximately 6-fold and 4-fold, respectively, in hepatic carcinomas sampled from TCA-treated mice.

As reviewed in IARC (1995d), TCA was not mutagenic to *S. typhimurium*, nor did it induce  $\lambda$  prophage in *E. coli*, with or without metabolic activation. TCA, neutralized to avoid the effects of low pH, was not clastogenic in cultured human lymphocytes. TCA did not induce DNA strand breaks in cultured or human CCRF-CEM cells, without metabolic activation, or in

mouse or rat hepatic cells. *In vivo*, TCA administered acutely induced DNA strand breaks in liver cells of rats and mice in one laboratory, while another laboratory using higher doses reported no increase in DNA strand breaks in rat and mouse hepatic cells, or in mouse epithelial cells from stomach and duodenum. TCA was reported as positive for the induction of micronuclei and chromosomal aberrations in bone marrow cells and abnormal sperm morphology after injection into Swiss mice, but negative for micronuclei induction at a 10-fold higher dose injected in C57BL/JfBL/Alpk mice.

#### 6.3.3.2 Chloral Hydrate

IARC evaluates chloral and chloral hydrate as not classifiable for carcinogenicity to humans, citing inadequate evidence in humans and limited evidence in animals (IARC, 1995a). In an experimental carcinogenicity study that IARC deemed adequate, male mice given chloral hydrate by gavage showed a significantly increased incidence of hepatic adenomas and carcinomas.

Chloral hydrate has been extensively evaluated for its ability to induce aneuploidy in various test systems (IARC, 1995a). It induced aneuploidy in the absence of metabolic activation in fungi, human lymphocytes *in vitro*, secondary spermatocytes of mice treated *in vivo* (in three of four studies), and in bone marrow cells of mice treated *in vivo*. Chloral hydrate induced a significant increase in the frequency of micronuclei in Chinese hamster cell lines and human lymphocytes *in vitro*, and in bone marrow erythrocytes (in two of four studies) and spermatids (in two of three studies) of mice treated *in vivo*. Where evaluated, the micronuclei were most frequently induced by numerical rather than structural chromosomal damage.

IARC (1995a) noted conflicting results for DNA damage caused by chloral hydrate. It was mutagenic, with and without metabolic activation, in *S. typhimurium* TA100 (two of four studies) and in TA104 (single study) but not in TA1535, TA1538, or TA98. It was negative for mitotic crossing over in *A. nidulans* in the absence of metabolic activation, but weakly positive for meiotic recombination and gene conversion (but not reverse mutations) in *S. cerevisiae* in the presence and absence of metabolic activation, respectively. It induced somatic mutations in *D. melanogaster*, but was negative for DNA protein cross-links in rat liver nuclei and for DNA single strand breaks/alkali-labile sites in primary rat hepatocytes. Chloral hydrate was a weak inducer of SCE in cultured human lymphocytes. *In vivo*, it induced mitotic gene conversion in a host-mediated assay with *S. cerevisiae* recovered from mouse lungs. One laboratory reported a significant increase in DNA strand breaks in liver DNA of treated rats and mice, while another laboratory reported a negative study. Chloral hydrate did not induce chromosomal aberrations in mouse bone marrow cells, spermatogonia, spermatocytes, or oocytes. However, a significant increase in chromosomal aberrations in mouse secondary spermatocytes was reported for one study.

#### 6.3.3.3 Dichlorovinylcysteine

Dichlorovinylcysteine is mutagenic in the Ames test and highly nephrotoxic (Vamvakas et al., 1993; Clewell et al., 1995). DNA damage in kidney tubules was found to be induced *in vivo* and *in vitro* by *S*-(1,2-dichlorovinyl)-*L*-cysteine, and in LLC-PK<sub>1</sub> cells, double-strand breaks were found (Jaffe et al., 1985; Vamvakas et al., 1992; both cited by Vamvakas et al., 1993). Radiolabeled cysteine conjugates added to bacterial and renal cells resulted in covalent binding to DNA (Bhattacharya and Schultze, 1972, 1973a,b; Vamvakas et al., 1988; cited by

Vamvakas et al., 1993). Pyridine nucleotide oxidation is induced by *S*-(1,2-dichlorovinyl)-*L*-cysteine incubated with kidney mitochondria (Meadows et al., 1988; Vamvakas et al., 1992; both cited by Vamvakas et al., 1993). At concentrations producing small or undetected decreases in cell growth, the cysteine metabolite induces Ca<sup>2+</sup>-dependent DNA damage. Following this DNA fragmentation, an increase is seen in ADP-ribosylation of nuclear proteins (Vamvakas et al., 1992; cited by Vamvakas et al., 1993), which, if moderate, has been shown in mouse fibroblasts to be associated with increased cell proliferation (Muehlematter et al., 1988; cited by Vamvakas et al., 1993).

Prior to the collapse of the mitochondrial membrane potential, cytosolic Ca<sup>2+</sup> concentrations are increased by *S*-(1,2-dichlorovinyl)-*L*-cysteine in renal cells (Vamvakas et al., 1990; cited by Vamvakas et al., 1993). Tumor promoters that induce oxidative stress commonly produce such an effect (Vamvakas et al., 1993). IARC has not yet determined a classification for dichlorovinylcysteine.

#### **6.4 Immune Suppression**

Sprague-Dawley rats and B6C3F1 mice given i.p. doses of TCE showed inhibition of immune system activity, as demonstrated by decreases in splenocyte viability, inhibition of lipopolysaccharide-stimulated mitogenesis, inhibition of hepatic natural killer cells, and inhibition of natural cytotoxic cell activities in all groups of effector cells (IARC, 1995e).

#### **6.5 Molecular Changes in Human Tumors**

Brüning et al. (1997) reported on a study that concluded that a linkage existed between a known molecular genetic cause for renal cell carcinoma [i.e., somatic mutations of the von Hippel-Lindau (*VHL*) tumor suppressor gene] and exposure to TCE. Somatic *VHL* mutations are a known causative molecular event in renal cell carcinoma (Gnarra et al., 1994). Tumor tissues from 23 patients with renal cell cancer and a history of occupational exposure to high levels of TCE were evaluated. The patients all had worked with TCE in small, poorly ventilated areas and frequently experienced room temperatures between 30° and 50 °C (85° - 124 °F). They reported dizziness, headache, nausea, and drowsiness, a pronounced smell of TCE in the work area, and a need for frequent breaks to get fresh air outside the work area. The average long-term exposure to TCE was 21.8 years. The cases did not come from a single source, but rather from two case-control studies and pending legal compensation cases.

DNA was isolated from microdissected tumor cells, amplified by polymerase chain reaction (PCR), and analyzed using single-strand conformation polymorphism (SSCP) and sequencing. Renal cell carcinoma tissue from all 23 TCE-exposed patients had an abnormal SSCP pattern in at least one of the *VHL* exons (30% of the of the aberrations were in exon 1, 44% of the band shifts occurred in exon 2, and 26% were in exon 3). Although sequencing analyses were not yet completed, four SSCP band shifts were confirmed as *VHL* mutations. Based on the much lower reported frequency of *VHL* mutations (33-55%) in renal cell carcinomas from non-exposed patients (Gnarra et al., 1994; Shuin et al., 1994; Foster et al., 1994; Whaley et al., 1994) and the lower frequency of exon 2 mutations (24%) in cases where a *VHL* mutation was present (Gnarra et al., 1994), Brüning et al. (1997) concluded that these data provided further proof for human renal carcinogenicity induced by high occupational exposure to TCE. This analysis provides interesting new data suggesting a possible direct molecular

association between exposure and a potentially important somatic alteration in renal cell carcinoma. These preliminary findings should be regarded with caution. Not all VHL gene mutations had been confirmed by sequencing. Exposure was not precisely determined for each individual, cases were not selected systematically from a well-defined study base, and comparison subjects from the same base were not used.

## 7.0 MECHANISMS OF CARCINOGENESIS

### 7.1 Liver Cancer

Hepatocellular carcinomas have been reported in some strains of mice but not in rats treated with TCE (section 4), and species and strain differences in metabolism of TCE to TCA and DCA are thought to account for this difference (Goeptar et al., 1995; Maronpot et al., 1995; Clewell et al., 1995). Both TCA and DCA induce hepatocellular adenomas and carcinomas in mice (section 6.3.3.1), possibly mediated through the induction of peroxisome proliferation, cytotoxicity, and reparative hyperplasia (Maronpot et al., 1995). TCE-induced peroxisome proliferation has not been demonstrated in the rat (Elcombe, 1985). Goeptar et al. (1995) concluded that the species difference in TCE-induced peroxisome proliferation was most likely due to the saturation of the oxidative metabolism of TCE in the rat, thereby limiting the maximal levels of TCE to below those required to induce this effect. The involvement of TCA and DCA in TCE-induced hepatocellular carcinomas in the mouse is further supported by studies in which strain differences in the incidence of liver tumors correlate with differences in the oxidative metabolism of TCE. For example, TCE induces liver tumors in Swiss and B6C3F<sub>1</sub> mice (NTP, 1986; Maltoni et al., 1986, cited by Goeptar et al., 1995) but not NMRI mice (Henschler et al., 1980; cited by Goeptar et al., 1995). In the former strains, TCA and DCA account for 7-12 and 2% of the TCE administered, respectively (Green and Prout, 1985; cited by Goeptar et al., 1995), while in the latter strain, TCA and DCA each accounts for only 0.1% of the TCE dose (Dekant et al., 1984; cited by Goeptar et al., 1995). Based on this line of reasoning, the ability of TCE to induce liver tumors in humans depends on the rate of formation of TCA and DCA and on the induction of peroxisome proliferation in liver cells. Although humans appear more similar to mice than to rats in their ability to oxidatively metabolize TCE, they metabolize approximately 60 times less TCE on a body-weight basis than mice at similar exposure levels, and TCA does not appear to induce peroxisome proliferation in human hepatocytes (Goeptar et al., 1995).

### 7.2 Lung Cancer

TCE, when administered by inhalation, induces a significant increase in the incidence of lung tumors (adenomas and carcinomas) in female (but not male) B6C3F<sub>1</sub> mice and male (but not female) Swiss mice. Mechanistic studies on mouse lung tumor formation suggest that chloral formation in Clara cells may explain the sex and species differences (Goeptar et al., 1995; Green et al., 1997). Mouse Clara cells studied *in vitro* were found to have relatively high cytochrome P450 activity and relatively low activity for alcohol dehydrogenase (ADH), the enzyme that converts chloral to trichloroethanol, and for uridine diphosphate (UDP) glucuronosyl transferase, the enzyme responsible for the glucuronidation of trichloroethanol (Odum et al., 1992; cited by Clewell et al., 1995). Thus, chloral would be anticipated to accumulate in mouse Clara cells, which may explain the formation of lung tumors in mice. Consistent with this hypothesis, exposure of mice to chloral resulted in lesions in lung Clara cells similar to those caused by a 10-

fold higher concentration of TCE (Odum et al., 1992; cited by Clewell et al., 1995). Goepfert et al. (1995) hypothesized that the absence of smooth endoplasmic reticulum in human lung Clara cells (Smith et al., 1979; cited by Goepfert et al., 1995) implies a lack of cytochrome P450 activity and a corresponding lack of risk for chloral accumulation.

### **7.3 Kidney Cancer**

In contrast to tumors of the lung and liver, kidney tumors are found in rats but not in mice, and at doses associated with a high incidence of nephrotoxicity (Goepfert et al., 1995; Clewell et al., 1995). In a minor mercapturic metabolic pathway, TCE is conjugated to glutathione in the liver. The conjugated TCE is further metabolized in the kidney to cysteine conjugate dichlorovinylcysteine (DCVC) and then to a reactive intermediate (Birner et al., 1993; cited by Clewell et al., 1995). The mutagenic and nephrotoxic properties of the *S*-1,2 isomer of DCVC are described in section 6.3.3.3.

Goepfert et al. (1995) concluded that it seemed improbable that the oxidative pathway would become saturated in humans at the levels of TCE to which they are likely to be exposed. However, urinary excretion of *N*-acetylated DCVC (a detoxification product of DCVC) has been detected in humans occupationally exposed to TCE (Birner et al., 1993; cited by Clewell et al., 1995).

Furthermore, one human study strongly suggests that kidney damage is associated with exposure to TCE. Brüning et al. (1996) compared the urinary protein patterns of 17 patients diagnosed with renal cell cancer after many years of high-level occupational exposure to TCE with that for 35 renal cell cancer patients not exposed to TCE. Exposure to TCE was associated with degreasing, production of rubber boxes, and cleaning of cardboard-making machines. These exposures were without protection from hoods, ventilating systems, or the use of gloves. The average year of initial exposure was 1959, mean exposure duration was 15.2 years, mean time of diagnosis for renal cell carcinoma was 1990, and mean latency period was 30.4 years. Symptoms of exposure included dizziness, headache, a sense of drunkenness, and drowsiness. The postoperative period of the unexposed patients was similar to that of the TCE-exposed patients.

For all 17 exposed patients, protein excretion patterns indicated tubule damage in their remaining kidney. In the 35 non-exposed patients, 12 had tubule damage, 4 had glomerular/tubule damage, and 1 had glomerular damage. Brüning et al. concluded that although their data are limited, the findings support the likelihood that chronic tubule damage is a contributing factor to the induction of renal cell cancer by TCE. This finding is consistent with the involvement of mercapturic metabolic pathway in the metabolism of TCE in humans (Brüning et al., 1996).

There is excellent biological plausibility of the kidney tumors observed and TCE exposures because (1) site and histopathological characteristics of the tumors observed in patients and in experimental animals are identical (Vamvakas et al., 1993); (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant et al., 1986; cited by IARC, 1995e); (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE are identical in humans and in experimental animals (Birner et al., 1993; cited by Clewell et al., 1995); and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner et al., 1993; cited by Clewell et al.,

1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

#### **7.4 Structural Analogues**

As discussed in 6.3.2, the structural analogues of TCE include vinyl chloride (chloroethylene), vinylidene chloride (1,1-dichloroethylene), and 1,1,2,2-tetrachloroethylene. Of the three analogues, TCE appears to be most similar in tumor sites to vinylidene chloride and tetrachloroethylene.

Vinyl chloride is carcinogenic in humans and experimental animals. Occupational exposure to vinyl chloride is associated with increased risks for angiosarcoma of the liver, hepatocellular carcinoma, brain and lung tumors, and malignancy of the hematopoietic and lymphatic system. In experimental animal studies, oral administration or inhalation of vinyl chloride induced Zymbal's gland tumors in rats and hamsters, nephroblastomas in rats, forestomach papillomas and melanomas in hamsters, and pulmonary and mammary gland tumors in mice, and hemangiosarcoma of the liver in all three species. Vinyl chloride is considered a genotoxic carcinogen.

In contrast, vinylidene chloride was not classifiable as a human carcinogen because of inadequate evidence and also the evidence for its carcinogenicity to animals is considered to be limited. In experimental carcinogenicity studies, vinylidene chloride induces kidney adenocarcinomas in males and mammary carcinomas in females; both males and females showed an increase in pulmonary adenomas. Vinylidene chloride was genotoxic in some assays, inducing mutations in bacteria and yeast, UDS in primary rat hepatocytes, and UDS in treated mice.

Tetrachloroethylene is classified as probably carcinogenic to humans, based on limited evidence in humans and sufficient evidence in experimental animals. In epidemiological studies, occupational exposure to tetrachloroethylene presented increased risk for esophageal cancer, non-Hodgkin's lymphoma, and cervical cancer. In experimental carcinogenicity studies, mice given tetrachloroethylene by gavage showed an increased incidence of hepatocellular carcinomas. Mice exposed to high doses by inhalation showed exposure-related increases in hepatocellular adenomas and carcinomas. Rats exposed to high doses by inhalation showed a dose-related increase of mononuclear-cell leukemia; also observed but not statistically significant was an increase in the incidence of renal tubule cell adenomas and adenocarcinomas in male rats. Tetrachloroethylene is generally negative in most genetic toxicology assays.

## 8.0 REFERENCES

- ACGIH (American Conference of Governmental Industrial Hygienists). 1992. 1992-1993 threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH. (Cited by Rappaport, 1993)
- ACGIH (American Conference of Governmental Industrial Hygienists). 1996. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.
- Anna, C. H., R. R. Maronpot, M. A. Pereira, J. F. Foley, D. E. Malarkey, and M. W. Anderson. 1994. *ras* Proto-oncogene activation in dichloroacetic-, trichloroethylene- and tetrachloroethylene-induced liver tumors in B6C3F1 mice. *Carcinogenesis (London)* 15:2255-2261. (Cited by IARC, 1995c)
- Anttila, A., E. Pukkala, M. Sallmén, S. Hernberg, and K. Hemminki. 1995. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. *J. Occup. Med.* 37:797-806. (Cited as in press by IARC, 1995e)
- ATSDR (Agency For Toxic Substances and Disease Registry). 1995. Toxicological Profile for Trichloroethylene. (Update). Draft for public comment. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.
- Axelsson, O., A. Seldén, K. Andersson, and C. Hogstedt. 1994. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J. Occup. Med.* 36:556-562. (Cited by IARC, 1995e)
- Bergman, K. 1983. Application and results of whole-body autoradiography in distribution studies of organic solvents. *Arch. Toxicol.* 12:59-118. (Cited by IARC, 1995e)
- Bernauer, U., G. Birner, W. Dekant, and D. Henschler. 1996. Biotransformation of trichloroethene: Dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. *Arch. Toxicol.* 70:338-346.
- Bhattacharya, R. K., and M. O. Schultze. 1972. Properties of DNA treated with *S*-(1,2-dichlorovinyl)-*L*-cysteine and  $\beta$ -lyase. *Arch. Biochem. Biophys.* 153:105-115. (Cited by Vamvakas et al., 1993)
- Bhattacharya, R. K., and M. O. Schultze. 1973a. Modification of polynucleotides by a fragment produced by enzymatic cleavage of *S*-(1,2-dichlorovinyl)-*L*-cysteine. *Biochem. Biophys. Res. Commun.* 53:172-181. (Cited by Vamvakas et al., 1993)

## **NTP Report on Carcinogens 1997 Background Document for Trichloroethylene**

Bhattacharya, R. K., and M. O. Schultze. 1973b. Hybridization of DNA modified by interaction with a metabolic fragment from *S*-(1,2-dichlorovinyl)-*L*-cysteine. *Biochem. Biophys. Res. Commun.* 54:538-543. (Cited by Vamvakas et al., 1993)

Birner, G., S. Vamvakas, W. Dekant, and D. Henschler. 1993. Nephrotoxic and genotoxic *N*-Acetyl-*S*-dichlorovinyl-*L*-cysteine is a urinary metabolite after occupational 1,1,2-trichloroethylene exposure in humans: Implications for the risk of trichloroethylene exposure. *Environ. Health Perspect.* 99:281-284. (Cited by IARC, 1995e, and Clewell et al., 1995)

Bloemen, L. J., and J. Tomenson. 1995. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Comment. Arch. Toxicol.* 70:129-133.

Bonse, G., T. Urban, D. Reichert, and D. Henschler. 1975. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. *Biochem. Pharmacol.* 24:1829-1834. (Cited by Vamvakas et al., 1993)

Brüning, T., K. Golka, V. Makropoulos, and H. M. Bolt. 1996. Preexistence of chromic tubule damage in cases of renal cell cancer after long and high exposure to trichloroethylene [letter]. *Arch. Toxicol.* 70:259-260.

Brüning, T., G. Weirich, M. A. Hornauer, H. Hofler, and H. Brauch. 1997. Renal cell carcinomas in trichloroethene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. *Arch. Toxicol.* 71:332-335.

Buben, J. A., and E. J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose-effect study. *Toxicol. Appl. Pharmacol.* 78:105-122. (Cited by WHO, 1993)

Budavari, S., Ed. 1996. *The Merck Index*, 12th ed. Merck & Co., Inc., Whitehall, NJ, p. 1643.

Butler, T. C. 1949. Metabolic transformations of trichloroethylene. *J. Pharmacol. Exp. Ther.* 97:84-92. (Cited by IARC, 1995e)

Byington, K. H., and K. C. Leibman. 1965. Metabolism of trichloroethylene in liver microsomes II. Identification of the reaction product as chloral hydrate. *Mol. Pharmacol.* 1:247-254 (Cited by Bernauer et al., 1996)

CHEMLIST. 1997. Online database produced by the American Chemical Society and provided by STN International.

Clewell, H. J., P. R. Gentry, J. M. Gearhart, B. C. Allen, and M. E. Andersen. 1995. Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: Examples with vinyl chloride and trichloroethylene. *Chemosphere* 31:2561-2578.

CMR (Chemical Marketing Reporter). 1983. Chemical profile—trichloroethylene. Chem. Mark. Rep.: February 14. (Cited by Gist and Burg, 1995)

Cole, W. J., R. G. Mitchell, and R. F. Salamonsen. 1975. Isolation, characterization, and quantitation of chloral hydrate as a transient metabolite of trichloroethylene in man using electron capture gas chromatography and mass fragmentography. J. Pharm. Pharmacol. 27:167-171. (Cited by IARC, 1995e)

Commandeur, J. N. M., and N. P. E. Vermeulen. 1990. Identification of *N*-acetyl(2,2-dichlorovinyl)- and *N*-acetyl(1,2-dichlorovinyl)-*L*-cysteine as two regioisomeric mercapturic acids of trichloroethylene in the rat. Chem. Res. Toxicol. 3:212-218. (Cited by IARC, 1995e, and by Bernauer et al., 1996)

Crebelli, R., C. Andreoli, A. Carere, G. Conti, L. Conti, M. Conti Ramusino, and R. Benigni. 1992. The induction of mitotic chromosome malsegregation in *Aspergillus nidulans*. Quantitative structure-activity relationship (QSAR) analysis with chlorinated aliphatic hydrocarbons. Mutat. Res. 226:117-134. (Cited by Rosenkranz and Klopman, 1996)

Daniel, J. W. 1963. The metabolism of <sup>36</sup>Cl-labelled trichloroethylene and tetrachloroethylene in the rat. Biochem. Pharmacol. 12:795-802. (Cited by IARC, 1995e)

Dekant, W., M. Metzler, and D. Henschler. 1984. Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. Biochem. Pharmacol. 33:2021-2027. (Cited by Bernauer et al., 1996; Goeptar et al., 1995; IARC, 1995e; and Vamvakas et al., 1993)

Dekant, W., M. Metzler, and D. Henschler. 1986. Identification of *S*-1,2-Dichlorovinyl-*N*-acetylcysteine as a urinary metabolite of trichloroethylene: A possible explanation for its nephrocarcinogenicity in male rats. Biochem. Pharmacol. 35:2455-2458. (Cited by Bernauer et al., 1996, and IARC, 1995e)

Dekant, W., M. Koob, and K. Henschler. 1990. Metabolism of trichloroethene "*in vivo* and *in vitro* evidence for activation by glutathione conjugation. Chem. Biol. Interact. 73:89-101. (Cited by IARC, 1995e, and Bernauer et al., 1996)

Elcombe, C. R. 1985. Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: A biochemical human hazard assessment. Arch. Toxicol. Suppl. 8:6-17. (Cited by IARC, 1995e)

Fazzalari, F. A., Ed. 1978. Compilation of odor and taste threshold values data. ASTM Data Series DS 48A (Committee E-18). American Society for Testing and Materials, Philadelphia, PA, p. 159. (Cited by HSDB, 1997)

- Fisher, J. W., M. L. Gargas, B. C. Allen, and M. E. Andersen. 1991. Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse. *Toxicol. Appl. Pharmacol.* 109:183-195. (Cited by IARC, 1995e)
- Foster, K., A. Prowse, F. St. van den Bergh, M. M. F. Hulsbeek, P. A. Crossey, F. M. Richards, P. Cairns, N. A. Affara, M. A. Ferguson-Smith, C. H. C. M Buys, and E. R. Maher. 1994. Somatic mutations of the von Hippel-Lindau disease tumor suppressor gene in non-familial clear cell renal carcinoma. *Hum. Mol. Genet.* 3:2169-2173.
- Fritschi, L., and J. Siemiatycki. 1996. Melanoma and occupation: Results of a case control study. *Occup. Environ. Med.* 53:168-173.
- Gargas, M. L., M. E. Anderson, and H. J. Clewell. 1986. A physiologically based simulation approach for determining metabolic constants from gas uptake data. *Toxicol. Appl. Pharmacol.* 86:341-352. (Cited by Rappaport, 1993)
- Gist, G. L., and J. R. Burg. 1995. Trichloroethylene – A review of the literature from a health effects perspective. *Toxicol. Ind. Health* 11:253-307.
- Gist, G. L., J. Burg, and T. M. Radtke. 1994. The site selection process for the National Exposure Registry. *J. Environ. Health* 56:7-12.
- Gnarra, J. R., K. Tory, Y. Weng, L. Schmidt, M. W. Wei, H. Li, F. Latif, S. Liu, F. Chen, F. M. Duh, I. Lubensky, D. R. Duan, C. Florence, R. Pozzati, M. M. Walther, N. H. Bander, H. B. Grossman, H. Brauch, S. Pomer, J. D. Brooks, W. B. Isaacs, M. I. Lerman, B. Abar, and W. M. Linehan. 1994. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nature Genet.* 7:85-89.
- Goeptar, A. R., J. N. M. Commandeur, B. Vanommen, P. J. Vanbladeren, and N. P. E. Vermeulen. 1995. Metabolism and kinetics of trichloroethylene in relation to toxicity and carcinogenicity. Relevance of the mercapturic acid pathway. *Chem. Res. Toxicol.* 8:3-21. (Cited by Bernauer et al., 1996)
- Green, T. 1990. Chloroethylenes: A mechanistic approach to human risk evaluation. *Annu. Rev. Pharmacol. Toxicol.* 30:73-89.
- Green, T., and M. S. Prout. 1985. Species differences in response to trichloroethylene. II. Biotransformation in rats and mice. *Toxicol. Appl. Pharmacol.* 79:401-411. (Cited by Goeptar et al., 1995, and IARC, 1995e)
- Green, T., Mainwaring, G. W., and J. R. Foster. 1997. Trichloroethylene-induced mouse lung tumors: Studies of the mode of action and comparisons between species. *Fundam. Appl. Toxicol.* 37:125-130.

Hathway, D. E. 1980. Consideration of the evidence for mechanisms of 1,1,2-trichloroethylene metabolism, including new identification of its dichloroacetic acid and trichloroacetic acid metabolites in mice. *Cancer Lett.* 8:263-269. (Cited by Goeptar et al., 1995, and IARC, 1995e)

Henschler, D., W. Romen, H. M. Elsässer, D. Reichert, E. Eder, and Z. Radwan. 1980. Carcinogenicity study of trichloroethylene by long term inhalation in three animal species. *Arch. Toxicol.* 43:237-248. (Cited by Goeptar et al., 1995, and IARC, 1995e)

Henschler, D., S. Vamvakas, M. Lammert, W. Dekant, B. Kraus, B. Thomas, and K. Ulm. 1995a. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Arch. Toxicol.* 69:291-299.

Henschler, D., S. Vamvakas, M. Lammert, W. Dekant, B. Kraus, B. Thomas, and K. Ulm. 1995b. Increased incidence of renal cell tumours in a cohort of cardboard workers exposed to trichloroethene. Reply. *Arch. Toxicol.* 70:131-133.

HSDB (Hazardous Substances Data Bank). 1997. Online database produced by the National Library of Medicine. Trichloroethylene profile last updated March 27, 1997.

IARC (International Agency for Research on Cancer). 1979. Vinyl chloride, polyvinyl chloride, and vinyl chloride-vinyl acetate copolymers. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.* 19(Some Monomers, Plastics, and Synthetic Elastomers, and Acrolein):377- 438.

IARC (International Agency for Research on Cancer). 1987a. Vinyl Chloride. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum. Supplement 7(Overall Evaluations of Carcinogenic Risks to Humans: An Updating of IARC Monographs Volumes 1 to 42):*40-55.

IARC (International Agency for Research on Cancer). 1987b. Vinylidene chloride. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum. Supplement 7(Overall Evaluations of Carcinogenic Risks to Humans: An Updating of IARC Monographs Volumes 1 to 42):*376-377.

IARC (International Agency for Research on Cancer). 1995a. Chloral and chloral hydrate. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.* 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):245-270.

IARC (International Agency for Research on Cancer). 1995b. Dichloroacetic acid. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.* 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):271-290.

IARC (International Agency for Research on Cancer). 1995c. Tetrachloroethylene. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.* 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):159-222.

IARC (International Agency for Research on Cancer). 1995d. Trichloroacetic acid. IARC Monogr. Eval. Carcinog. Risk Chem. Hum. 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):291-314.

IARC (International Agency for Research on Cancer). 1995e. Trichloroethylene. IARC Monogr. Eval. Carcinog. Risk Chem. Hum. 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):75-158.

Ikeda, M. 1977. Metabolism of trichloroethylene and perchloroethylene in human subjects. *Environ. Health Perspect.* 21:239-245. (Cited by Lee et al., 1996)

Ikeda, M., Y. Miyake, O. Ogata, and S. Ohmori. 1980. Metabolism of trichloroethylene. *Biochem. Pharmacol.* 29:2983-2992. (Cited by IARC, 1995e)

Jaffe, D. R., C. D. Hassall, A. J. Gandolfi, and K. Brendel. 1985. Production of DNA single strand breaks in renal tissue after exposure to 1,2-dichlorovinylcysteine. *Toxicology* 35:25-33. (Cited by Vamvakas et al., 1993)

Kilburn, K. H., and R. H. Warshaw. 1993. Effects of neurobehavioral performance of chronic exposure to chemically contaminated well water. *Toxicol. Ind. Health* 9:391-404. (Cited by Gist and Burg, 1995)

Kimmerle, G., and A. Eben. 1973. Metabolism, excretion and toxicology of trichloroethylene after inhalation. 1. Experimental exposure on rats. *Arch. Toxicol.* 30:115-126. (Cited by IARC, 1995e)

Land, P. E., E. L. Owen, and H. W. Linde. 1979. Mouse sperm morphology following exposure to anesthetics during early spermatogenesis [abstract]. *Anesthesiology* 51:S259. (Cited by Gist and Burg, 1995)

Larson, J. L., and R. J. Bull. 1992b. Metabolism and lipoperoxidative activity of trichloroacetate and dichloroacetate in rats and mice. *Toxicol. Appl. Pharmacol.* 115:268-277. (Cited by IARC, 1995e)

Lee, K. M., J. V. Bruckner, S. Muralidhara, and J. M. Gallo. 1996. Characterization of presystemic elimination of trichloroethylene and its nonlinear kinetics in rats. *Toxicol. Appl. Pharmacol.* 139:262-271.

Leibman, K. C. 1965. Metabolism of trichloroethylene in liver microsomes. I. Characteristics of the reaction. *Mol. Pharmacol.* 1:239-246. (Cited by Bernauer et al., 1996)

Lipscomb J. C., C. M. Garret, and J. E. Snawder. 1997. Cytochrome p450-dependent metabolism of trichloroethylene: Interindividual differences in humans. *Toxicol. Appl. Pharmacol.* 142:311-318.

Ludwig, H., Ed. 1994. NIOSH Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, U.S. Government Printing Office Stock No. 017-033-00473-1, Washington, DC, pp. 316, 342, 350.

Maltoni, C., G. Cotti, and P. Chieco. 1984a. Chronic toxicity and carcinogenicity bioassays of vinyl chloride. *Acta. Oncol.* 5:91. (Cited by Green, 1990)

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti, and D. Carretti. 1984b. Experimental research on vinyl chloride carcinogenesis. In: *Archives of Research on Industrial Carcinogenesis*. Vol. II. Maltoni, C., and M. A. Mehlman, Eds. Princeton Scientific Publishing Co., Princeton, NJ. (Cited by Green, 1990)

Maltoni, C., G. Lefemine, and G. Cotti. 1986. Experimental research on trichloroethylene carcinogenesis. In: *Archives of Research on Industrial Carcinogenesis*. Vol. V. Maltoni, C., and M. A. Mehlman, Eds. Princeton Scientific Publishing Co., Princeton, NJ, pp 1-393. (Cited by Goeptar et al., 1995)

Maltoni, C., G. Lefemine, G. Cotti, and G. Perino. 1988. Long-term carcinogenic bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. *Ann. N. Y. Acad. Sci.* 534:316-342. (Cited by IARC, 1995e)

Manson, J. M., M. Murphy, N. Richdale, and M. K. Smith. 1984. Effects of oral exposure to trichloroethylene on female reproductive function. *toxicology. Toxicology* 32:229-242. (Cited by Gist and Burg, 1995)

Maronpot, R. R., C. H. Anna, T. R. Devereux, G. W. Lucier, B. E. Butterworth, and M. W. Anderson. 1995. Considerations concerning the murine hepatocarcinogenicity of selected chlorinated hydrocarbons. *Prog. Clin. Biol. Res.* 391:305-323.

Matsuoka, A., K. Yamakage, H. Kusakabe, S. Wakuri, M. Asakura, T. Noguchi, T. Sugiyama, H. Shimada, S. Nakayama, Y. Kasahara, Y. Takahashi, K. F. Miura, M. Hatanaka, M. Ishidate, Jr., T. Morita, K. Watanabe, M. Hara, K. Odawara, N. Tanaka, M. Hayashi, and T. Sofuni. 1996. Re-evaluation of chromosomal aberration induction of nine mouse lymphoma assay "unique positive" NTP carcinogens. *Mutat. Res.* 369:243-252.

Meadows, S. D., A. J. Gandolfi, R. B. Nagle, and J. W. Shively. 1988. Enhancement of DMN-induced kidney tumors by 1,2-dichlorovinylcysteine in Swiss-Weber mice. *Drug Chem. Toxicol.* 11:307-318. (Cited by Vamvakas et al., 1993)

Miller, R. E., and F. P. Guengerich. 1982. Oxidation of trichloroethylene by liver microsomal cytochrome P-450: Evidence for chlorine migration in a transition state not involving trichloroethylene oxide. *Biochemistry* 21:1090-1097. (Cited by Vamvakas et al., 1993)

- Miyagawa, M., H. Takasawa, A. Sugiyama, Y. Inoue, T. Murata, Y. Uno, and K. Yoshikawa. 1995. The *in vivo-in vitro* replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. *Mutat. Res.* 343:157-183.
- Monster, A. C., G. Boersma, and W. C. Duba. 1979. Kinetics of trichloroethylene in repeated exposure of volunteers. *Int. Arch. Occup. Environ. Health* 42:283-292. (Cited by IARC, 1995e)
- Muehlematter, D., R. Larsson, and P. Cerutti. 1988. Active oxygen induced DNA strand breakage and poly ADP-ribosylation in promotable and non-promotable JB6 mouse epidermal cells. *Carcinogenesis (London)* 9:239-245. (Cited by Vamvakas et al., 1993)
- Müller, G., M. Spassovski, and D. Henschler. 1972. Trichloroethylene exposure and trichloroethylene metabolites in urine and blood. *Arch. Toxicol.* 29:335-340. (Cited by IARC, 1995e)
- Müller, G., M. Spassovski, and D. Henschler. 1974. Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. *Arch. Toxicol.* 32:283-295. (Cited by IARC, 1995e)
- Müller, G., M. Spassowski, and D. Henschler. 1975. Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. *Arch. Toxicol.* 33:173-189. (Cited by Gist and Burg, 1995)
- Müller, W. F., F. Coulston, and F. Korte. 1982. Comparative metabolism of [<sup>14</sup>C]trichloroethylene in chimpanzees, baboons, and rhesus monkeys. *Chemosphere* 11:215-218. (Cited by IARC, 1995e)
- NCI (National Cancer Institute). 1976. Carcinogenesis Bioassay of Trichloroethylene (CAS No. 79-01-6). Report no. NCI-CG-TR-2. National Cancer Institute, Carcinogenesis Program, Bethesda, MD. Available from NTIS, Springfield, VA; PB-264122.
- NIOSH (National Institute for Occupational Safety and Health). 1990. National Occupational Exposure Survey (1980-1983). Unpublished provisional data as of 7/1/90. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, NIOSH Division of Surveillance, Hazard Evaluations and Field Studies, Surveillance Branch, Hazard Section, Cincinnati, OH.
- Nomiyama, K., and H. Nomiyama. 1977. Dose-response relationship for trichloroethylene in man. *Int. Arch. Occup. Environ. Health* 39:237-248. (Cited by Lee et al., 1996)
- NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) [CAS No. 127-18-4] in F344/N Rats and B6C3F<sub>1</sub> Mice (Inhalation Studies). NTP Report No. 311. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute for Environmental Health Sciences, Research Triangle Park, NC.

NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of Trichloroethylene [CAS No. 79-01-6] in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendell) (Gavage Studies) NTP Report No. 273. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute for Environmental Health Sciences, Research Triangle Park, NC.

NTP (National Toxicology Program). 1990. Toxicology and Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) [CAS No. 79-01-6] in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP Report No. 243. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. National Institute for Environmental Health Sciences, Research Triangle Park, NC.

Odum, J., J. R. Foster, and T. Green. 1992. A mechanism for the development of Clara cell lesions in the mouse lung after exposure to trichloroethylene. *Chem. Biol. Interact.* 83:135-153. (Cited by Clewell et al., 1995)

Powell, J. F. 1945. Trichloroethylene absorption, elimination and metabolism. *Br. J. Ind. Med.* 2:142-147. (Cited by Vamvakas et al., 1993)

PPG Industries, Inc. 1997. Product Information Sheet: Trichloroethylene. PPG Industries, Inc., Pittsburgh, PA.

Rappaport, S. M. 1993. Biological considerations in assessing exposures to genotoxic and carcinogenic agents. *Int. Arch. Occup. Environ. Health* 65:S29-S35.

Rosenkranz, H. S., and G. Klopman. 1996. A study of the structural basis of the ability of chlorinated alkanes and alkenes to induce aneuploidy and toxicity in the mold *Aspergillus nidulans*. *Mutat. Res.* 354:183-93.

Sato, A., and T. Nakajima. 1987. Pharmacokinetics of organic solvent vapors in relation to their toxicity. *Scand. J. Work Environ. Health* 13:81-93. (Cited by Rappaport, 1993)

Seiji, K., C. Jin, T. Watanabe, H. Nakatsuka, and M. Ikeda. 1990. Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits. *Int. Arch. Occup. Environ. Health* 62:171-176. (Cited by IARC, 1995c)

Shiun, T., K. Kondo, S. Torigoe, T. Kishida, Y. Kabota, M. Hosaka, Y. Nagahisma, H. Kitamura, F. Latif, B. Zbar, M.I. Lerman, and M. Yao. 1994. Frequent somatic mutations and loss of heterozygosity of the von Hippel-Lindau tumor suppressor gene in primary human renal cell carcinoma. *Cancer Res.* 54:2852-2856.

Smith, M. N., S. D. Greenberg, and H. J. Spjut. 1979. The Clara cell: A comparative ultrastructure study in mammals. *Am. J. Anat.* 155:15-30. (Cited by Goeptar et al., 1995)

Spirtas, R., P. A. Stewart, J. S. Lee, D. E. Marano, C. D. Forbes, D. J. Grauman, H. M. Pettigrew, A. Blair, R. N. Hoover, and J. L. Cohen. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br. J. Ind. Med.* 48:515-530. (Cited by IARC, 1995e)

SRI. 1996. *Directory of Chemical Producers, United States*. SRI International, Menlo Park, CA.

Stenner, R. D., J. L. Merdink, D. K. Stevens, D. L. Springer, and R. J. Bull. 1997. Enterohepatic recirculation of trichloroethanol glucuronide as a significant source of trichloroacetic acid: Metabolites of trichloroethylene. *Drug Metab. Dispos.* 25:529-535.

Swaen, G. M. 1995. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethylene [letter]. *Arch. Toxicol.* 70:127-133.

Templin, M. V., J. C. Parker, and R. J. Bull. 1993. Relative formation of dichloroacetate and trichloroacetate from trichloroethylene in male B6C3F1 mice. *Toxicol. Appl. Pharmacol.* 123:1-8. (Cited by Stenner et al., 1997)

TRI95 (Toxic Chemical Release Inventory). 1997. Data reported for the year 1995. Data contained in the Toxic Chemical Release Inventory (TRI) file are submitted to the Environmental Protection Agency (EPA) by industrial facilities in compliance with section 313 of the Emergency Planning and Community Right-To-Know Act of 1986.

U.S. Environmental Protection Agency. 1989. *Contract Laboratory Program Statistical Database*, Washington, DC. (Cited by IARC, 1995e)

Vamvakas, S., D. A. Müller, W. Dekant, and D. Henschler. 1988. DNA-binding of sulfur-containing metabolites from <sup>35</sup>S-(pentachlorobutadienyl)-L-cysteine in bacteria and isolated renal tubular cells. *Drug Metab. Drug Interact.* 6:349-358. (Cited by Vamvakas et al., 1993)

Vamvakas, S., M. Herkenhoff, W. Dekant, and D. Henschler. 1989. Mutagenicity of tetrachloroethylene in the Ames test—metabolic activation by conjunction with glutathione. *J. Biochem. Toxicol.* 4:21-27. (Cited by IARC, 1995c)

Vamvakas, S., V. K. Sharma, S.-S. Shen, and M. W. Anders. 1990. Perturbations of intracellular Ca<sup>2+</sup> distribution in kidney cells by nephrotoxic haloalkenyl cysteine S-conjugates. *Mol. Pharmacol.* 38:455-461. (Cited by Vamvakas et al., 1993)

Vamvakas, S., D. Bittner, W. Dekant, and M. W. Anders. 1992. Events that precede and that follow S-(1,2-dichlorovinyl)-L-cysteine induced release of mitochondrial Ca<sup>2+</sup> and their association to cytotoxicity in renal cells. *Biochem. Pharmacol.* 44:1131-1138. (Cited as in press by Vamvakas et al., 1993)

Vamvakas, S., W. Dekant, and D. Henschler. 1993. Nephrocarcinogenicity of haloalkenes and alkynes. In: Renal Disposition and Nephrotoxicity of Xenobiotics. Academic Press Inc., San Diego, CA, pp. 323-342.

Varkonyi, P., J. V. Bruckner, and J. M. Gallo. 1995. Effect of parameter variability on physiologically-based pharmacokinetic model predicted drug concentrations. *J. Pharm. Sci.* 84:381-384.

Verschueren, K. 1983. Handbook of Environmental Data of Organic Chemicals. 2nd ed. Van Nostrand Reinhold Co., New York, p.1133. (Cited by HSDB, 1997)

Vogel, E. W., and M. J. Nivard. 1993. Performance of 181 chemicals in a *Drosophila* assay predominantly monitoring interchromosomal mitotic recombination. *Mutagenesis* 8:57-81.

Wallace, L., T. Buckley, E. Pellizzari, and S. Gordon. 1996. Breath measurements as volatile organic compound biomarkers. *Environ. Health Perspect.* 104:861-869.

Weiss, N. S. 1996. Cancer in relation to occupational exposure to trichloroethylene. *Occup. Environ. Med.* 53:1-5.

Whaley, J. M., J. Naglich, L. Gelbert, Y. E. Hsia, J. M. Lamiell, J. S. Green, D. Collins, H. P. H. Neumann, J. Laidlaw, F. P. Li, A. J. P. Klein-Szanto, B. Seizinger, and N. Kley. 1994. Germline mutations in the von Hippel-Lindau tumor suppressor gene are similar to somatic von Hippel-Lindau aberrations in sporadic renal cell carcinoma. *Am. J. Hum. Genet.* 55:1092-1102.

WHO (World Health Organization). 1993. Guidelines for drinking-water quality, 2nd ed. Vol. 1: Recommendations. World Health Organization, Geneva, Switzerland, pp. 62-63, 175.

**APPENDIX A**

**Excerpts from the IARC Monograph on the Evaluation  
of the Carcinogenic Risk of Chemicals to Humans  
Volume 63 (Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals)  
Trichloroethylene  
pp. 75-158 (1995)**

# TRICHLOROETHYLENE

This substance was considered by previous working groups, in June 1978 and March 1987 (IARC, 1979, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Chemical and physical data

#### 1.1.1 Nomenclature

*Chem. Abstr. Serv. Reg. No.:* 79-01-6

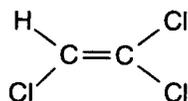
*Deleted CAS Reg. No.:* 52037-46-4

*Chem. Abstr. Name:* Trichloroethene

*IUPAC Systematic Name:* Trichloroethylene

*Synonyms:* Ethinyl trichloride; ethylene trichloride; TCE; 1,1,2-trichloroethylene

#### 1.1.2 Structural and molecular formulae and relative molecular mass



$\text{C}_2\text{HCl}_3$

Relative molecular mass: 131.39

#### 1.1.3 Chemical and physical properties of the pure substance

- (a) *Description:* Mobile liquid with chloroform-like odour (Budavari, 1989)
- (b) *Boiling-point:* 87 °C (Lide, 1993)
- (c) *Melting-point:* -73 °C (Lide, 1993)
- (d) *Density:* 1.4642 at 20 °C/4 °C (Lide, 1993)
- (e) *Spectroscopy data:* Infrared (prism [185]; grating [62]), nuclear magnetic resonance (proton [9266]; C-13 [410]) and mass [583] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).
- (f) *Solubility:* Slightly soluble in water (1.1 g/L at 25 °C); soluble in ethanol, diethyl ether, acetone and chloroform (Lide, 1993; PPG Industries, Inc., 1994)
- (g) *Volatility:* Vapour pressure, 100 mm Hg [13.3 kPa] at 31.4 °C (Lide, 1993); relative vapour density (air = 1.0), 4.53 (Budavari, 1989)

- (h) *Stability*: Photo-oxidized in air by sunlight (half-time, five days) giving phosgene and dichloroacetyl chloride (United States Environmental Protection Agency, 1985)
- (i) *Reactivity*: Incompatible with strong caustics and alkalis and with chemically active metals such as barium, lithium, sodium, magnesium, titanium and beryllium (United States National Institute for Occupational Safety and Health, 1994a)
- (j) *Octanol/water partition coefficient (P)*: log P, 2.61 (Hansch *et al.*, 1995)
- (k) *Conversion factor*:  $\text{mg/m}^3 = 5.37 \times \text{ppm}^1$

#### 1.1.4 Technical products and impurities

Commercial grades of trichloroethylene, formulated to meet use requirements, differ in the amount and type of added inhibitor. Typical grades contain > 99% trichloroethylene; they include a neutrally inhibited vapour-degreasing grade and a technical grade for use in formulations. Stabilizers that have been used in formulations of trichloroethylene include neutral inhibitors and free-radical scavengers, amyl alcohol, *n*-propanol, isobutanol, 2-pentanol, diethylamine, triethylamine, dipropylamine, diisopropylamine, diethanolamine, triethanolamine, morpholine (see IARC, 1989a), *N*-methyldmorpholine, aniline (see IARC, 1987b), acetone, ethyl acetate, borate esters, ethylene oxide (see IARC, 1994a), propylene oxide (see IARC, 1994b), 1,2-epoxybutane (see IARC, 1989b), cyclohexene oxide, butadiene dioxide, styrene oxide (see IARC, 1994c), pentene oxide, 2,3-epoxy-1-propenol, 3-methoxy-1,2-epoxypropane, stearates, 2,2,4-trimethyl-1-pentene, 2-methyl-1,2-epoxypropanol, epoxycyclopentanol, epichlorohydrin (see IARC, 1987c), tetrahydrofuran, tetrahydropyran, 1,4-dioxane (see IARC, 1987d), dioxalane, trioxane, alkoxyaldehyde hydrazones, methyl ethyl ketone, nitromethanes, nitropropanes, phenol (see IARC, 1989c), *ortho*-cresol, thymol, *para-tert*-butylphenol, *para-tert*-amylphenol, isoeugenol, pyrrole, *N*-methylpyrrole, *N*-ethylpyrrole, (2-pyrryl)trimethylsilane, glycidyl acetate, isocyanates and thiazoles (United States Environmental Protection Agency, 1985; WHO, 1985).

Apart from added stabilizers, commercial grades of trichloroethylene should not contain more than the following amounts of impurities: water, 100 ppm [mg/L]; acidity (as HCl), 5 ppm; insoluble residue, 10 ppm (Mertens, 1993). Free chlorine should not be detectable (PPG Industries, Inc., 1994). Impurities that have been found in commercial trichloroethylene products include: carbon tetrachloride (see IARC, 1987e), chloroform (see IARC, 1987f), 1,2-dichloroethane (see IARC, 1987g), *trans*-1,2-dichloroethylene, *cis*-1,2-dichloroethylene, pentachloroethane (see IARC, 1987h), 1,1,1,2-tetrachloroethane (see IARC, 1987i), 1,1,2,2-tetrachloroethane (see IARC, 1987j), 1,1,1-trichloroethane (see IARC, 1987k), 1,1,2-trichloroethane (see IARC, 1991), 1,1-dichloroethylene, tetrachloroethylene (see monograph, this volume), bromodichloromethane, bromodichloroethylene and benzene (see IARC, 1987l) (WHO, 1985; Mertens, 1993).

Trade names for trichloroethylene include: Algylen, Anamenth, Chlorilen, Chlorylen, Densinfluat, Fluat, Germalgene, Narcogen, Narkosoid, Threthylen, Threthylene, Trethylene,

<sup>1</sup> Calculated from:  $\text{mg/m}^3 = (\text{relative molecular mass}/24.45) \times \text{ppm}$ , assuming normal temperature (25 °C) and pressure (101 kPa)

Tri, Trichloran, Trichloren, Triclene, Trielene, Trielin, Trieline, Trilen, Trilene, Trimar and Westrosol.

### 1.1.5 Analysis

Selected methods for the analysis of trichloroethylene in various matrices are identified in Table 1.

**Table 1. Methods for the analysis of trichloroethylene**

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg/sample	Eller (1994); US Occupational Safety and Health Administration (1990)
	Draw air into sample bag; inject aliquot into gas chromatograph	GC/PID	0.25 ng/sample	Eller (1994)
	Draw air through Tenax sample tube; heat; desorb on cold trap	GC/MS	20 ng	US Environmental Protection Agency (1988a)
	Draw air into cryogenically cooled trap; heat	GC/FID and/or GC/EC	1–5 ng	US Environmental Protection Agency (1988a)
	Draw air into SUMMA® passivated stainless-steel canister; desorb on cold trap	GC/MS or GC/EC-FID-PID	NR	US Environmental Protection Agency (1988a)
Coffee	Isolate sample by closed-system vacuum distillation with toluene	GC/EC or GC/ECD	NR	US Food and Drug Administration (1983)
Grain	Add sample to acetone; store 48 h in the dark; add sodium chloride; add calcium chloride	GC/ECD	NR	Sawyer <i>et al.</i> (1990)
Spice oleoresins	Add sample to absolute alcohol/1,2-dichloropropane mixture; dilute with absolute alcohol and shake	GC	NR	Fazio (1990)
	Isolate sample by closed-system vacuum distillation with toluene	GC/EC	NR	US Food and Drug Administration (1983)
Water	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD or GC/MCD	0.001 and 0.12 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/MS	0.4 and 1.9 µg/L	US Environmental Protection Agency (1988b, 1994)

**Table 1 (contd)**

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Water (contd)	Purge and trap as above; desorb as vapour onto capillary gas chromatographic column	GC/PID-ECD	0.01–0.06 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/PID	0.02–0.19 µg/L	
	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto gas chromatographic column	GC/PID	0.01 µg/L	US Environmental Protection Agency (1988b, 1994)
	Add internal standard (isotope-labelled trichloroethylene); purge, trap and desorb as above	GC/MS	10 µg/L	US Environmental Protection Agency (1994)
Liquid and solid wastes	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD	0.12 µg/L	US Environmental Protection Agency (1986a)
		GC/MS	PQL	US Environmental Protection Agency (1986b)

GC, gas chromatography; FID, flame ionization detection; PID, photoionization detection; MS, mass spectrometry; NR, not reported; EC, electron capture detection; ECD, electrolytic conductivity detection; MCD, microcoulometric detection; PQL, practical quantification limit: 5 µg/L for groundwater; 5 µg/kg for soil and sediment samples; 250–2500 µg/kg for liquid wastes

Three gas chromatography/mass spectrometry (GC/MS) and three purge-and-trap GC methods for purgeable organic compounds, including trichloroethylene, are usually used for analysing aqueous samples (see also Table 1). The first method (EPA Method 624 and APHA/AWWA/WEF Method 6210B) is a packed-column method useful for the determination of trichloroethylene in municipal and industrial wastes. A similar purge-and-trap method (EPA Method 503.1 and APHA/AWWA/WEF Method 6220C), which includes photoionization detection, is applicable for the determination of trichloroethylene in drinking-water and raw source water. The second GC/MS method (EPA Method 524.1 and APHA/AWWA/WEF Method 6210C), also involving a packed column, is also applicable for the determination of trichloroethylene in drinking-water and raw source water. Similar purge-and-trap methods (EPA Methods 601 and 502.1 and APHA/AWWA/WEF Methods 6230B and 6230C), including electrolytic conductivity and microcoulometric detection, are applicable for the determination of trichloroethylene in municipal and industrial discharges (6230B) and in drinking-water and raw source water (6230C). The third group of GC/MS and purge-and-trap methods (EPA Method 524.2 and APHA/AWWA/WEF Method 6210D; EPA Method 502.2 and APHA/AWWA/WEF Method 6230D) are identical to the previous ones except that a capillary column is used. The second and third methods are intended primarily for the detection of large numbers of contaminants at very low concentrations, which are not detectable with the first method (Greenberg *et al.*, 1992).

Trichloroethylene can also be determined by colorimetry in the Fujiwara test, in which it is treated with pyridine in an alkaline environment. Solution absorbency is then determined at 535

or 470 nm, with a sensitivity of about 1 mg/kg. Trichloroethylene can also be determined by infrared spectroscopy. Gaseous compound is measured from the optical density of the mixture at a wavelength of 11.8  $\mu\text{m}$  (detection sensitivity,  $\geq 0.5 \mu\text{g/L}$ ). High-resolution GC with electron capture detection has been used for determining trichloroethylene in soil. High-resolution GC with MS have been used for confirmation, with a detection threshold of about 10 mg/kg. Similar methods can be used to determine trichloroethylene and its major metabolites, trichloroacetic acid and trichloroethanol, in human tissues and fluids (WHO, 1985).

## 1.2 Production and use

### 1.2.1 Production

Trichloroethylene was first prepared in 1864 by Fischer in experiments on the reduction of hexachloroethane with hydrogen (Hardie, 1964). Commercial production of trichloroethylene began in Germany in 1920 and in the United States of America in 1925 (Mertens, 1993).

Until 1968, about 85% of United States production capacity of trichloroethylene was based on acetylene. The acetylene-based process consists of two steps: acetylene is first chlorinated to 1,1,2,2-tetrachloroethane, with a ferric chloride, phosphorus chloride or antimony chloride catalyst, and the product is then dehydrohalogenated to trichloroethylene (Mertens, 1993). The current method of manufacture is from ethylene or 1,2-dichloroethane. In a process used by one plant in the United States, trichloroethylene is produced by noncatalytic chlorination of ethylene dichloride or other  $\text{C}_2$  chlorinated hydrocarbons. Another method is to react ethylene dichloride and other  $\text{C}_2$  hydrocarbons with a mixture of oxygen and chlorine or hydrogen chloride (Linak *et al.*, 1992).

Trichloroethylene can also be produced by direct chlorination of ethylene in the absence of oxygen, giving a mixture of tetrachloroethane and pentachloroethane. The products are thermally cracked to produce a mixture of trichloroethylene, tetrachloroethylene and hydrochloric acid. This process was developed in Japan and is used there (Linak *et al.*, 1992).

Table 2 shows the production of trichloroethylene in selected countries between 1941 and 1990. Production has declined in recent years. Trichloroethylene is manufactured by one company each in Austria (with an annual capacity of 6000 tonnes), Germany (10 000 tonnes), Italy (15 000 tonnes) and Spain (29 000 tonnes). Two companies manufacture trichloroethylene in France (90 000 tonnes) and the United States (145 000 tonnes). Three companies in Japan produce trichloroethylene, with an estimated annual capacity of 85 000 tonnes (Linak *et al.*, 1992). Two companies in Canada were the only domestic manufacturers of trichloroethylene. In 1976, the total capacity of these plants was 38 000 tonnes, and 22 500 tonnes were produced. One plant closed in 1985, and imports have increased as a result (Moore *et al.*, 1991).

Trichloroethylene is also produced in Argentina, Australia, Belgium, China, India, Macedonia, Poland, Romania, the Russian Federation, Slovakia, South Africa and the United Kingdom (Chemical Information Services Ltd, 1994).

**Table 2. Production of trichloroethylene in selected countries (thousand tonnes)**

Year	Western Europe	Japan	USA <sup>a</sup>
1941			25
1945			84
1955			143 <sup>b</sup>
1960			160
1965			197
1970			277
1975		85	133
1980	210	82	121
1981	205	74	177
1982	210	67	86
1983	200	67	91
1984	215	74	91
1985	205	73	79
1986	183	71	77
1987	166	64	88
1988	169	70	82
1989	154	65	79
1990	131	57	79

From Linak *et al.* (1992)

<sup>a</sup> The US International Trade Commission stopped reporting trichloroethylene production and sales in 1982. The data for 1983–90 are estimates from the *Chemical Economics Handbook* (Linak *et al.*, 1992).

<sup>b</sup> From Su & Goldberg (1976)

### 1.2.2 Use

Trichloroethylene was used earlier as an extraction solvent for natural fats and oils, such as palm, coconut and soya bean oils. It was also an extraction solvent for spices, hops and the decaffeination of coffee (Linak *et al.*, 1992). The United States Food and Drug Administration (1977) banned these uses of trichloroethylene because of its toxicity; its use in cosmetic and drug products was also discontinued (Mertens, 1993).

Demand for trichloroethylene was generated mainly by the development of vapour degreasing after the 1920s and by the growth of the dry cleaning industry in the 1930s, but trichloroethylene was replaced in dry cleaning by tetrachloroethylene in the mid-1950s. By 1989, about 85% of the trichloroethylene produced in the United States was used in metal cleaning; the remaining 15% was equally divided between exports and miscellaneous applications. The pattern in Japan was similar to that in the United States, at 83 and 17%, respectively. In western Europe, 95% was used in vapour degreasing and 5% in other uses (Mertens, 1993). Similar use patterns have been reported for Canada (Moore *et al.*, 1991) and

Finland (Mroueh, 1993). Tables 3–5 present the uses of trichloroethylene in western Europe, Japan and the United States. Because of environmental and occupational health concerns, industry has attempted to restrict solvent emissions and maximize recovery and recycling. Trichloroethylene is, however, replacing 1,1,1-trichloroethane in some applications (Linak *et al.*, 1992).

**Table 3. Use of trichloroethylene in western Europe (thousand tonnes)**

Year	Metal cleaning (vapour degreasing)	Metal cleaning (cold cleaning)	Other
1980	164	25	26
1984	137	10	23
1987	124	10	16
1990	120	10	5

From Linak *et al.* (1992), estimates

**Table 4. Use of trichloroethylene in Japan (thousand tonnes)**

Year	Metal cleaning	Other
1980	49	16
1983	52	11
1987	49	12
1990	30	8

From Linak *et al.* (1992), estimates

Trichloroethylene has also been used, in limited quantities, to control relative molecular mass (by chain transfer) in the manufacture of polyvinyl chloride. An estimated 5500 tonnes are used annually for this application in the United States. It has also been used as a solvent in the rubber industry, some adhesive formulations and in research laboratories. In the textile industry, it is used as a carrier solvent for spotting fluids and as a solvent in dyeing and finishing (Fishbein, 1976; Linak *et al.*, 1992; Mertens, 1993). It is also used as a solvent in printing inks, paint, lacquers, varnishes, adhesives and paint strippers. It was used as both an anaesthetic and an analgesic in obstetrics (Smith, 1966). Trichloroethylene has been used in the aerospace industry for flushing liquid oxygen (Sax & Lewis, 1987). In a study of potential sources of indoor air pollution in the United States, 25 of 1159 (2.2%) common household products were found to contain trichloroethylene (Sack *et al.*, 1992).

The major use of trichloroethylene is in metal cleaning or degreasing. Degreasing is important in all metalworking and maintenance operations to remove oils, greases, waxes, tars and moisture before final surface treatments, such as galvanizing, electroplating, painting, anodizing and application of conversion coatings. Trichloroethylene is used in degreasing

operations in five main industrial groups: furniture and fixtures, fabricated metal products, electric and electronic equipment, transport equipment and miscellaneous manufacturing industries. It is also used in plastics, appliances, jewellery, automobile, plumbing fixtures, textiles, paper, glass and printing (Papdullo *et al.*, 1985; Linak *et al.*, 1992).

**Table 5. Use of trichloroethylene in the United States (thousand tonnes)**

Year	Metal cleaning	Other
1971	200	15
1974	153	4
1977	102	20
1980	84	13
1984	72	14
1987	57	9
1990	46	5

From Linak *et al.* (1992), estimates

Metal cleaning operations are of two types: cold cleaning and vapour cleaning. In cold cleaning, trichloroethylene is applied at room temperature; in vapour degreasing, the solvent vapours are condensed on the part to be cleaned. In cold cleaning, the metal parts are either dipped into the solvent solution or the solution is sprayed and wiped onto the object. The cold process is frequently used in maintenance operations and on small parts. Vapour degreasing requires a tank with heating coils on the bottom and a condensing zone near the top. The solvent is heated to boiling, and the hot vapour fills the condensing zone near the top of the tank. Soiled objects are lowered into this zone, where the vapour condenses into a pure liquid solvent on the piece and dissolves and carries off dirt as it drains back into the tank. The part dries immediately (Papdullo *et al.*, 1985; Linak *et al.*, 1992).

### 1.3 Occurrence

#### 1.3.1 Natural occurrence

Natural production of trichloroethylene has been reported in temperate, subtropical and tropical algae and in one red microalga (Abrahamsson *et al.*, 1995).

#### 1.3.2 Occupational exposure

The United States National Institute for Occupational Safety and Health (1994b) indicated that about 401 000 employees in 23 225 plants in the United States are potentially exposed to trichloroethylene. This estimate is based on a survey of companies and did not involve actual measurements. Table 6 summarizes the results of studies of occupational exposure.

**Table 6. Occupational exposures to trichloroethylene**

Country	No. of plants	Job, task or industry	No. of samples <sup>a</sup>	Air concentration (mg/m <sup>3</sup> )		Reference
				Mean	Range	
Finland 1982-85	11	Vapour degreasing	24 (A) 13 (P) TWA	[43.0] [37.6]	< [5.4-20.9] < [5.4-161]	Rantala <i>et al.</i> (1992)
	1	Rubber bonding	1 (A) TWA		[32.2]	
	1	Museum textile restoration	2 (P) 1-h		[3303]	
Netherlands	9	Rubber degreasing, cementing	137	4		Kromhout <i>et al.</i> (1994)
Sweden	14	Degreasing	336 (A)	[328]	[0-2230]	Ahlmarm <i>et al.</i> (1963)
	570	Degreasing	35 000- 40 000 (A)	[86]	3% [> 161]	
	19	Degreasing	29 (P)	27	3-144	
Switzerland	10	Degreasing	96 (P)	[304]	[5.4-1799]	Grandjean <i>et al.</i> (1955)
United Kingdom	32	Degreasing	212 (P)	91% < [161] 97% < [269] 99% < [537]		Shipman & Whim (1980)
USA	60	Degreasing	433 (P)			Morse & Goldberg (1943)
		Condenser, nonvented	187	[725]	[16-4833]	
		Condenser, vented	149	[515]	[27-2110]	
	NR	Degreasing	146 (A) <sup>b</sup>	86% < [537] 96% < [1074]		Hargarten <i>et al.</i> (1961)
	1	Degreasing	11 (P)	[302]	[199-419]	Vandervort & Polakoff (1973)
	1	Degreasing ignition coils	(P)		0-[537]	Bloom <i>et al.</i> (1974)
	1	Electronic cleaning	3 (P)	[446]	[408-483]	Gilles & Philbin (1976)
	1	Semi-conductor degreasing	10 (P)	16.1	2-57	Gunter (1977)
	1	Degreasing operator	20 (P)	[736]	[140-2024]	Kominsky (1978)
		Degreasing operator	7 (P)	[88.1]	[37.6-456]	
	Degreasing operator	6 (P)	[67.7]	[37.6-199]		
	Lathe operator next to degreaser	7 (P)	[52.1]	[37.6-129]		
1	Aircraft degreasing	4 (P)	[21.5]	[5.4-37.6]	Okawa <i>et al.</i> (1978)	
1	Tank relining	8 (P)	[1.3]	ND-[5.4]	Burroughs (1980)	

Table 6 (contd)

Country	No. of plants	Job, task or industry	No. of samples <sup>a</sup>	Air concentration (mg/m <sup>3</sup> )		Reference
				Mean	Range	
USA (contd)	1	Degreasing sheet metal	2 (P)	11	10-12	Johnson (1980)
			2 (A)	11	4-18	
	1	Degreasing, custom finishing	23 (P)	8.3	1-38	Ruhe & Donohue (1980)
			2 (A)	6	4-8	
	1	Vapour degreasing	14 (P)	[333]	[26.9-1670]	Burgess (1981)
	1	Degreasing, bus maintenance	3 (A)	3.0	ND-8.9	Love & Kern (1981)
	1	Degreasing	24 (STEL) 9 (TWA)	742 145	56-2000 37-357	Ruhe <i>et al.</i> (1981)
	1	Degreasing, plastics	2 (P)	[4.8]	[2.7-7.0]	Burroughs & Moody (1982)
	1	Degreasing, electronics	79 (P)	10.2	ND-209	Lee & Parkinson (1982)
	1	Degreasing, medical	5 (P)	5.4	1-16	Ruhe (1982)
			2 (A)	6.5	4-9	
	1	Degreasing, energy conservation products	2 (P)	[36.5]	[22-51]	Almaguer <i>et al.</i> (1984)
			10 (A)	[1.1]	[0.54-3.2]	
	1	Degreasing	9 (P)	[716]	[39-2288]	Belanger & Coye (1984)
			2 (A)	[184]	[0.54-367]	
5 (P)			[23.6]	[1.6-81.1]		
1	Degreasing aircraft	29 (TWA, P)	[30.7]	[ND-208]	Gorman <i>et al.</i> (1984)	
		11 (TWA, A)	[28.5]	[2-121]		
		22 (STEL)	[320]	[ND-1256]		
1	Taxidermy	2 (A)	[8.9]	[1.1-16.6]	Kronoveter & Boiano (1984)	
		2 (P)	[8.9]	[1.7-16]		
1	Degreasing	(TWA)	205	117-357	Landrigan <i>et al.</i> (1987)	
		(STEL)	1084	413-2000		

ND, not detected; NR, not reported. Most measurements were taken after observation of operating deficiencies of degreasers between 1952 and 1957.

<sup>a</sup> P, personal air samples (breathing zone); A, area samples; STEL, short-term exposure limit; TWA, time-weighted average

### 1.3.3 Environmental occurrence

Trichloroethylene has been reported in the air, rainwater, surface waters, drinking-water, seawater, marine sediments, marine invertebrates, marine mammals, foods and human tissues (McConnell *et al.*, 1975).

#### (a) Air

The levels of trichloroethylene in air have been measured throughout the world (Table 7). In a compilation of the results of surveys of ambient air in the United States before 1981 (Brodzinsky & Singh, 1983; United States Agency for Toxic Substances and Disease Registry, 1989), representing 2353 monitoring points, the mean concentrations were 30 ppt [ $0.2 \mu\text{g}/\text{m}^3$ ] in rural areas, 460 ppt [ $2.5 \mu\text{g}/\text{m}^3$ ] in urban and suburban areas and 1200 ppt [ $64 \mu\text{g}/\text{m}^3$ ] in industrialized areas near sources of trichloroethylene emissions. Industrial releases of trichloroethylene to the environment in the United States were 24 430 tonnes in 1988, 22 400 tonnes in 1989, 17 680 tonnes in 1990 and 15 950 tonnes in 1991 (United States Environmental Protection Agency, 1993).

Air emissions in western Europe in 1980 are reported in Table 8. In the Netherlands, emissions of trichloroethylene to the air were 6.5 tonnes in 1970, 5.4 tonnes in 1975, 4.2 tonnes in 1979, 3.7 tonnes in 1980, 2.6 tonnes in 1981 and 2.2 tonnes in 1982 (Besemer *et al.*, 1984).

Indoor air concentrations of trichloroethylene can increase when trichloroethylene-contaminated water is used domestically. A community water supply that contained 40 mg/L of trichloroethylene was estimated to contribute about  $40 \text{ mg}/\text{m}^3$  to the air of a bathroom during showering, and the weekly dose through inhalation was estimated to be 48 mg trichloroethylene (assuming 1-h showering), due to off-gassing of trichloroethylene from the water. About 42 mg of trichloroethylene were ingested from the water per week (Andelman, 1985). Similar conclusions were reached by Bogen *et al.* (1988).

#### (b) Water

Trichloroethylene occurs at low levels in all water supplies and frequently in groundwater, owing to its widespread use and physical characteristics. Table 9 summarizes the concentrations of trichloroethylene found in surface waters, groundwater and drinking-water worldwide.

Trichloroethylene was detected in an estimated 3% of surface water samples and 19% of groundwater samples analysed, at geometric mean concentrations of 27.3 ppb [ $\mu\text{g}/\text{L}$ ] in groundwater and 40.2 ppb in surface water (United States Environmental Protection Agency, 1989). In a computerized database on water quality, the reported median concentrations of trichloroethylene in 1983–84 were 5.0  $\mu\text{g}/\text{L}$  in industrial effluents (19.6% detectable, 1480 samples), 0.1  $\mu\text{g}/\text{L}$  (28% detectable, 9295 samples) in ambient water, < 50  $\mu\text{g}/\text{kg}$  dry weight (6% detectable, 338 samples) in sediment and < 50  $\mu\text{g}/\text{kg}$  (none detectable, 93 samples) in biota (Staples *et al.*, 1985).

The concentrations of trichloroethylene in sediment and animal tissue collected near the discharge zone of the Los Angeles County, CA, waste-treatment plant in 1980–81, were 17  $\mu\text{g}/\text{L}$  in the effluent, < 0.5  $\mu\text{g}/\text{kg}$  dry weight in sediment and 0.3–7  $\mu\text{g}/\text{kg}$  wet weight in various marine animal tissues (Gossett *et al.*, 1983).

**Table 7. Concentrations of trichloroethylene in ambient air**

Area	Year	Concentration [ $\mu\text{g}/\text{m}^3$ ]		Reference
		Mean	Range	
<b>Remote</b>				
Pacific Ocean (latitude 37°N)	1977	[0.07]		US Environmental Protection Agency (1985)
Panama Canal Zone (latitude 9°N)	1977	[0.08]		US Environmental Protection Agency (1985)
Northern hemisphere	1985		[0.06–0.09]	US Environmental Protection Agency (1985)
Southern hemisphere	1981		[< 0.02]	Singh <i>et al.</i> (1983)
<b>Rural</b>				
Badger Pass, CA, USA	1977	[0.06]	[0.005–0.09]	US Environmental Protection Agency (1985)
Whiteface Mountains, NY, USA	1974	[0.5]	[< 0.3–1.9]	Lillian <i>et al.</i> (1975)
Reese River, NV, USA	1977	[0.06]	[0.005–0.09]	US Environmental Protection Agency (1985)
Jetmar, KS, USA	1978	[0.07]	[0.04–0.11]	US Environmental Protection Agency (1985)
Western Ireland	1974	[0.08]		Lovelock (1974)
<b>Urban and suburban</b>				
Phoenix, AZ, USA	1979	[2.6]	[0.06–16.7]	Singh <i>et al.</i> (1981)
Los Angeles, CA, USA	1976	[1.7]	[0.14–9.5]	US Environmental Protection Agency (1985)
Lake Charles, LA, USA	1976–78	[8.6]	[0.4–11.3]	US Environmental Protection Agency (1985)
New Jersey, USA	1973–79	[9.1]	[ND–97]	Lillian <i>et al.</i> (1975); US Environmental Protection Agency (1985)
New York City, NY, USA	1974	[3.8]	[0.6–5.9]	Lillian <i>et al.</i> (1975)
Denver, CO, USA	1980	[1.07]	[0.15–2.2]	US Environmental Protection Agency (1985)
St Louis, MO, US	1980	[0.6]	[0.1–1.3]	US Environmental Protection Agency (1985)
Portland, OR, USA	1984	[1.5]	[0.6–3.9]	Ligocki <i>et al.</i> (1985)
Philadelphia, PA, USA	1983–84	[1.9]	[1.6–2.1]	Sullivan <i>et al.</i> (1985)
Brussels, Belgium	1974–75	[21.5]	[5.9–31.2]	Su & Goldberg (1976)
Geneva, Switzerland	1974	[31.2]		Su & Goldberg (1976)
Moscow, Russian Federation	1974	[19.3]	[14.0–28.5]	Su & Goldberg (1976)
Paris, France	1975	[4.0]		Su & Goldberg (1976)
Grenoble, France	1975	[19.3]	[6.4–28.5]	Su & Goldberg (1976)
Kyoto, Japan	1975	[5.1]		Su & Goldberg (1976)
Tokyo, Japan	1975	[1.8]		Su & Goldberg (1976)
Yokohama, Nagoya and Kawasaki, Japan	1985–86	[5.4]	[3.4–7.5]	Urano <i>et al.</i> (1988)

**Table 8. Estimated emissions of trichloroethylene to the air in western Europe, 1981**

Country or region	Air emission (tonnes/year)
Netherlands	2.7
Belgium/Grand Duchy of Luxembourg	2.9
Western Germany	46.0
France	45.0
Italy	27.0
Spain	15.0
Austria	5.5
United Kingdom	50.0
Norway	0.9
Sweden	12.0
Finland	2
Portugal	1
Switzerland	7
Denmark	2

From Besemer *et al.* (1984); figures include secondary emissions from water and solid waste

**Table 9. Concentrations of trichloroethylene in water**

Area	Concentration ( $\mu\text{g/L}$ )		Reference
	Mean	Range	
<b>Surface waters</b>			
<i>Seawater</i>			
Eastern Pacific Ocean	0.0003	0.0001–0.0007	Singh <i>et al.</i> (1983)
<i>Coastal waters</i>			
Sea coast, industrial area, United Kingdom		0.1–1	Herbert <i>et al.</i> (1986)
West coast, Sweden	0.015		Herbert <i>et al.</i> (1986)
Northern coast, Greece		0.06–2.8	Fytianos <i>et al.</i> (1985)
<i>Rivers</i>			
Tributaries of the Rhine		0.06–7.0	Herbert <i>et al.</i> (1986); Bauer (1981a); Hellman (1984)
Elbe, Germany		0.7–52.3	Hellman (1984)
Weser, Germany		0.5–1.5	Herbert <i>et al.</i> (1986)
Rhine		0.1–2.4	Herbert <i>et al.</i> (1986)
United Kingdom		0.01–1.0	Herbert <i>et al.</i> (1986)
Danube, Vienna, Austria	0.6		Herbert <i>et al.</i> (1986)
Netherlands		0.1–1.5	Herbert <i>et al.</i> (1986)

Table 9 (contd)

Area	Concentration ( $\mu\text{g/L}$ )		Reference
	Mean	Range	
Jackfish Bay, Canada		4.1-120	Comba <i>et al.</i> (1994)
Canada		< 0.001-42	Moore <i>et al.</i> (1991)
<b>Rainwater</b>			
Portland, OR, USA	0.006	0.002-0.02	Ligocki <i>et al.</i> (1985)
<b>Groundwater</b>			
Gloucester, Ontario, Canada		< 1-583	Lesage <i>et al.</i> (1990)
Zurich, Switzerland		1.1-1.9	Herbert <i>et al.</i> (1986)
Dubendorg, Germany	85		Herbert <i>et al.</i> (1986)
Northern Switzerland	0.92		Herbert <i>et al.</i> (1986)
Frankfurt, Germany		0.4-159	Herbert <i>et al.</i> (1986)
Mannheim, Germany		< 0.16-120	Herbert <i>et al.</i> (1986)
Italy		0.1-158	Ziglio <i>et al.</i> (1984a,b)
United Kingdom		< 0.1-70	Fielding (1981)
Netherlands		< 0.1-1100	Zoeteman <i>et al.</i> (1980); Trouwborst (1981)
Minnesota, USA, near landfill		0.7-125	Sabel & Clark (1984)
New Jersey, USA, near landfill		$\leq$ 1530	Burmester (1982)
Pennsylvania, near landfill		$\leq$ 27 300	Burmester (1982)
Japan, near electronics factory		$\leq$ 10 000	Hirata <i>et al.</i> (1992)
Phoenix, Arizona, USA		8.9-29	Flood <i>et al.</i> (1990)
<b>Drinking-water</b>			
Southern Philippines		0.03	Trussell <i>et al.</i> (1980)
Northern Philippines		0.01	Trussell <i>et al.</i> (1980)
Egypt		1.2	Trussell <i>et al.</i> (1980)
United Kingdom		0.4	Trussell <i>et al.</i> (1980)
Nicaragua		0.05	Trussell <i>et al.</i> (1980)
USA 1976-77		0.2-49	Thomas (1989)
1977-81		Trace-53	
1978		0.5-210	
		Trace-35 000 (with local contamination)	
New Jersey	23.4	Max. 67	Cohn <i>et al.</i> (1994)
Woburn, Massachusetts		Max. 267	Lagakos <i>et al.</i> (1986)

#### 1.3.4 Food

The concentrations of trichloroethylene in food in the United Kingdom were: 0.3-10 ppb [ $\mu\text{g/kg}$ ] in dairy products, 12-22 ppb in meat, none detected (ND)-19 ppb in oils and fats, ND-60 ppb in beverages, ND-7 ppb in fruits and vegetables and 7 ppb in cereals. In marine organisms, the concentrations varied from  $\leq$  1 ppb in invertebrates to 10 ppb in the flesh of fish

to a maximum of 50 ppb in the eggs of sea birds and the blubber of seals (McConnell *et al.*, 1975). Molluscs from Liverpool Bay, United Kingdom, contained a mean of 85 µg/kg on a dry-weight basis (range, 2–250 µg/kg). Various fish had a mean concentration of 106.5 µg/kg (range, 7–479 µg/kg) (Dickson & Riley, 1976).

The average concentrations of trichloroethylene in food in the United States were 0.9 (0–2.7) µg/kg in grain-based foods, 1.8 (0–12) µg/kg in 'table-ready' foods, 73.6 (1.6–980) µg/kg in butter and margarine, 3.8 (0–9.5) µg/kg in cheese products, 0.5 (0–1.7) µg/kg in peanut butter, 3.0 (0–9.2) µg/kg in ready-to-eat cereal products and 1.3 (0–4) µg/kg in highly processed foods (Heikes & Hopper, 1986; Heikes, 1987). In an evaluation of process waters and food commodities collected at 15 food processing plants, trichloroethylene was found at 3–7.8 ppb [µg/L] in three process waters but in none of the food products (Uhler & Diachenko, 1987). It was detected in five of 372 fatty and non-fatty food samples at concentrations of 2–94 µg/kg, with a mean of 49 µg/kg (Daft, 1989).

Trichloroethylene was found at a concentration of 100–500 ppb [µg/kg] in one of 70 samples of margarine taken from shops in the United States in 1980–82 and 1984 but at < 50 ppb in 20 samples. In 1984, the levels were all < 50 ppb (Entz & Diachenko, 1988). The mean daily intake of trichloroethylene from food, water and air in Germany was estimated to be 32–51 µg/day (Bauer, 1981b; von Düselen *et al.*, 1982).

### 1.3.5 Biological monitoring

Individual exposure to trichloroethylene in Germany was determined in non-occupational and a number of occupational environments by biological monitoring. Trichloroethylene was detected in 31% of all blood samples from persons not occupationally exposed to volatile halogenated hydrocarbons (median, < 0.1 µg/L; range, < 0.1–1.3 µg/L). The median levels of trichloroacetic acid, a metabolite of trichloroethylene, were 21.4 µg/L (range, 4.8–221 µg/L) in 43 blood samples and 6.0 µg (range, 0.6–261 µg) in 94 samples of 24-h urine from these unexposed persons. The blood levels of trichloroethylene were < 0.1–0.2 µg/L in nine motor vehicle mechanics, < 0.1 µg/L in three painters, 0.1–15.5 µg/L in three precision instrument makers and 0.2–7.1 µg/L in six dry cleaners (Hajimiragha *et al.*, 1986).

In a plant in the United States where trichloroethylene was used in five degreasing operations in the manufacture of steel tubing, the concentrations of trichloroethylene in air were 117–357 mg/m<sup>3</sup>, with short-term exposures as high as 2000 mg/m<sup>3</sup>. Urine samples collected from exposed workers before the shift contained, on average, 298 mg/L (range, 4–690 mg/L) of total trichloroethylene metabolites, while the mean concentration after the shift was 480 mg/L (range, 63–1050 mg/L) (Ruhe *et al.*, 1981).

The average blood plasma levels of trichloroethylene of 157 employees at two metal-working plants in the United States were 2.5 ppb [µg/L] (range, 0–22 ppb) and undetectable; in the second plant, the major exposure was to a solvent that contained chloroform. A control population living several miles from the first plant also had undetectable levels of trichloroethylene (Pfaffenberger *et al.*, 1984).

The concentration of total trichloro compounds in the urine of workers in a degreasing operation at a United States aircraft factory were 0.5–83.4 mg/g creatinine. These concentrations

correlated well with the air concentrations, which averaged 5.7 ppm [30.6 mg/m<sup>3</sup>] (Gorman *et al.*, 1984).

The levels of trichloroacetic acid in the urine of 73 workers in 24 workshops in Switzerland where degreasing was performed were 8–444 mg/L, with a mean of 86.7 mg/L. The levels in the 96 air samples were 1–335 ppm [5.37–1800 mg/m<sup>3</sup>] with a mean of 56.7 ppm [304 mg/m<sup>3</sup>] (Grandjean *et al.*, 1955).

The relationship between concentrations of trichloroethylene in the air near degreasing operations and urinary excretion of total trichloro compounds was reported in Japan. Eight workers had an average urinary concentration of 243.9 mg/L (range, 95–787 mg/L) total trichloro compounds after exposure to 40.7 ppm [217 mg/m<sup>3</sup>] trichloroethylene in air. The calculated estimated air levels corresponding to the urine levels found were 41.7 (range, 22.3–67.4) ppm [224 (120–362) mg/m<sup>3</sup>] (Nomiyama, 1971).

A total of 31 employees in 19 vapour degreasing plants in central Sweden were exposed to trichloroethylene at a mean level in ambient air of 27 mg/m<sup>3</sup>; 86% of the air samples contained < 50 mg/m<sup>3</sup>. A weak correlation was found between the concentrations of *N*-acetyl- $\beta$ -D-glucosaminidase and trichloroacetic acid in urine ( $r = 0.48$ ;  $p < 0.01$ ), but no correlation was seen with ambient air levels ( $r = 0.08$ ;  $p = 0.66$ ) (Seldén *et al.*, 1993).

In China, the relationship between the time-weighted average exposure to trichloroethylene at the end of a work week and the concentrations of metabolites in urine was investigated in 140 exposed and 114 control workers. In a plant where trichloroethylene was manufactured by chlorination of acetylene followed by dehydrochlorination, 61 men who were exposed to trichloroethylene in air at a concentration of 3–94 ppm [16.1–505 mg/m<sup>3</sup>] and 17 women exposed to 2–47 ppm [11–253 mg/m<sup>3</sup>] had  $\leq 127$  mg/L (men) and  $\leq 111$  mg/L (women) total trichloro compounds in their urine. In a metal-plating plant where trichloroethylene was used for degreasing, 52 men were exposed to concentrations of 1–63 ppm [5.37–338 mg/m<sup>3</sup>] and 10 women were exposed to 2–13 ppm [10.7–69.8 mg/m<sup>3</sup>]; the urinary levels were  $\leq 89$  mg/L for the men and  $\leq 98$  mg/L for the women (Inoue *et al.*, 1989).

The Danish Labour Inspection Service conducted biological monitoring of workers exposed to trichloroethylene in various factories between 1947 and 1987. The concentrations of trichloroacetic acid in 2272 urine samples from workers in 330 factories were similar from the mid-1950s to the mid-1970s and then began to decrease. The average urinary concentrations were 82 mg/L (range, 0–750 mg/L) in 1947–51, 40 mg/L (0–1975 mg/L) in 1950–56, 32 mg/L (0–680 mg/L) in 1957–61, 55 mg/L (0–730 mg/L) in 1962–66, 53 mg/L (0–850 mg/L) in 1967–71, 35 mg/L (0–370 mg/L) in 1972–76, 30 mg/L (0–365 mg/L) in 1977–81 and 18 mg/L (0–130 mg/L) in 1982–86 (Christensen & Rasmussen, 1990).

Blood and urine samples were collected in 1990 from 10 people working in four dry cleaning shops in Croatia, where trichloroethylene was used as the cleaning solvent. The concentration of trichloroethylene in the air was 25–40 ppm [134–215 mg/m<sup>3</sup>]. The mean blood levels of trichloroethylene were 0.38  $\mu$ mol/L [50  $\mu$ g/L] on Monday morning (range, 0.15–3.58  $\mu$ mol/L) [20–470  $\mu$ g/L] and 3.39  $\mu$ mol/L [445  $\mu$ g/L] on Wednesday afternoon (range, 0.46–12.71  $\mu$ mol/L) [60–1670  $\mu$ g/L]). The mean trichloroethanol levels in blood were 3.02  $\mu$ mol/L (0–10.7  $\mu$ mol/L) [451 (0–1600  $\mu$ g/L)] and 7.70  $\mu$ mol/L (0–26.1  $\mu$ mol/L) [1150 (0–3894  $\mu$ g/l)] for the same period, respectively, and the results for trichloroacetic acid were 165  $\mu$ mol/L (6.12–302

$\mu\text{mol/L}$ ) [27 (1–49 mg/L)] and 194  $\mu\text{mol/L}$  (13.5–394  $\mu\text{mol/L}$ ) [31 (2–64 mg/L)]. The mean trichloroacetic acid level in urine was 32.5 mmol/mol creatinine (1.3–61.2) [47 (2–89) mg/g] on Monday morning and 37.2 mmol/mol creatinine (1.9–77.4) [54 (3–112) mg/g] on Wednesday afternoon. The mean trichloroethanol levels in urine were 9.7 mmol/mol creatinine (0.4–35.7) [13 (0.5–47 mg/g)] in the Monday morning sample and 54.9 mmol/mol creatinine (5.3–177.7) [73 (7–235) mg/g] in the Wednesday afternoon sample (Skender *et al.*, 1991).

A number of researchers have studied the influence of hourly and daily variations in exposure concentrations on the alveolar concentrations of trichloroethylene and on the urinary excretion of trichloroethanol and trichloroacetic acid (Ogata *et al.*, 1971; Droz & Fernández, 1978). The estimated concentrations of trichloroacetic acid in urine at the end of a workday in which workers were exposed to 270  $\text{mg/m}^3$  trichloroethylene for 8 h per day, five days a week, were 100 mg/g creatinine 0.5 h after exposure, 80 mg/g creatinine after 16 h and 50 mg/g creatinine after 64 h (Monster, 1984).

People exposed to 50 ppm (270  $\text{mg/m}^3$ ) trichloroethylene for 8 h per day on five days a week were estimated to have alveolar air concentrations of 10–15 ppm [53.7–80.6  $\text{mg/m}^3$ ] at the end of exposure and 0.1 ppm [0.5  $\text{mg/m}^3$ ] 64 h after exposure. The blood concentrations were estimated to range from 0.9 to 0.006 mg/L (Monster, 1984).

The airborne concentrations of trichloroethylene at a liquid–vapour degreasing operation in the United States in 1980 were 117–357  $\text{mg/m}^3$ , with short-term sampling peaks of 413–2000  $\text{mg/m}^3$ . Nine exposed workers had a mean pre-shift urinary concentration of total trichloroethylene metabolites of 298  $\mu\text{g/L}$ ; the mean post-shift concentration was 480  $\mu\text{g/L}$  (Landrigan *et al.*, 1987).

Swedish producers of trichloroethylene offered an exposure control programme to customers using trichloroethylene in which free analysis of trichloroacetic acid in urine was conducted annually. On this basis, Axelson *et al.* (1994) categorized the average exposure of 1670 workers as 0–49 mg/L, 50–99 mg/L and  $\geq 100$  mg/L; 81% were placed in the lowest group. The analytical method used to determine trichloroacetic acid in urine indicated that 50 mg/L was approximately equivalent to an 8-h time-weighted average exposure to 20 ppm [107  $\text{mg/m}^3$ ] trichloroethylene.

In an ongoing biological monitoring study of workers in various occupations who are exposed to trichloroethylene, tetrachloroethylene or 1,1,1-trichloroethane, conducted by the Finnish Institute of Occupational Health, 11 534 samples representing 3976 workers in 600 workplaces were obtained for the three compounds between 1965 and 1983. Of these workers, 94.4% were monitored for one solvent, 5.2% for two solvents and 0.4% for three solvents. The overall median concentrations of trichloroethylene, reported as trichloroacetic acid in urine, were 63  $\mu\text{mol/L}$  [10.3 mg/L] for women and 48  $\mu\text{mol/L}$  [7.8 mg/L] for men. Before 1970, the mean urinary levels were 80–90  $\mu\text{mol/L}$  [13.1–14.7 mg/L] for men and 60–80  $\mu\text{mol/L}$  [9.8–13.1 mg/L] for women (Anttila *et al.*, 1995).

Trichloroethylene was detected in the blood of 22 of 39 subjects in Zagreb, Croatia, who had no known exposure to solvents, and trichloroacetic acid was found in all plasma and urine samples. The geometric mean concentrations of trichloroethylene were 0.023  $\mu\text{g/L}$  (range, < 0.020–0.090  $\mu\text{g/L}$ ) in blood; those of trichloroacetic acid were 45.4  $\mu\text{g/L}$  (13.5–160  $\mu\text{g/L}$ ) in

plasma and 24.2 µg/L (1.67–292 µg/L) in urine. The concentration of trichloroethylene in the drinking-water was 4.20 µg/L (0.69–35.9 µg/L) (Skender *et al.*, 1993).

The mean concentration of trichloroacetic acid in sera from 94 subjects who were not exposed to organic solvents in Germany was 23.8 µg/L (range, 4.8–221 µg/L), and the average level of trichloroacetic acid in 24-h urine samples was 7.6 µg (range, 0.6–261.4 µg) (Hajimiragha *et al.*, 1986).

Of the 14 million inhabitants of the Netherlands in the 1980s, 14 000 were estimated to be exposed by all routes to an average trichloroethylene concentration of 10 µg/m<sup>3</sup>, resulting in a daily intake of 200 µg; 350 000 were exposed to 4 µg/m<sup>3</sup> with a daily intake of 80 µg; and 13.6 million inhabitants were exposed to 0.8 µg/m<sup>3</sup> for a daily intake of 16 µg (Besemer *et al.*, 1984).

The serum levels of trichloroacetic acid in inhabitants of Milan, Italy, who drank water containing > 2000 µg/L of trichloroethylene was 36.5 µg/L; that in an unexposed group was 8 µg/L (Ziglio *et al.*, 1984c). The ambient air level of trichloroethylene in Milan in 1979 was 7.6 µg/m<sup>3</sup> (Ziglio *et al.*, 1983).

Analysis of human tissue taken *post mortem* showed trichloroethylene concentrations of 2–32 µg/kg wet weight in body fat, 2–5.8 µg/kg in liver, < 1–3 µg/kg in kidney and ≤ 1 µg/kg in brain (McConnell *et al.*, 1975).

#### 1.4 Regulations and guidelines

Occupational exposure limits and guidelines for trichloroethylene in a number of countries are presented in Table 10.

WHO (1993) has established a provisional guideline of 70 µg/L trichloroethylene in drinking-water.

The American Conference of Governmental Industrial Hygienists (1994) has recommended several biological exposure indices for trichloroethylene. That for trichloroacetic acid in urine at the end of the work week is 100 mg/g creatinine; that for trichloroacetic acid and trichloroethanol in urine at the end of the shift at the end of the work week is 300 mg/g creatinine; and that for free trichloroethanol in blood at the end of the shift at the end of the work week is 4 mg/L. It is noted that these indices are nonspecific, i.e. other exposures can affect the measurement, and that trichloroethylene in exhaled air and in blood can be used as an indicator of exposure but interpretation of the measurement is only semiquantitative.

Biological indices for exposure to trichloroethylene have been reported. In Finland, the action level for trichloroacetic acid in urine is 360 µmol/L [47.3 mg/L] (Aitio *et al.*, 1995); in Germany, the biological tolerance values are 5 mg/L trichloroethanol in blood and 100 mg/L trichloroacetic acid in urine (Deutsche Forschungsgemeinschaft, 1993); and in Switzerland, the biological tolerance values are 5 mg/L trichloroethanol in blood and 100 mg/g creatinine trichloroacetic acid in urine (Schweizerische Unfallversicherungsanstalt, 1994).

**Table 10. Occupational exposure limits and guidelines for trichloroethylene**

Country	Year	Concentration (mg/m <sup>3</sup> )	Interpretation
Australia	1993	270	TWA
		1080	STEL
Austria	1987	260	TWA
Belgium	1993	269	TWA
		1070	STEL
Brazil	1987	420	TWA
Bulgaria	1993	269	TWA
		537	STEL
Canada	1987	75	TWA
		402	STEL (15 min)
Chile	1987	428	TWA
China	1987	535	TWA
Colombia	1993	269	TWA
		537	STEL
Czech Republic	1993	250	TWA
		1250	STEL
Denmark	1993	160	TWA
Egypt	1987	269	TWA
Finland	1993	160	TWA
		240	STEL
France	1993	405	TWA
		1080	STEL
Germany	1993	270	TWA; suspected carcinogen
Hungary	1987	10	TWA
		40	STEL
India	1987	535	TWA
		800	STEL
Indonesia	1987	535	TWA
Italy	1987	400	TWA
Japan	1993	270	TWA
Jordan	1993	269	TWA
		537	STEL
Mexico	1987	535	TWA
Netherlands	1994	190	TWA
		538	STEL (15 min)
New Zealand	1993	269	TWA
		537	STEL
Norway	1984	105	TWA; carcinogen
Philippines	1993	535	TWA
Republic of Korea	1993	269	TWA
		537	STEL
Poland	1993	50	TWA

**Table 10 (contd)**

Country	Year	Concentration (mg/m <sup>3</sup> )	Interpretation
Romania	1987	200	TWA
		300	STEL
Russian Federation	1993	269	TWA
Singapore	1993	269	TWA
		537	STEL
Sweden	1993	50	TWA
		140	STEL
Switzerland	1994	260	TWA
		1300	STEL
Thailand	1993	537	TWA
		1074	STEL
Turkey	1993	535	TWA
United Kingdom	1993	535	TWA
		805	STEL
USA			
ACGIH	1994	269	TWA
		537	STEL
NIOSH	1994	134	TWA; carcinogen
		11	Ceiling (60 min <sup>a</sup> )
OSHA	1994	537	TWA
		1074	Ceiling
		1611	Peak
Venezuela	1987	535	TWA
		800	STEL
Viet Nam	1993	269	TWA
		537	STEL

From Cook (1987); ILO (1991); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); Schweizerische Unfallversicherungsanstalt (1994); United Kingdom Health and Safety Executive (1994); United States National Institute for Occupational Safety and Health (NIOSH) (1994c); United States Occupational Safety and Health Administration (OSHA) (1994)

TWA, time-weighted average; STEL, short-term exposure limit; ceiling, level not to be exceeded during any part of the workday; peak, acceptable maximum peak above acceptable ceiling concentration for an 8-h shift (maximum duration, 5 min in any 2 h)

<sup>a</sup>During use as an anaesthetic

## 2. Studies of Cancer in Humans

### 2.1 Case reports

Málek *et al.* (1979) followed-up 57 men who had worked for at least one year in dry cleaning in Prague, Czech Republic, since the 1950s. Nearly 60% of those tested had a urinary trichloroacetic acid concentration in excess of 100 mg/L, with sporadic values in the region of 1000 mg/L. The follow-up period was 5–50 years. Six men were found to have cancer: three had lung cancer, one had cancer of the tongue, one had rectal cancer and one had a bladder cancer and two rectal tumours.

Novotná *et al.* (1979) reviewed the occupational histories of all 63 subjects diagnosed with histologically confirmed carcinoma of the liver in 1972 and 1974 in Prague, Czech Republic. None of them had been employed in workshops where trichloroethylene was used. Paraf *et al.* (1990) reported a case of gall-bladder cancer in a woman aged 64 who had worked as a technician in a laboratory in France where trichloroethylene was used for degreasing metal.

Jalihal and Barlow (1984) reported a case of acute myeloid leukaemia in a 60-year-old dry cleaner in the United Kingdom. He had had heavy exposure for many years first to trichloroethylene and later to tetrachloroethylene.

### 2.2 Descriptive studies

Risks for cancer among workers in industries where there is potential exposure to trichloroethylene have been addressed in a number of studies but in which exposure to this compound was not specified (e.g. Krain, 1972; Blair, 1980; Blair & Mason, 1980; Brandt-Rauf *et al.*, 1982, 1986; Brandt-Rauf & Hathaway, 1986; Malke *et al.*, 1986; Dubrow & Gute, 1987). These descriptive studies were not considered relevant in view of the availability of cohort and case-control studies.

Paddle (1983) retrieved records from the Mersey Regional Cancer Registry (United Kingdom) for 1951–77 for all 95 subjects with a diagnosis of primary liver cancer and an address near Runcorn, where there is a plant in which trichloroethylene has been manufactured since 1909. Two members of the personnel department of the company compared the records of tens of thousands of people who had worked at the Runcorn site during 1934–76 with the registry list, and the records of two potential matched persons were subsequently checked at the Department of Health and Social Security. It was concluded that none of the subjects had ever worked at the Runcorn site. [The Working Group noted that the interpretation of this result was hindered by the lack of expected numbers.]

### 2.3 Cohort studies

The cohort studies available to the Working Group addressed three occupational groups: dry cleaners, workers who had undergone biological monitoring for exposure to trichloroethylene and workers employed in miscellaneous manufacturing industries. The Working Group did not consider that the first group of studies (see the monograph on dry cleaning) was relevant to an evaluation of trichloroethylene *per se*, given the extensive exposure of these people to other

solvents. Workers who were biologically monitored were considered likely to have been exposed to trichloroethylene, but the proportion of workers in the third group of studies who were actually exposed to trichloroethylene varied.

### 2.3.1 Exposure evaluated by biological monitoring

Axelsson *et al.* (1978, 1984 [abstract], 1994) studied a cohort of workers in Sweden who had been exposed to trichloroethylene. Between 1930 and 1986, only one plant in central Sweden produced trichloroethylene for the domestic market, and this producer offered its customers free surveillance of their exposed workers by analysis for trichloroacetic acid in the urine. Files containing data from such monitoring constitute the basis of the study, but some of the files had been destroyed. Axelsson *et al.* (1978) originally retrieved records for 518 men, later expanded the cohort to 1424 men (Axelsson *et al.*, 1984, abstract) and finally included 1727 persons drawn from 115 companies that had used the surveillance service at least once between 1955 and 1975 (Axelsson *et al.*, 1994). Records were incomplete for 23 persons, four people could not be found in the population register, and 30 had emigrated. The final analysis was thus based on 1670 persons, 1421 men and 249 women, who were followed up for mortality from 1955 through 1986 and for cancer incidence from 1958 through 1987. Swedish national rates were used for the calculation of expected numbers. Exposure was assessed as the mean concentration of trichloroacetic acid in all urinary samples available for a given person: 78% of the person-years for men were accumulated in the category 0–49 mg/L, 14% in the category 50–99 mg/L and 8% in the > 100 mg/L category. A total of 253 deaths were observed [giving an overall standardized mortality ratio (SMR) of 1.0; 95% confidence interval (CI), 0.89–1.1]; and 129 incident cancer cases occurred [giving an overall standardized incidence ratio (SIR) of 1.0; 95% CI, 0.84–1.2]. Among men, a significant excess risk was found for skin cancer (SIR, 2.4; 95% CI, 1.0–4.7; eight observed). There were five cases of non-Hodgkin's lymphoma (1.6; 0.51–3.6) and four cases of liver and biliary tract cancer (1.4; 0.38–3.6). Of the incident cancer cases in men, 77 occurred in men in the lowest exposure category [SIR, 0.92], 18 in the medium category [SIR, 0.93] and 12 [SIR, 1.4] in the highest exposure category.

Anttila *et al.* (1995) studied a cohort of 3974 persons in Finland who were biologically monitored for occupational exposure to three halogenated hydrocarbons (3089 for trichloroethylene, 849 for tetrachloroethylene and 271 for 1,1,1-trichloroethane) during 1965–83. The cohort consisted of those people for whom 10 743 measurements were taken; the persons for whom a further 791 measurements were taken could not be identified. The overall median urinary concentration of trichloroacetic acid was higher for women (63  $\mu\text{mol/L}$  [10.3 mg/L]) than for men (48  $\mu\text{mol/L}$  [7.8 mg/L]). The cohort was followed up for incident cancer cases through 1992, and the expected numbers were calculated on the basis of Finnish national rates. There were 208 cancer cases among people monitored for exposure to trichloroethylene (SIR, 1.1; 95% CI, 0.92–1.2). A significant excess risk was seen for cervical cancer (2.4; 1.1–4.8; eight observed), and the risk was further increased for women with a mean level of exposure  $\geq 100 \mu\text{mol/L}$  [ $\geq 16.3 \text{ mg/L}$ ] (4.4; 1.4–10; five observed); no further increase in risk was seen with increasing latency since the time the first measurement was made. The SIR for liver cancer among people with high exposure was 2.7 (0.33–9.9; two observed); a significantly increased SIR was seen with a 20-year latency since first measurement (6.1; 1.3–18; three observed). The

SIR for cancers of the lymphohaematopoietic tissues was increased among people with high exposure (2.1; 0.95–4.0; nine observed) and was further increased with the 20-year latency (3.0; 1.2–6.1; seven observed). The SIRs for stomach cancer were 0.91 (0.25–2.3; four cases) for high exposure and 3.0 (1.2–6.1; seven cases) with a 20-year latency. The SIR for prostatic cancer was 0.68 (0.08–2.4; two cases) with high exposure and 3.6 (1.5–7.0; eight cases) with a 20-year latency.

The population studied by Anttila *et al.* (1995) included most of the workers investigated in a previous study that comprised 2117 Finnish workers in whom urinary trichloroacetic acid was measured or were reported as having been exposed to trichloroethylene during 1963–76 (Tola *et al.*, 1980). A total of 11 cancer deaths (14.3 expected) was reported.

### 2.3.2 Exposure in miscellaneous manufacturing industries

Barret *et al.* (1984) reported in an abstract a study of the death certificates of 235 workers who had been exposed to trichloroethylene and cutting oils; a total of 14 500 had been so employed in 1983. In a comparison of SMRs [method not described] for each site of cancer, the authors found a high risk for cancer of the naso- and oropharynx (SMR, 2.5 [95% CI, 1.4–4.1]; 15 deaths).

Shindell and Ulrich (1985) studied a plant in northern Illinois, United States, where trichloroethylene had been used extensively as a degreasing agent and where the workers drank water containing traces (43 ppb [ $\mu\text{g/L}$ ]) of trichloroethylene. The plant began operation in 1957. The study included all office employees at this plant and all production employees who had worked for three months or more in this or a nearby facility between 1 January 1957 and 31 July 1983. The cohort consisted of 2646 individuals, of whom 2140 were white men, 76 were non-white men and 430 were women. The cohort was followed up until 31 July 1983; vital status was determined for all but 52 persons. National mortality rates were used to calculate the expected numbers of deaths. A total of 141 persons had died, whereas 181.6 deaths were expected [SMR, 0.78; 95% CI, 0.65–0.92]. There were nine deaths from respiratory cancer [0.74; 0.34–1.4] and 12 deaths from non-respiratory cancer [0.49; 0.25–0.85]. The employees who had the greatest opportunity for occupational exposure to trichloroethylene were assemblers, but their mortality rate generally conformed to the expected value for all types of diseases.

Garabrant *et al.* (1988) followed a cohort of 14 067 persons who had worked for at least four years for a large aircraft manufacturing company in the United States and for at least one day at the company facility in San Diego County between January 1958 and 31 December 1982. The cohort was followed up through 1982. Persons lost to follow-up were included up to the last date at which they were known to be alive. United States national rates and rates from San Diego County were used to calculate the expected numbers of deaths. Data from a relatively small case-control study nested in the cohort indicated that 37% of the jobs held in the plant entailed exposure to trichloroethylene. A total of 1804 deaths was observed (SMR, 0.75; 95% CI, 0.72–0.79), and there were 453 deaths from cancer (0.84; 0.77–0.93). None of the SMRs for individual cancer sites was significantly elevated. There were eight deaths from cancer of the biliary passages and liver (0.94; 0.40–1.9).

Spiras *et al.* (1991) analysed a cohort of 14 457 civilian employees who had worked for at least one year at an air force base in Utah, United States, between 1 January 1952 and 31

December 1956, where they maintained and overhauled aircraft and missiles, cleaning and repairing small parts. The analysis included 12 538 white workers and 1528 workers of unknown race, who were followed up until 31 December 1982; 97% were successfully traced. At the end of follow-up, 3832 persons had died, and their death certificates were obtained from the State vital statistics office and coded by a nosologist. The expected number of deaths was based on rates for the Utah population. In the early years of operation of the base, 1939–54, cold solvents were used to clean metal parts, and these were primarily Stoddard solvent, carbon tetrachloride, trichloroethylene and alcohols. Of these, Stoddard solvent was used most frequently; however, in 1955, trichloroethylene replaced Stoddard solvent, and in 1968 1,1,1-trichloroethane replaced trichloroethylene. Trichloroethylene was the primary solvent used in vapour degreasing in the base shops from 1939 to 1979, when it was replaced by 1,1,1-trichloroethane. Of the 14 467 cohort members, 10 256 were classified as having been exposed to mixed solvents, 7282 to trichloroethylene, 6977 to Stoddard solvent and 6737 to carbon tetrachloride (Stewart *et al.*, 1991). Actual exposure levels could not be quantified, but for each combination of job and organization an index of exposure to trichloroethylene was calculated on the basis of the frequency of exposure, the frequency of peak exposure and duration of use. Cumulative exposure categories were derived by multiplying the exposure index assigned to each combination of job and organization by the time spent in this job and by adding these products. The 3832 deaths in the total cohort resulted in an overall SMR of 0.92 (95% CI, 0.90–0.95). Among white men exposed to trichloroethylene, there were 1508 deaths (0.92; 0.87–0.96), 248 of which were from cancer (0.92; 0.81–1.1). When the data for men and women exposed to trichloroethylene were combined, there were 1694 deaths from all causes [0.90; 0.86–0.95] and 281 deaths from cancer [0.88; 0.78–0.99]; there was an elevated risk for cancer of the biliary passages [2.2; 0.96–4.4]. Nonsignificantly excess risks were also seen for cancer of the bone in men (2.6; 0.54–7.7; three deaths) and for cancer of the cervix (2.2; 0.61–5.7; four deaths) and for non-Hodgkin's lymphoma (2.9; 0.78–7.3; four deaths) in women. There were two deaths from primary liver cancer [1.1; 0.12–4.0]. No evidence of a dose–response relationship was seen when the data were analysed by cumulative exposure to trichloroethylene (scored as categories of < 5, 5–25, > 25) for cancer at any site, including cancer of biliary passages, for which the SMRs were [2.5] (three deaths) for exposure to < 5, [4.3] (three deaths) for exposure to 5–25 and [1.3] (two deaths) for exposure to > 25. Both deaths from liver cancer occurred among men in the lowest category of cumulative exposure.

A retrospective cohort study of renal cancer among workers exposed to trichloroethylene in a cardboard manufacturing factory in Germany was reported by Henschler *et al.* (1995). Measurements of exposure were not available, and workers were classified as exposed or not exposed on the basis of categories of job held in the factory. The exposed group consisted of 169 men who had worked for at least one year during 1956–75; a control group consisting of 190 unexposed workers from the same factory was included for comparison. The average observation period was 34 years. Assessment of cancer occurrence was based on abdominal sonography, records of the medical, personnel and pension departments and interviews with relatives. Causes of death were obtained from hospital records or from the treating physician. During the period of follow-up, four histologically verified cases of renal-cell carcinoma and one case of urothelial cancer of the renal pelvis were seen in the exposed group, and no case was

observed in the controls ( $p = 0.03$ ). The five cancers occurred 18–34 years after first exposure; four of the five men had been exposed for more than 13 years. The excess was confirmed in comparisons with population rates for Denmark (SIR, 8.0; 95% CI, 2.6–19) and for the former German Democratic Republic (9.7; 3.1–23). The incidences of cancers at other sites were not reported. There were 50 deaths from all causes among exposed workers and 52 among controls; 16 cases of cancer of any organ were seen in both exposed and control workers; and two deaths from renal cancer occurred in exposed workers and none in controls. In a comparison with the local population, the SMR for renal cancer in the exposed group was 3.3 (95% CI, 0.40–12). [The Working Group noted that the use of sonography suggested that the study originated from the observation of a cluster of cases of renal cancer.]

The main cohort studies are summarized in Table 11.

## 2.4 Case-control studies

### 2.4.1 Primary liver cancer

Hernberg *et al.* (1984) identified 374 cases of primary liver cancer (ICD 155.0) that had been reported to the Finnish Cancer Registry in 1979–80. The notifying hospital could not be identified in nine cases, the hospital refused contact with 38 patients, and the diagnosis was incorrect in 83 cases. For the remaining 244 cases, a questionnaire was sent to either the patient or the next-of-kin. Three deceased patients had no relatives, and in 79 instances no reply was obtained. A further check of the diagnoses revealed that only 126 of the 162 cases for which a reply was obtained were primary liver cancers. For each of the 162 cases, two controls with coronary infarct and without cancer were selected, from the hospital register for living cases and from autopsy records for dead cases. Complete replies were obtained from only 174 controls or their next-of-kin. An industrial hygienist evaluated exposure to solvents on the basis of the reported occupational histories. Eight patients had been exposed to solvents for at least one year (odds ratio, 2.3; 95% CI, 0.8–7.0). Six of the exposed patients were women, one of whom had possibly been exposed to trichloroethylene; none of the female controls had been exposed.

Hernberg *et al.* (1988) subsequently identified 618 persons reported as having primary liver cancer to the Finnish Cancer Registry in 1976–78 and 1981. Five patients alive at the start of the study were excluded, and no relative was found for 87 patients. Questionnaires were sent to relatives of the remaining 526 cases, and a response was obtained from 377. Thirty-three cases were omitted on the basis of an incorrect or unconfirmed diagnosis, leaving 344 cases in the study. Two control groups were selected: one, as in the previous study, comprised 674 patients who had died with a coronary infarct, of whom 116 had no relatives and for 385 of whom the questionnaire was returned; the second control group consisted of 720 deceased stomach cancer patients, 66 of whom had no relatives and for 476 of whom a questionnaire was returned from next-of-kin. Two industrial hygienists coded occupational histories for potential exposure to solvents. In comparison with the two control groups combined, the odds ratios for exposure to solvents were 0.6 [95% CI, 0.3–1.4] for men and 3.4 [1.1–10] for women. None of the exposed women had been a heavy or moderate alcohol drinker. One of the seven solvent-exposed female patients and none of the solvent-exposed controls had been exposed to trichloroethylene.

Table 11. Summary of data from four cohort studies of trichloroethylene

Cancer site	Axelson <i>et al.</i> (1994) 1421 men using trichloroethylene and monitored for exposure (Sweden, 1958-87)			Anttila <i>et al.</i> (1995) 3089 men and women using trichloroethylene and monitored for exposure (Finland, 1967-92)			Spirias <i>et al.</i> (1991) 7282 men and women employed in aircraft maintenance and exposed to trichloroethylene (USA, 1953-82)			Garabrant <i>et al.</i> (1988) 14 067 men and women employed in aircraft manufacture (USA, 1958-82)		
	SIR	95% CI	Obs	SIR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs
All cancers	0.96	0.80-1.2	107	1.1	0.92-1.2	208	[0.88]	[0.78-0.99]	281	0.84	0.77-0.93	453
Oesophagus	NR			NR			[1.0]	[0.37-2.2]	6	1.1	0.62-1.9	14
Stomach	0.70	0.23-1.6	5	1.3	0.75-2.0	17	[0.78]	[0.43-1.3]	14	0.40	0.18-0.76	9
Colon	1.0	0.44-2.0	8	0.84	0.36-1.7	8	[1.0]	[0.67-1.4]	29	0.96	0.71-1.3	47
Liver and biliary tract	1.4	0.38-3.6	4	[1.9]	[0.86-3.6]	9	[1.9]	[0.91-3.5]	10	0.94	0.40-1.9	8
Primary liver cancer				2.3	0.74-5.3	5	[1.1]	[0.14-4.0]	2			
Biliary tract				1.6	0.43-4.0	4	[2.2]	[0.96-4.4]	8			
Cervix	NR			2.4	1.1-4.8	8	2.2	0.61-5.7	4	0.61 <sup>a</sup>	0.25-1.3	7
Prostate	1.3	0.84-1.8	26	1.4	0.73-2.4	13	0.80	0.50-1.2	22	0.93	0.60-1.4	25
Kidney	1.2	0.42-2.5	6	0.87	0.32-1.9	6	[1.1]	[0.46-2.1]	8	0.93	0.48-1.6	12
Urinary bladder	1.0	0.44-2.0	8	0.82	0.27-1.9	5	[1.4]	[0.70-2.5]	11	1.3	0.74-2.0	17
Skin	2.4	1.0-4.7	8	NR			[1.0] <sup>b</sup>	[0.38-2.3]	6	0.7 <sup>c</sup>	0.29-1.5	7
Brain and nervous system	NR			1.1	0.50-2.1	9	[0.78]	[0.36-1.5]	9	0.78	0.42-1.3	13
Lymphohaematopoietic system				1.5	0.92-2.3	20	[0.94]	[0.66-1.3]	37	0.78	0.56-1.1	38
Non-Hodgkin's lymphoma	[1.5] <sup>d</sup>	0.5-3.6	5	1.8 <sup>d</sup>	0.78-3.6	8	[1.3] <sup>d</sup>	[0.68-2.1]	14	0.82	0.44-1.4	13
Hodgkin's disease	1.1	0.03-6.0	1	1.7	0.35-5.0	3	[0.87]	[0.24-2.2]	4	0.73	0.20-1.9	4
Leukaemia	NR			1.1	0.35-2.5	5	[0.73] <sup>e</sup>	[0.37-1.3]	11	0.82 <sup>d</sup>	0.47-1.3	16

SIR, standardized incidence ratio; CI, confidence interval; Obs, observed; SMR, standardized mortality ratio; NR, not reported

<sup>a</sup>Female genital organs<sup>b</sup>Malignant melanoma<sup>c</sup>Includes five cases of malignant melanoma<sup>d</sup>Including ICD 202<sup>e</sup>Including aleukaemia

Hardell *et al.* (1984) studied all cases of liver cancer reported to the Swedish Cancer Registry in 1974–81 in men aged 25–80 living in the Umeå region of Sweden. Six patients who were alive at the start of the study in 1981 were excluded, leaving 166 cases. The diagnosis of 114 cases was confirmed on review. Six patients had been used as controls in a previous study, relatives could not be identified for five patients, and the relatives of one patient refused participation, leaving 102 patients (78 with hepatocellular, 15 with cholangiocellular, five with mixed and four with other types of liver cancer) for whom completed questionnaires were obtained. Two deceased controls matched for age, sex, year of death and municipality were selected from the National Population Register for each case, excluding people who had died from suicide or cancer. Exposure to solvents was assessed on the basis of responses to a questionnaire. The risk ratio for all primary liver cancers (hepatocellular and/or cholangiocellular) was 1.8 (95% CI, 0.99–3.4); that for hepatocellular carcinoma was 2.1 (1.1–4.0). Two of the 22 solvent-exposed patients and one of the 27 solvent-exposed controls had been exposed to trichloroethylene.

#### 2.4.2 Malignant lymphoma

Hardell *et al.* (1981) studied 169 men aged 25–85 with histologically confirmed malignant lymphoma (60 with Hodgkin's disease, 105 with non-Hodgkin's lymphoma and four with unclassified lymphomas) in the Umeå region of Sweden between 1974 and 1978. For each of the 107 living patients, two controls matched for sex, age and residence were selected from the National Population Registry. For each of the 62 deceased patients, two controls matched for sex, age, year of death and municipality were selected from the National Registry for Causes of Death, excluding people who had died from suicide or cancer. Exposure to solvents was assessed on the basis of responses to a questionnaire. Three of the 338 controls did not return the questionnaire but were considered not to have been exposed in matched analyses. The relative risk associated with exposure to styrene, trichloroethylene, tetrachloroethylene or benzene was 4.6 (95% CI, 1.9–11). Seven cases and three controls reported exposure to trichloroethylene.

#### 2.4.3 Hodgkin's disease

Olsson and Brandt (1980) studied 25 men aged 20–65 who were admitted consecutively to the Department of Oncology at the University Hospital of Lund, Sweden, in 1978–79 with Hodgkin's disease. For each case, two male controls, matched for age and residence, were selected from the population register. Twelve of the patients had been exposed to organic solvents, giving a relative risk of 6.6 (95% CI, 1.8–24). Three cases and no control reported exposure to trichloroethylene.

#### 2.4.4 Renal-cell carcinoma

Sharpe *et al.* (1989) identified 403 patients who had been diagnosed with renal-cell carcinoma in nine hospitals in Montréal, Canada, in 1982–87. Of these, 168 were still alive in 1987 and agreed to complete a questionnaire. For each case, one control originally suspected to have renal-cell carcinoma but for whom a non-neoplastic diagnosis was given was matched for sex, age and urologist. Ultimately, 164 patients and 161 controls provided information. Ten

patients and three controls had been exposed to degreasing solvents (odds ratio, 3.4; 95% CI, 0.92–13). Tetrachloroethylene, 1,1,1-trichloroethane, trichloroethylene and dichloromethane were reported to be the agents most widely used.

#### 2.4.5 *Cancer of the colon*

Fredriksson *et al.* (1989) carried out a case-control study of patients aged 30–75 in whom adenocarcinoma of the large bowel had been diagnosed in 1980–83 in the Umeå region of Sweden. A total of 402 incident cases were identified, but only patients alive in 1984–86 were included, leaving 344 patients, of whom 312 participated. Two population controls, matched by age, sex and county, were included for each case. Data on exposure were collected by a postal questionnaire. The odds ratio for exposure to trichloroethylene was 1.5 (95% CI, 0.4–5.7) and that for exposure to trichloroethylene among dry cleaners was 7.4 (1.1–47).

#### 2.4.6 *Brain tumours*

Heineman *et al.* (1994) undertook a case-control study of 741 white men who had died from astrocytic brain tumours in two states of the United States between 1978 and 1981. Next-of-kin were identified for 654 patients; 483 of these were interviewed, and a hospital diagnosis of astrocytic brain tumour was confirmed in 300 cases. Of 741 selected deceased controls, 320 were included in the study. Exposure to solvents was assessed on the basis of a job-exposure matrix; 128 case patients had been employed in jobs with potential exposure to trichloroethylene (odds ratio, 1.1; 95% CI, 0.8–1.6). None of the risk estimates for subgroups reached significance.

#### 2.4.7 *Childhood leukaemia*

Lowengart *et al.* (1987) identified 216 children aged 10 years or less from the Los Angeles County (United States) Cancer Surveillance Program in whom acute leukaemia had been diagnosed in 1980–84. Permission for contact with families was obtained for 202 patients; 159 mothers were interviewed, and information about the fathers was obtained for 154 cases. The mothers of the patients were asked to name a control child from among their child's friends. A total of 136 control mothers were interviewed; information about the fathers was obtained for 130 controls. Data on occupational exposure were obtained by telephone interview. The odds ratios associated with father's exposure to trichloroethylene were 2.0 ( $p = 0.16$ ) for exposure one year before pregnancy, 2.0 ( $p = 0.16$ ) for exposure during pregnancy and 2.7 ( $p = 0.07$ ; 95% CI, 0.64–16) for exposure after delivery. The results of this study were also reported in an abstract (Peters *et al.*, 1984).

#### 2.4.8 *Childhood brain tumours*

Peters *et al.* (1981) studied the occupations of the parents of 92 children under the age of 10 with brain tumours and of 92 matched controls in Los Angeles County, United States. Interviews with the fathers showed that those of 12 children with brain tumours and those of two controls had worked in the aircraft industry; the fathers of only two children with brain tumours reported exposure to trichloroethylene. The results of this study were also reported in an abstract (Peters *et al.*, 1984).

#### 2.4.9 Multiple sites

Siemiatycki (1991) studied men aged 35–70 in Montréal, Canada, during 1979–85. A total of 3730 people with cancers at 21 sites and 533 population controls were interviewed about their occupations in detail, and their exposure to 293 agents or mixtures was then estimated by a group of chemists. The estimated prevalence of exposure to trichloroethylene was 2%. Both case–case and case–control comparisons were conducted. After control for confounding, increased odds ratios were found in the case–case comparison for cancer of the rectum (1.9 [95% CI, 0.9–3.9] and for skin melanoma (2.6 [1.2–5.8]) in relation to presumed exposure to trichloroethylene; for ‘substantial’ exposure (at least five years of exposure at a presumably medium or high concentration and frequency), elevated odds ratios were reported for prostatic cancer (1.8 [0.7–4.7]) and for skin melanoma (2.3 [0.8–7.0]), while the risk for rectal cancer was no longer elevated (0.8 [0.2–2.8]). The increased risk for skin melanoma was restricted to French Canadians; in the latter group, the risk for lung adenocarcinoma was also elevated (odds ratio for any exposure, 2.6 [0.8–8.4]; odds ratio for substantial exposure, 4.5 [1.1–18]). The risk was not increased for cancers of the bladder (0.6 [0.3–1.4]) or kidney (0.8 [0.3–2.1]) or for non-Hodgkin’s lymphoma (1.1 [0.5–2.4]).

#### 2.5 Studies of drinking-water

Cancer occurrence in populations exposed to drinking-water contaminated with various concentrations of trichloroethylene has been compared in a number of studies. The interpretation of some of these studies is complicated by several methodological problems:

(i) information on the concentration of trichloroethylene in water was obtained subsequently to or contemporaneously with the period over which cancer occurrence was measured, although cancer rates should be correlated with exposure before occurrence of the disease;

(ii) exposure was generally measured at the community level and does not necessarily reflect the exposure of individuals;

(iii) the problem of migration in and out of the populations under study was not addressed; and

(iv) the possible confounding effects of other characteristics of the populations being compared (socioeconomic, industrial and cultural factors) were not taken into account.

Isacson *et al.* (1985) tabulated the average annual age-adjusted incidence rates of cancers of the bladder, breast, colon, lung, prostate or rectum per 100 000 population in towns in Iowa, United States, in 1969–81 by the level of detectable volatile organic compounds in finished groundwater supplies. The levels of trichloroethylene were < 0.15 µg/L in one group of areas and ≥ 0.15 µg/L in another. There were virtually no differences in the incidences between these two groups.

Lagakos *et al.* (1986) studied childhood leukaemia in a community in Massachusetts, United States, where water from two wells was contaminated with trichloroethylene. Measurements made in 1979 showed a concentration of 267 ppb [µg/L] trichloroethylene in the well water. Twenty cases of childhood leukaemia were diagnosed in the community in 1964–83, and these were associated with a significantly higher estimated cumulative exposure to water from

the two contaminated wells than a random sample of children from the community (observed cumulative exposure, 21.1; expected cumulative exposure, 10.6;  $p = 0.03$ ).

A study conducted in New Jersey, United States, during 1979–87 included 75 towns (Cohn *et al.*, 1994), of which 27 were included in a study reported by Fagliano *et al.* (1990). Trichloroethylene concentrations were measured during 1984–85, and an average level was assigned to each town. The highest level assigned was 67  $\mu\text{g/L}$ . The water supply of six towns contained  $> 5 \mu\text{g/L}$  trichloroethylene (average, 23.4  $\mu\text{g/L}$ ). Women in these towns had a significantly higher total incidence of leukaemia than the inhabitants of towns where the concentration of trichloroethylene in drinking-water was  $< 0.1 \mu\text{g/L}$  (relative risk, 1.4; 95% CI, 1.1–1.9); no such effect was seen for men (1.1, 0.84–1.4). The risk among women was particularly elevated for acute lymphocytic leukaemia, chronic lymphocytic leukaemia and chronic myelogenous leukaemia. The risk for acute lymphocytic leukaemia in childhood was also significantly increased, in girls but not in boys. Increased risks for non-Hodgkin's lymphoma were apparent in towns in the highest category of trichloroethylene contamination (0.2; 0.94–1.5 for men and 1.4; 1.1–1.7 for women) and was particularly elevated for high-grade lymphomas.

Studies were conducted in two counties in Arizona, United States, to address the possible association between consumption of drinking-water from trichloroethylene-contaminated wells and childhood leukaemia (Maricopa County, Flood *et al.*, 1990) or all childhood neoplasms and testicular cancer (Pima County, Arizona Department of Health Services, 1990). In Maricopa County, two wells that were occasionally used to supplement the water supply were found to contain 8.9 and 29.0 ppb [ $\mu\text{g/L}$ ] trichloroethylene in 1982; they were then taken out of service. The concentrations of trichloroethylene in contaminated wells in Pima County were 1–239  $\mu\text{g/L}$ , with levels as high as 4600  $\mu\text{g/L}$  in wells at an Air Force facility in the area. No association was found between cancer at any of the sites examined and residence in the counties with contaminated wells, as opposed to residence in other areas of the county. The incidence rates in both Maricopa and Pima counties were comparable to those in other areas included in the United States SEER programme.

Vartiainen *et al.* (1993) collected 24-h urine samples from 95 and 21 inhabitants of two Finnish villages where the groundwater was contaminated with trichloroethylene ( $\leq 212 \mu\text{g/L}$ ) and tetrachloroethylene ( $\leq 180 \mu\text{g/L}$ ). The average excretion of trichloroethylene by inhabitants of the two villages was 0.55 and 0.45  $\mu\text{g/day}$ , and that of two control groups was 0.36 and 0.32  $\mu\text{g/day}$ ; the corresponding figures for excretion of dichloroacetic acid were 0.78 and 1.3  $\mu\text{g/day}$  versus 1.3 and 1.3  $\mu\text{g/day}$ , and those for the excretion of trichloroacetic acid were 19 and 7.9  $\mu\text{g/day}$  versus 2.0 and 4.0  $\mu\text{g/day}$ . With the possible exception of non-Hodgkin's lymphoma, which occurred in a marginal excess in one of the villages (SIR, 1.4; 95% CI, 1.0–2.0; 31 cases) but not in the other (0.6; 0.3–1.1; 14 cases), neither overall cancer incidence nor the incidence of liver cancer or lymphohaematopoietic cancers was increased in the two villages.

### 3. Studies of Cancer in Experimental Animals

#### 3.1 Oral administration

##### 3.1.1 Mouse

Groups of 50 male and 50 female B6C3F1 mice, five weeks of age, were administered trichloroethylene (purity, > 99%; containing 0.19% epoxybutane and 0.09% epichlorohydrin [see IARC, 1987c] as stabilizers) in corn oil by gavage on five days a week for 78 weeks. The time-weighted average doses of trichloroethylene were 1169 and 2339 mg/kg bw per day for males and 869 and 1739 mg/kg bw per day for females. All surviving animals were killed 90 weeks after the start of treatment and submitted to complete necropsy and histopathological evaluation. Groups of 20 male and 20 female vehicle controls were included. The numbers of survivors at the end of the study were 8/20 male vehicle controls, 36/50 males at the low dose and 22/48 males at the high dose; and 20/20 female vehicle controls, 42/50 females at the low dose and 39/47 females at the high dose. The survival-adjusted (Cox and Tarone test) incidences of hepatocellular carcinomas were increased in animals of each sex in relation to dose; males: 1/20 in vehicle controls, 26/50 ( $p = 0.004$ ) at the low dose, 31/48 ( $p < 0.001$ ) at the high dose; females: 0/20 in vehicle controls, 4/50 at the low dose, 11/47 ( $p = 0.008$ ) at the high dose. One male at the high dose developed a forestomach papilloma (United States National Cancer Institute, 1976).

In a subsequent study, groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, were administered 1000 mg/kg bw trichloroethylene (purity, > 99.9%; containing no epichlorohydrin) in corn oil by gavage on five days a week for up to 103 weeks. Groups of 50 mice of each sex served as vehicle controls. Survival of treated males was significantly reduced ( $p = 0.004$ ) in comparison with controls; at the end of the experiment, 33 control and 16 treated males and 32 control and 23 treated females were still alive. Histopathological evaluation revealed increased incidences (incidental tumour test) of hepatocellular tumours in treated animals. In males, hepatocellular adenomas occurred in 7/48 controls and 14/50 ( $p = 0.048$ ) treated animals; hepatocellular carcinomas were found in 8/48 controls and 31/50 ( $p < 0.001$ ) treated animals; and the combined numbers of animals bearing hepatocellular adenomas and/or carcinomas were 14/48 controls and 39/50 ( $p < 0.001$ ) treated animals. In females, hepatocellular adenomas were seen in 4/48 control and 16/49 ( $p = 0.001$ ) treated animals; hepatocellular carcinomas occurred in 2/48 control and 13/49 ( $p = 0.002$ ) treated animals; and the combined numbers of animals bearing hepatocellular adenomas and/or carcinomas were 6/48 controls and 22/49 ( $p < 0.001$ ) treated animals. There was no significant treatment-related increase in the incidence of tumours at other sites. Toxic nephrosis (cytomegaly) was seen in 90% of treated males and in 98% of treated females (United States National Toxicology Program, 1990).

Two groups of 30 male and 30 female ICR:Ha Swiss mice, six to eight weeks of age, were each administered 0 or 0.5 mg trichloroethylene [purity unspecified] by gavage in 0.1 ml trioctanoin once a week for at least 74 weeks. Only sections of lung, liver and stomach were taken for histopathological examination. The incidence of forestomach tumours was reported not to be increased; findings were not given for other sites (Van Duuren *et al.*, 1979). [The Working Group noted the low dose used and the inadequate conduct and reporting of the study.]

### 3.1.2 Rat

Groups of 50 male and 50 female Osborne-Mendel rats, six weeks of age, were administered trichloroethylene (purity, > 99%; containing 0.19% epoxybutane and 0.09% epichlorohydrin as stabilizers) in corn oil by gavage on five days a week for 78 weeks. The time-weighted average doses of trichloroethylene were 549 (low dose) and 1097 mg/kg bw per day (high dose) for animals of each sex. All surviving animals were killed 110 weeks after the start of treatment and were submitted to complete necropsy. Groups of 20 male and 20 female vehicle controls were included. Large proportions of treated and control rats died during the experiment; the numbers of animals alive at the end of the study were 3/20 male vehicle controls, 8/50 males at the low dose and 3/50 males at the high dose; of the females, there were 8/20 vehicle controls, 13/48 at the low dose and 13/50 at the high dose. There was no significant difference in tumour incidence at any site between treated and control rats (United States National Cancer Institute, 1976). [The Working Group noted the high rates of early mortality in both control and treated rats and the limited duration of treatment.]

In a subsequent study, groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were administered 0, 500 or 1000 mg/kg bw trichloroethylene (purity, > 99.9%; containing no epichlorohydrin) in corn oil by gavage on five days a week for up to 103 weeks. A group of 50 male and 50 female rats were used as untreated controls. Survival of low-dose and high-dose males was significantly reduced ( $p < 0.005$ ) in comparison with vehicle controls; the numbers of survivors at the end of the experiment were 35 male vehicle controls, 20 at the low dose and 16 at the high dose; and 37 female vehicle controls, 33 at the low dose and 26 at the high dose. An increased incidence of renal tubular-cell adenocarcinomas was seen in males: 0/49 untreated controls, 0/48 vehicle controls, 0/49 at the low dose and 3/49 at the high dose ( $p = 0.028$ ; incidental tumour test). Two males at the low dose had renal tubular-cell adenomas. The incidence of tumours in female rats was not increased at any site. Toxic nephrosis of the kidney occurred in 96/98 treated males and in all of the treated females but not in vehicle control rats of either sex (United States National Toxicology Program, 1990). [The Working Group noted the uncommon occurrence of renal tubular-cell tumours in untreated Fischer 344/N rats.]

Groups of 50 males and 50 females of four strains (ACI, August, Marshall and Osborne-Mendel), 6.5–8 weeks of age, were administered 0, 500 or 1000 mg/kg bw trichloroethylene (purity, > 99.9%) in corn oil by gavage on five days a week for 103 weeks. Additional groups of 50 rats of each sex and strain served as untreated controls. Survival was reduced significantly in low-dose and high-dose males and high-dose females of the ACI strain, in both treated groups of males and females of the Marshall strain, and in high-dose female Osborne-Mendel rats. The numbers of survivors at the end of the study were: ACI males – 36 untreated controls, 37 vehicle controls, 19 at the low dose, 11 at the high dose; ACI females – 36 untreated controls, 33 vehicle controls, 20 at the low dose, 17 at the high dose; August males – 24 untreated controls, 21 vehicle controls, 13 at the low dose, 15 at the high dose; August females – 26 untreated controls, 23 vehicle controls, 26 at the low dose, 24 at the high dose; Marshall males – 32 untreated controls, 26 vehicle controls, 12 at the low dose, 6 at the high dose; Marshall females – 31 untreated controls, 30 vehicle controls, 12 at the low dose, 10 at the high dose; Osborne-Mendel males – 18 untreated controls, 22 vehicle controls, 17 at the low dose, 14 at the high dose; Osborne-Mendel females – 19 untreated controls, 18 vehicle controls, 10 at the low dose, 7 at the

high dose. Many early deaths occurred accidentally. The incidence of renal cytomegaly was > 80% in all treated males and females, and toxic nephropathy (described as dilated tubules lined by elongated and flattened epithelial cells) occurred at rates of 17–80% in the treated groups; however, there was no difference in kidney toxicity between males and females of any strain. Neither of these two renal lesions was seen in untreated or vehicle controls. The incidences of renal tubular-cell hyperplasia and tubular-cell adenoma were increased in male Osborne-Mendel rats at the low dose: hyperplasia – 0/50 untreated controls, 0/50 vehicle controls, 5/50 at the low dose, 3/50 at the high dose; adenoma – 0/50 untreated controls, 0/50 vehicle controls, 6/50 ( $p = 0.007$ ; survival-adjusted incidental tumour test) at the low dose, 1/50 at the high dose. One renal tubular-cell adenocarcinoma occurred in a male at the high dose. The incidences of interstitial-cell tumours of the testis were increased in Marshall rats exposed to trichloroethylene: 16/46 untreated controls, 17/46 vehicle controls, 21/48 ( $p < 0.001$ ; survival-adjusted incidental tumour test) at the low dose, 32/48 ( $p < 0.001$ ) at the high dose. No significant increase in tumour incidence was reported for ACI or August rats (United States National Toxicology Program, 1988). [The Working Group noted the poor survival among all strains and the fact that five of the six renal adenomas in male Osborne-Mendel rats at the low dose occurred among the 17 rats alive at the end of the study.]

Groups of 30 male and 30 female Sprague-Dawley rats, 12–13 weeks of age, were administered 0, 50 or 250 mg/kg bw trichloroethylene (purity, 99.9%; containing no epoxide) in olive oil by gavage on four to five days per week for 52 weeks and observed for life. Data on survival were not provided, but the authors reported a nonsignificant increase in mortality among treated females. Renal tubular-cell cytomegaly was observed only in male rats at the high dose (46.7% [14/30];  $p < 0.01$ ). A nonsignificant increase in the incidence of leukaemias was observed in males: none in controls, 6.7% [2/30] at the low dose and 10.0% [3/30] at the high dose (Maltoni *et al.*, 1986). [The Working Group noted the short period of exposure.]

## 3.2 Inhalation

### 3.2.1 Mouse

Groups of 30 male and 30 female NMRI mice [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at a concentration of 0, 100 or 500 ppm (0, 540 or 2700 mg/m<sup>3</sup>) for 6 h per day on five days per week for 18 months. The experiment was terminated after 30 months. At the end of exposure (75 weeks), there was no difference in the probability of survival among the females; in males, the probability of survival was reduced from 83% in controls to 63% in low-dose and 56% in high-dose groups. Histopathological examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours indicated increased age-adjusted incidences of lymphomas in treated female mice: 9/29 controls, 17/30 at the low dose ( $p < 0.001$ ) and 18/28 ( $p = 0.01$ ) at the high dose (Henschler *et al.*, 1980).

Groups of 49–50 female ICR mice, seven weeks of age, were exposed to air containing trichloroethylene (purity, 99.8%; containing 0.13% carbon tetrachloride and > 0.02% benzene and epichlorohydrin) at concentrations of 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m<sup>3</sup>) for 7 h per day on five days per week for up to 104 weeks. There were no significant differences in

survival between the control and exposed groups. Complete necropsy was carried out on all animals. Histopathological evaluation revealed a significant increase (Fisher's exact test) in the incidence of lung adenocarcinomas: 1/49 controls, 3/50 at the low dose, 8/50 ( $p < 0.05$ ) at the middle dose and 7/46 ( $p < 0.05$ ) at the high dose. [The Working Group found a significant dose-response trend:  $p = 0.034$ , Cochran-Mantel-Haenszel test.] The incidences of adenomas and adenocarcinomas of the lung combined in the groups at the middle (13/50) and high doses (11/46) were not significantly increased in comparison with controls (6/49). The average number of lung tumours was, however, increased in mice at the middle and high doses in comparison with controls: 0.12 in controls, 0.10 at the low dose, 0.46 at the middle dose and 0.39 at the high dose (Fukuda *et al.*, 1983).

Groups of 90 male and 90 female Swiss mice, 11 weeks of age, and groups of 90 male and 90 female B6C3F1 mice, 12 weeks of age, were exposed to air containing trichloroethylene (purity, 99.9%; containing no epoxide) at concentrations of 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m<sup>3</sup>) for 7 h per day on five days a week for 78 weeks and were then observed for life. Data on survival were not provided, but the authors reported that mortality was higher ( $p < 0.05$ ) in treated male B6C3F1 mice than in controls. Dose-related increases in the incidences of lung and liver tumours were observed in male Swiss mice [Fisher's exact test or Cochran-Armitage linear trend test]. The percentages of male Swiss mice bearing a malignant pulmonary tumour were: control, 11.1% [10/90]; low-dose, 12.2% [11/90]; mid-dose, 25.5% [23/90] ( $p < 0.05$ ); and high-dose, 30.0% [27/90] ( $p < 0.01$ ); the percentages of male mice bearing a hepatoma were: control, 4.4% [4/90]; low-dose, 2.2% [2/90]; mid-dose, 8.9% [8/90]; and high-dose, 14.4% [13/90] ( $p < 0.05$ ). In B6C3F1 mice, a dose-related increase in the incidence of lung tumours was observed in females: control, 4.4% [4/90]; low-dose, 6.7% [6/90]; mid-dose, 7.8% [7/90]; and high-dose, 16.7% [15/90] ( $p < 0.05$ ) (Maltoni *et al.*, 1986, 1988).

### 3.2.2 Rat

Groups of 30 male and 30 female Wistar rats [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at concentrations of 0, 100 or 500 ppm (0, 540 or 2700 mg/m<sup>3</sup>) for 6 h per day on five days per week for 18 months. The experiment was terminated after 36 months. No differences in survival were reported; the probability of survival in each group at the end of the experiment was: 46.7% of male controls, 23.3% of males at the low dose, 36.7% of males at the high dose, 16.7% of female controls, 13.3% of females at the low dose and 16.7% of females at the high dose. Histopathological and gross examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours revealed no increase in tumour incidence (Henschler *et al.*, 1980).

Groups of 49–51 female Sprague-Dawley rats, seven weeks of age, were exposed to air containing trichloroethylene (purity, 99.8%) at concentrations of 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m<sup>3</sup>) for 7 h per day on five days per week for 104 weeks. Survival was significantly higher in the exposed groups than in controls: about 75% of the rats in the three treated groups and 50% of controls were alive at 100 weeks. Gross and histopathological examination revealed no difference in the incidence of tumours between the control and exposed groups (Fukuda *et al.*, 1983).

Groups of 130–145 male and female Sprague-Dawley rats, 12 weeks of age, were exposed to air containing trichloroethylene (purity, 99.9%; containing no epoxide) at a concentration of 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m<sup>3</sup>) for 7 h per day on five days per week for 104 weeks. All animals were observed for their lifetime. Data on survival were not provided, but the authors reported no excess mortality in any of the exposed groups. A significant, dose-related increase in the incidence of Leydig cell (interstitial) tumours of the testis was observed [ $p < 0.001$ ; Cochran-Mantel-Haenszel test]; the percentages of male rats bearing these tumours were 4.4% [6/135] of controls, 12.3% [16/130] at the low dose [ $p < 0.05$ ; Fisher's exact test], 23.1% [30/130] at the middle dose [ $p < 0.01$ ; Fisher's exact test] and 23.8% [31/130] at the high dose [ $p < 0.01$ ; Fisher's exact test]. Four renal tubular adenocarcinomas (3.1%) were observed in the high-dose male rats; no such tumours were observed in the lower dose groups, in controls or in the historical control database for Sprague-Dawley rats at the study laboratory. Cytokaryomegaly of renal tubular cells was also observed: in none of the control or low-dose rats, in 16.9% at the middle dose and in 77.7% at the high dose (Maltoni *et al.*, 1986, 1988).

### 3.2.3 Hamster

Groups of 30 male and 30 female Syrian hamsters [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at concentrations of 0, 100 or 500 ppm (0, 540 or 2700 mg/m<sup>3</sup>) for 6 h per day on five days per week for 18 months. The experiment was terminated after 30 months. The probability of survival was similar in exposed and control groups. Histopathological examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours revealed no significant increase in tumour incidence (Henschler *et al.*, 1980).

## 3.3 Topical application

*Mouse:* In a study of two-stage carcinogenesis on mouse skin, single doses of 1.0 mg trichloroethylene [purity unspecified] in 0.1 ml of acetone were applied to the shaven dorsal skin of 30 female ICR:Ha Swiss mice aged six to eight weeks; 14 days later, topical applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 2.5 µg in 0.1 ml of acetone, three times per week) were begun, for at least 49 weeks. Nine skin papillomas were found in 4/30 treated mice, and 10 papillomas were found in 9/120 TPA-treated controls. Trichloroethylene was also administered by repeated topical application (three times per week) to groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, for 83 weeks at a dose of 1.0 mg per mouse. No tumours were observed at the site of application (Van Duuren *et al.*, 1979).

## 3.4 Subcutaneous injection

*Mouse:* Groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, were given subcutaneous injections of 0.5 mg trichloroethylene [purity unspecified] in 0.05 ml trioctanoin once a week for at least 74 weeks, or received the vehicle alone. No tumours were observed at the injection site in either group (Van Duuren *et al.*, 1979).

### 3.5 Administration with known carcinogens

*Mouse:* Five groups of 50 male and 50 female ICR:Ha Swiss mice, five weeks of age, were administered either industrial-grade trichloroethylene (purity, 99.4%; containing 0.11% epichlorohydrin and 0.20% 1,2-epoxybutane) in corn oil by gavage, purified trichloroethylene (purity, > 99.9%) in corn oil by gavage, purified trichloroethylene with added epichlorohydrin (0.8%), purified trichloroethylene with added 1,2-epoxybutane (0.8 %) or purified trichloroethylene with 0.25% epichlorohydrin plus 0.25% 1,2-epoxybutane, on five days per week for 18 months. The doses of trichloroethylene that were administered were 2.4 g/kg bw for males and 1.8 g/kg bw for females. Groups of 50 mice of each sex given corn oil served as vehicle controls. The treatment period was followed by a six-month observation period. The probabilities of survival were significantly reduced ( $p < 0.001$ ) in all groups of treated males in comparison with controls; in females, the probabilities of survival were reduced ( $p < 0.05$ ) in the group receiving purified trichloroethylene and in that receiving purified trichloroethylene plus epichlorohydrin ( $p < 0.001$ ). At the end of the study, there were no more than two survivors in any treatment group. Complete necropsies were performed on all animals. The incidence of squamous-cell carcinomas of the forestomach was increased in several of the treatment groups over that in controls (0/50 for males and females); males: purified trichloroethylene, 0/50; industrial-grade trichloroethylene, 0/49; purified trichloroethylene plus epichlorohydrin, 5/49 ( $p < 0.001$ ); purified trichloroethylene plus 1,2-epoxybutane, 3/49 ( $p = 0.029$ ); and purified trichloroethylene plus epichlorohydrin and 1,2-epoxybutane, 2/49 ( $p = 0.036$ ); females: controls, 0/50; purified trichloroethylene, 0/50; industrial-grade trichloroethylene, 3/50; purified trichloroethylene plus epichlorohydrin, 9/50 ( $p < 0.001$ ); purified trichloroethylene plus 1,2-epoxybutane, 1/48; and purified trichloroethylene plus epichlorohydrin and 1,2-epoxybutane, 9/50 ( $p < 0.001$ ). No significant increase in the incidences of tumours at other sites was reported. The authors attributed the increased incidence of forestomach cancers to the direct alkylating effects of epichlorohydrin and 1,2-epoxybutane (Henschler *et al.*, 1984). [The Working Group noted that the incidences of hepatocellular tumours (adenomas and carcinomas combined) in male mice were: controls, 3/50; purified trichloroethylene, 6/50; and industrial-grade trichloroethylene, 9/50; and that no survival-adjusted analysis of tumour incidence was performed.]

Groups of 23–33 male B6C3F1 mice, 15 days of age, were given a single intraperitoneal injection of *N*-ethylnitrosourea in 0.1 mol/L sodium acetate at doses of 0, 2.5 or 10 mg/kg bw. When the mice were four weeks of age, a 61-week treatment period was begun with 0, 3 or 40 mg/L trichloroethylene (purity, > 99%) in the drinking-water. The highest concentration of trichloroethylene was equivalent to a daily dose of 6 mg/kg bw. The incidences of hepatocellular adenomas and carcinomas were not increased in mice that received trichloroethylene alone in comparison with vehicle controls, and trichloroethylene did not promote liver tumours in mice initiated with *N*-ethylnitrosourea (Herren-Freund *et al.*, 1987). [The Working Group noted the low dose of trichloroethylene used.]

### 3.6 Carcinogenicity of metabolites

Studies of the carcinogenicity of the known metabolites of trichloroethylene, dichloroacetic acid, trichloroacetic acid and chloral hydrate, are summarized in separate monographs in this volume.

#### 3.6.1 Mouse

A single dose of 1.0 mg of trichloroethylene oxide, a putative metabolite [purity unspecified], in 0.1 ml of acetone was applied to the dorsal skin of 30 female ICR:Ha Swiss mice, six to eight weeks of age; 14 days later, topical applications of TPA (2.5  $\mu\text{g}$  in 0.1 ml of acetone, three times per week) were begun and continued for more than 61 weeks. The incidence of tumours at the site of application was not increased in the group treated with trichloroethylene plus TPA (three mice each had a single papilloma) in comparison with mice receiving TPA alone (10 papillomas in 9/120 mice) (Van Duuren *et al.*, 1979).

Trichloroethylene oxide was administered to a group of 30 female ICR:Ha Swiss mice, six to eight weeks of age, by repeated skin application for 82 weeks (2.5 mg/mouse in 0.1 ml acetone three times weekly); 30 mice served as vehicle controls. No tumour was observed at the site of application in either group. Further groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, were given 0 or 500  $\mu\text{g}$ /mouse trichloroethylene oxide in 0.05 ml tricapylin once a week for up to 80 weeks. One fibrosarcoma occurred at the injection site in treated animals (Van Duuren *et al.*, 1983).

1,2-Dichlorovinyl cysteine, a minor metabolite [purity unspecified], was administered at a concentration of 0, 10 or 50 mg/L in drinking-water to three groups of 30 Swiss-Webster mice [age and sex unspecified] for 14 weeks, beginning one day after administration of *N*-nitrosodimethylamine (NDMA) (six intraperitoneal injections of 5.0 mg/kg bw administered every other day). The average daily doses of 1,2-dichlorovinyl cysteine were 2.4 and 12.6 mg/kg bw, respectively. Renal tumours occurred after 50 weeks in 2/16 mice receiving NDMA alone, 2/15 receiving NDMA plus the low dose of 1,2-dichlorovinyl cysteine and 3/16 receiving NDMA plus the high dose of 1,2-dichlorovinyl cysteine [not significant]. Multiple renal tumours were found in 7/40 mice treated with NDMA plus 1,2-dichlorovinyl cysteine, whereas none were found in 21 mice treated with NDMA alone [ $p = 0.043$ ; Fisher's exact test] (Meadows *et al.*, 1988).

## 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

### 4.1 Absorption, distribution, metabolism and excretion

#### 4.1.1 Humans

The biotransformation and the kinetics of trichloroethylene have been described in many studies of workers and of volunteers. Pulmonary uptake of trichloroethylene is rapid, the rate of

uptake being dependent on the rate of respiration, and uptake increases about twofold with exercise (Monster *et al.*, 1976). Distribution to the tissues has not been described, but the concentrations of trichloroethylene should be proportional to the duration and concentration of exposure, and the distribution is probably similar to that in animals. The blood:air partition coefficient for trichloroethylene in human volunteers was about 15 (Monster *et al.*, 1979), and the fat:air partition coefficient was about 700 (Sherwood, 1976; Steward *et al.*, 1973); there is therefore a tendency for deposition in fat from blood, the fat:blood partition coefficient being about 50 (700/15).

After inhalation, 40–70% of an administered dose of trichloroethylene is metabolized, the unmetabolized fraction being cleared by exhalation. Metabolism was proportional to the concentration of trichloroethylene in air up to 315 mg/m<sup>3</sup> for 3 h (Ikeda & Imamura, 1973; Monster *et al.*, 1976; Ikeda, 1977; Nomiyama & Nomiyama, 1977). No saturation of biotransformation has been detected with concentrations up to 380 ppm [1976 mg/m<sup>3</sup>].

Trichloroethanol, its glucuronide and trichloroacetic acid are major metabolites in urine, and chloral hydrate is a transient metabolite in blood (Cole *et al.*, 1975). After controlled exposure of males to 200 ppm (1040 mg/m<sup>3</sup>) trichloroethylene for 6 h, oxalic acid and *N*-(hydroxyacetyl)aminoethanol were detected as minor metabolites (Dekant *et al.*, 1984). Traces of *N*-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-*L*-cysteine were present in the urine of workers exposed to unknown concentrations of trichloroethylene in air (Birner *et al.*, 1993). Trichloroethanol and its glucuronide are rapidly eliminated in urine, with half-lives of about 10 h, and trichloroacetic acid is eliminated slowly, with a half-life of about 52 h (range, 35–70 h) (Müller *et al.*, 1972, 1974). Repeated exposure of volunteers to 50 ppm (260 mg/m<sup>3</sup>) trichloroethylene for 4 h per day on five consecutive days resulted in slightly higher concentrations of trichloroethylene and trichloroethanol in blood than after a single exposure to 40 ppm (208 mg/m<sup>3</sup>) for 4 h (Ertle *et al.*, 1972). Urinary excretion of trichloroethanol by five male volunteers exposed to 70 ppm [364 mg/m<sup>3</sup>] for 4 h per day for five days stabilized rapidly and remained constant until the end of the exposure, whereas urinary excretion of trichloroacetic acid continued to rise (Monster *et al.*, 1979).

#### 4.1.2 Experimental systems

The biotransformation of trichloroethylene has been reviewed (Bonse & Henschler, 1976; Kimbrough *et al.*, 1985; Dekant, 1986; Bruckner *et al.*, 1989; Davidson & Beliles, 1991).

The absorption, distribution, metabolism and excretion of trichloroethylene at doses outside the range of those tested experimentally have been predicted from a number of physiologically based pharmacokinetic models constructed from the existing experimental data (Dallas *et al.*, 1991; Fisher *et al.*, 1991; Allen & Fischer, 1993).

The absorption and excretion of trichloroethylene have been studied in rats and mice. The compound is rapidly absorbed from the gastrointestinal tract and through the lungs; skin absorption after exposure to the vapour is negligible. In male Sprague-Dawley rats exposed to 50 ppm [260 mg/m<sup>3</sup>] or 500 ppm [2600 mg/m<sup>3</sup>] trichloroethylene for 2 h through a miniaturized one-way breathing valve (Dallas *et al.*, 1991), the uptake decreased from > 95% at the beginning of exposure to a relatively constant, almost steady-state level of 70%. The concentrations of trichloroethylene in exhaled breath towards the end of the exposure period were 34.6 ± 1.1 ppm

[ $185 \pm 6 \text{ mg/m}^3$ ] after exposure to 50 ppm and  $340.8 \pm 10.6 \text{ ppm}$  [ $1830 \pm 60 \text{ mg/m}^3$ ] after exposure to 500 ppm. This direct proportionality was not reflected in the arterial blood concentrations, where the 10-fold increase in dose resulted in a 25- to 30-fold increase in blood levels and only an 8.7-fold increase in total absorbed dose.

The blood:air partition coefficient is about 14 in mice (Fisher *et al.*, 1991) and about 18 in rats (Andersen *et al.*, 1987; Fisher *et al.*, 1989). The corresponding fat:blood values are about 36 and 27, and the liver:blood partition coefficients are about 1.8 and 1.3. At the end of 4-h exposures of Fischer 344 rats to 529 ppm [ $2751 \text{ mg/m}^3$ ] (males) and 600 ppm [ $3120 \text{ mg/m}^3$ ] (females), the concentrations of trichloroethylene in blood were about  $35.5 \text{ }\mu\text{g/ml}$  (males) and  $25.8 \text{ }\mu\text{g/ml}$  (females). The concentrations of trichloroethylene in the blood of B6C3F1 mice were much lower: the highest mean blood concentrations seen during exposure of males to 110–748 ppm [ $572\text{--}3890 \text{ mg/m}^3$ ] and females to 42–889 ppm [ $218\text{--}4623 \text{ mg/m}^3$ ] were  $7.3 \text{ }\mu\text{g/ml}$  after exposure to 748 ppm [ $3890 \text{ mg/m}^3$ ] (males) and  $6.3 \text{ }\mu\text{g/ml}$  after exposure to 368 ppm [ $1914 \text{ mg/m}^3$ ] (females) (Fisher *et al.*, 1991).

The distribution of trichloroethylene in mice after a 10-min inhalation (approximate dose,  $280 \text{ mg/kg bw}$ ) was studied by whole-body autoradiography of animals killed at intervals over 8 h. Trichloroethylene was distributed throughout the body into well-perfused organs; after 30 min, redistribution to adipose tissues had occurred (Bergman, 1983a).

The urinary excretion of trichloroacetic acid by rats exposed to 55 ppm [ $286 \text{ mg/m}^3$ ] trichloroethylene for 8 h per day for 14 weeks reached a maximum after two days and remained constant until the end of the exposure, whereas urinary excretion of trichloroethanol increased steadily over the first 10 weeks of the study (Kimmerle & Eben, 1973).

Mice have consistently higher rates of biotransformation than rats (Fisher *et al.*, 1991). The metabolism of trichloroethylene in rats can be described by Michaelis-Menten kinetics and is saturated after exposure by inhalation to more than 500–600 ppm ( $2600\text{--}3120 \text{ mg/m}^3$ ). Saturation of metabolism in rats at 500 ppm was also seen in the experiments of Dallas *et al.* (1991), described above. The atmospheric concentration at which elimination shifts from first-order to zero-order kinetics was found to be 65 ppm [ $338 \text{ mg/m}^3$ ] in rats in a closed exposure system (Filser & Bolt, 1979). Metabolic saturation occurs after oral administration of  $> 200\text{--}500 \text{ mg/kg bw}$  trichloroethylene to rats; in mice, the rate of biotransformation is linear up to a dose of 2000 ppm ( $10\,400 \text{ mg/m}^3$ ) by inhalation and up to  $2000 \text{ mg/kg bw}$  by oral administration (Stott *et al.*, 1982; Buben & O'Flaherty, 1985; Green & Prout, 1985; Prout *et al.*, 1985).

Mice have been shown to biotransform 2.6 times more trichloroethylene on a body weight basis than rats after exposure by inhalation to 600 ppm ( $3120 \text{ mg/m}^3$ ) (Dekant *et al.*, 1986a). Trichloroacetic acid concentrations in blood reached significantly higher values in B6C3F1 mice than in Fischer 344 rats at the end of a 4-h exposure by inhalation. The peak concentrations were  $23.3 \text{ }\mu\text{g/ml}$  in male rats and  $39.6 \text{ }\mu\text{g/ml}$  in female rats exposed to 505 ppm [ $2626 \text{ mg/m}^3$ ] and 600 ppm [ $3120 \text{ mg/m}^3$ ], respectively, while the values for mice were  $129.6 \text{ }\mu\text{g/ml}$  in males exposed to 748 ppm [ $3890 \text{ mg/m}^3$ ] and  $94.3 \text{ }\mu\text{g/ml}$  in females exposed to 889 ppm [ $4623 \text{ mg/m}^3$ ] (Fisher *et al.*, 1991). After exposure to low doses, the rate of metabolism in mice and rats is similar, and about 90% of an oral dose of 2 or  $10 \text{ mg/kg bw}$  trichloroethylene was eliminated as metabolites within 72 h by female Wistar and NMRI mice (Dekant *et al.*, 1986b). After an oral dose of 2000

mg/kg bw, 78% of the dose was exhaled as unchanged trichloroethylene by rats but only 14% by mice (Prout *et al.*, 1985).

As a result of the higher biotransformation rate in mice, their blood levels of trichloroethanol and trichloroacetic acid were four- and sixfold higher than those in rats, and peak concentrations were reached within 2 h in mice and up to 10 h in rats. In mice, the high levels of trichloroacetate in blood persisted for over 30 h (Prout *et al.*, 1985). After dosing by gavage with 1.5 mmol/kg bw (200 mg/kg bw) trichloroethylene, the peak blood concentrations of trichloroacetic acid and the area under the integrated time-concentration curve were higher in mice (216 nmol/ml [35 µg/ml] and 2.5 µmol-h/ml [408 µg-h/ml]) than in rats (81 nmol/ml [13 µg/ml] and 1.5 µmol-h/ml [245 µg-h/ml]) (Larson & Bull, 1992a). The highest concentration of trichloroacetic acid that was found in the blood of rats after oral administration of trichloroethylene in corn oil was equivalent to about 50 mg/kg bw of trichloroacetic acid (Elcombe, 1985). Blood concentrations of the chloroacetic acids resulting from their administration to mice and rats are described in the relevant monographs in this volume.

Several excretory metabolites have been identified in mice and rats (see Figure 1). Most of the metabolites in urine can be accounted for by cytochrome P450-catalysed oxidation reactions of trichloroethylene to chloral hydrate. Trichloroethanol and its glucuronide are formed by reduction of chloral hydrate; trichloroacetic acid is formed by oxidation of this intermediate (Butler, 1949; Daniel, 1963; Kimmerle & Eben, 1973). The glucuronide of trichloroacetic acid has been identified in the urine of non-human primates treated by intramuscular injection with trichloroethylene (Müller *et al.*, 1982). The mechanism of formation of dichloroacetic acid has been postulated as a rearrangement of 1,1,2-trichlorooxirane and subsequent hydrolysis (Hathway, 1980), but it may also be formed by biotransformation of chloral hydrate or trichloroacetic acid (Larson & Bull, 1992b). Oxalic acid may be formed as a urinary metabolite of trichloroethylene as an end-product of 1,1,2-trichlorooxirane, by enzymatic or non-enzymatic cleavage of the epoxide followed by spontaneous elimination of two equivalents of hydrochloric acid, reaction with water and oxidation (Dekant *et al.*, 1984). Oxalic acid may also be formed by oxidation of dichloroacetic acid (Larson & Bull, 1992a,b). The formation of *N*-(hydroxyacetyl)-aminoethanol is proposed to proceed by the reaction of trichloroethylene-derived oxidative intermediates with ethanol amine or with phosphatidylethanol amine and enzymic breakdown of the acylated lipids (Dekant *et al.*, 1984).

Traces of metabolites indicative of conjugation of trichloroethylene with glutathione are also excreted in urine after high oral doses of trichloroethylene. The presence of *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-L-cysteine indicates trichloroethylene conjugation with glutathione followed by catabolism and acetylation by the enzymes of the mercapturic acid pathway (Dekant *et al.*, 1986a; Commandeur & Vermeulen, 1990; Dekant *et al.*, 1990). Chloroacetic acid is another trace metabolite of trichloroethylene in rats (Green & Prout, 1985); it may be formed by hydrolysis of the intermediate electrophile, chlorothioketene, which is a cysteine conjugate  $\beta$ -lyase-catalysed cleavage product of *S*-(1,2-dichlorovinyl)-L-cysteine (Dekant *et al.*, 1986c, 1988). Monochloroacetate may be formed by reduction of dichloroacetic acid (Larson & Bull, 1992b).

Species and strain differences in the biotransformation of trichloroethylene have been reported. Higher peak blood levels of dichloroacetic acid were reported in B6C3F1 mice



(35 nmol/ml [4.5 µg/ml]) dosed with 1.5 mmol/kg bw (200 mg/kg bw) trichloroethylene orally than in rats (< 4 nmol/ml [< 0.5 µg/ml]) receiving 23 mmol/kg bw (3000 mg/kg bw) (Larson & Bull, 1992a). These differences are not, however, reflected in the urinary excretion of dichloroacetic acid (Green & Prout, 1985; Dekant *et al.*, 1986b): In both mice and rats, the blood levels of dichloroacetic acid are at least one order of magnitude lower than those of trichloroacetic acid (Larson & Bull, 1992a). Strain differences among mice in the metabolism of trichloroethylene to trichloroacetic acid are also apparent: In Swiss and B6C3F1 mice, trichloroacetic acid in urine accounts for 7–12% of an oral dose of trichloroethylene; in NMRI mice, trichloroacetic acid is only a trace metabolite of trichloroethylene (Dekant *et al.*, 1986b).

The elimination rates of the major trichloroethylene metabolites differ markedly. Trichloroethanol and chloral hydrate are cleared from the blood with a half-life of 1–2 h, whereas high concentrations of trichloroacetic acid are present for up to 30 h and are cleared only slowly (Kimmerle & Eben, 1973). The amounts of trichloroethylene that are cleared by exhalation depend on the administered dose.

No changes in metabolite profiles were observed after exposure of rats to 55 ppm (286 mg/m<sup>3</sup>) trichloroethylene by inhalation for 14 weeks (Kimmerle & Eben, 1973). Daily administration by gavage of 1000 mg/kg bw trichloroethylene to male B6C3F1 mice for 180 days did not induce the overall metabolism of trichloroethylene (Green & Prout, 1985).

Cytochrome P450 activity in mouse lung Clara cells was reduced following exposure to 100 ppm [537 mg/m<sup>3</sup>] trichloroethylene for 6 h; the activities of glutathione *S*-transferases were unaffected. Studies with isolated mouse lung Clara cells showed oxidative metabolism of trichloroethylene, leading to accumulation of chloral in the cells, which were presumably unable to metabolize chloral further to trichloroethanol, as occurs in the liver (Odum *et al.*, 1992).

The metabolism of trichloroethylene in liver microsomes from mice and rats has been studied by determining changes in trichloroethylene concentrations in the headspace of incubation vials containing liver subfractions. The apparent Michaelis-Menten constant ( $K_m$ ) and the maximal metabolic velocity ( $V_{max}$ ) in microsomal fractions were 4.2 µmol/L and 8.0 mmol/mg protein per 10 min, respectively, for substrate concentrations of 0.3–34 µmol/L (Kim *et al.*, 1994). Chloral hydrate was found consistently as an end-product of trichloroethylene biotransformation. The formation of chloral hydrate and the cofactor requirements suggest that a cytochrome P450 (probably 2E1) catalyses the formation of chloral hydrate from trichloroethylene (Byington & Leibman, 1965; Leibman & McAllister, 1967; Leibman, 1968; Costa *et al.*, 1980; Guengerich *et al.*, 1991). Other cytochrome P450 enzymes may also catalyse the oxidation of trichloroethylene but have a lower affinity (Nakajima *et al.*, 1990, 1992).

An epoxide (1,2,2-trichlorooxirane) was postulated as an intermediate during the oxidation of trichloroethylene to chloral hydrate (Bonse *et al.*, 1975; Greim *et al.*, 1975; Bonse & Henschler, 1976; Henschler, 1977; Henschler & Bonse, 1977; Hathway, 1980); however, later studies on the biotransformation of trichloroethylene and other chlorinated olefins and knowledge of the mechanisms of oxidation by cytochrome P450 enzymes suggest a stepwise oxidation of trichloroethylene to chloral hydrate, in which the epoxide is not an obligatory intermediate (Miller & Guengerich, 1982; Liebler & Guengerich, 1983; Miller & Guengerich, 1983). Mouse liver microsomes had a threefold higher capacity for the oxidative biotransformation of trichloroethylene than rat liver microsomes (Miller & Guengerich, 1982).

Incubation of trichloroethylene with liver microsomes and liver cytosol from rats in the absence of cofactors for oxidative biotransformation by cytochrome P450 and in the presence of glutathione resulted in the formation of *S*-(1,2-dichlorovinyl)glutathione at low rates (Dekant *et al.*, 1990).

#### 4.1.3 Comparison of humans and animals

A quantitative comparison of the metabolism of trichloroethylene in humans and rats and mice by application of physiologically based pharmacokinetic models suggests that humans have a lower rate of metabolism (14.9 mg/kg bw per h) than B6C3F1 mice (23.2 mg/kg bw per h in females and 32.7 mg/kg bw per h in males) but a slightly higher rate than Fischer 344 rats (11 mg/kg bw per h) (Allen & Fisher, 1993). In the absence of comparative studies, the role of saturable metabolism in humans cannot be assessed; however, in the occupationally and environmentally relevant range of exposures, the metabolism of trichloroethylene after exposure by inhalation seems to be similar in humans and rats. Qualitatively, the pathways of biotransformation in humans and animals are identical, and most metabolites identified in experimental animals have also been found in humans; however, whereas the urinary excretion of trichloroacetic acid remains constant in rats exposed repeatedly to trichloroethylene, the quantity increases steadily in humans over five days. The opposite trend is observed for trichloroethanol, the urinary excretion increasing in rats and remaining constant in humans. The kinetics of the biotransformation of trichloroethylene to trichloroacetic acid in isolated hepatocytes was markedly species dependent: The  $V_{\max}/K_m$  values ('intrinsic clearance') in mouse, rat and human hepatocytes were  $3.8 \times 10^{-6}$ ,  $1.2 \times 10^{-7}$  and  $3.25 \times 10^{-8}$  L/min per  $10^6$  cells, respectively (Elcombe, 1985).

## 4.2 Toxic effects

### 4.2.1 Humans

The acute toxicity of trichloroethylene in humans is characterized mainly by depression of the central nervous system: In 288 cases of acute intoxication with trichloroethylene, effects on the central nervous system were the major toxic manifestations. Liver toxicity was seen in only five individuals, and there was no renal damage (McCarthy & Jones, 1983).

Chronic exposure to trichloroethylene has been reported to be hepatotoxic, and trichloroethylene has also been implicated in the so-called 'psycho-organic syndrome' (McCarthy & Jones, 1983). There was no direct evidence for renal toxicity in humans exposed chronically to low levels of trichloroethylene ( $50 \text{ mg/m}^3$ ) (Seldén *et al.*, 1993).

### 4.2.2 Experimental systems

The oral  $LD_{50}$  values for trichloroethylene are 7183 mg/kg bw in rats (Smyth *et al.*, 1969) and 2400–2850 mg/kg bw in mice (Aviado *et al.*, 1976; Tucker *et al.*, 1982). The  $LC_{50}$  in rats was 26 300 ppm [ $136\,760 \text{ mg/m}^3$ ] for a 1-h exposure (Vernot *et al.*, 1977) and 12 500 ppm [ $65\,000 \text{ mg/m}^3$ ] for a 4 h-exposure (Siegel *et al.*, 1971).

The major toxic effects in animals are depression of central nervous function and sensitization of cardiac function to adrenalin. After acute exposure of Fischer 344 rats to high doses

of trichloroethylene, liver damage was observed, characterized by increased activities of serum glutamic-oxaloacetic acid and glutamic-pyruvic transaminases. Administration of high doses of trichloroethylene after pretreatment with phenobarbital also induced renal damage (Chakrabarti & Tuchweber, 1988). High oral doses of trichloroethylene (> 2000 mg/kg bw) damaged Clara cells in mouse lung (Scott *et al.*, 1988; Forkert & Birch, 1989), and dose-dependent damage to mouse Clara cells was observed after single exposures to 200–1000 ppm [1040–5200 mg/m<sup>3</sup>] by inhalation for 6 h; no effect was seen at 20 ppm [104 mg/m<sup>3</sup>]. The effect seems to be species-specific, since inhalation of 1000 ppm [5200 mg/m<sup>3</sup>] trichloroethylene for 6 h had no toxic effects on the rat lung (Odum *et al.*, 1992).

In male Sprague-Dawley rats injected once intraperitoneally with trichloroethylene at 1 mmol/kg bw [131 mg/kg bw], the activities of serum bile acids, particularly cholic and taurocholic acids, were increased 4 and 8 h after dosing. These times reflect those at which high levels of trichloroethylene and trichloroethanol appear in serum and liver. The selected dose did not induce hepatotoxic effects, and it was suggested that the changes in bile acid activity were due to perturbation of a physiological process (Bai & Stacey, 1993; Hamdan & Stacey, 1993).

Studies on the longer-term toxicity of trichloroethylene in rats and mice exposed orally and by inhalation showed consistent increases in relative liver weight and associated histopathological and biochemical changes. The effects described in kidney included increased relative weights in mice exposed continuously to > 75 ppm (> 390 mg/m<sup>3</sup>) trichloroethylene for 30 days and renal dysfunction in the absence of marked histopathological changes in rats exposed to > 50 ppm [> 260 mg/m<sup>3</sup>] for 12 weeks (Kjellstrand *et al.*, 1981a,b; Stott *et al.*, 1982; Tucker *et al.*, 1982; Kjellstrand *et al.*, 1983a,b; Elcombe *et al.*, 1985; Nomiyama *et al.*, 1986).

Oral administration of 500–1500 mg/kg bw trichloroethylene for 10 consecutive days increased the weight of the liver and the synthesis of DNA and decreased hepatic DNA concentrations in B6C3F1 and Alderley Park mice (Elcombe *et al.*, 1985). Increased hepatic DNA synthesis and mitosis, but no unscheduled DNA synthesis (see section 4.4.2), have been reported in mice dosed with trichloroethylene by gavage or inhalation (Stott *et al.*, 1982; Dees & Travis, 1993).

Trichloroethylene has been shown to induce hepatic peroxisome proliferation in mice, causing substantial increases in cyanide-insensitive palmitoyl coenzyme-A oxidase activity and peroxisomal volume density. The minimal daily dose of trichloroethylene reported to induce this effect in mice is 100 mg/kg bw over 10 days (Elcombe, 1985). Increased hepatic cyanide-insensitive palmitoyl coenzyme A oxidase activity has been reported in Fischer 344 rats treated by gavage with much higher doses of trichloroethylene (1200 mg/kg bw for 14 days, 130%; 1000 mg/kg bw for 10 days, 180% increase) (Goldsworthy & Popp, 1987; Melnick *et al.*, 1987). Increases of 786% and 625% in the activity of this enzyme were reported in B6C3F1 mice treated with 1000 mg/kg bw per day for 10 days (Elcombe *et al.*, 1985; Goldsworthy & Popp, 1987).

Trichloroethylene has been shown to induce a small increase in cyanide-insensitive palmitoyl coenzyme A oxidation activity in the kidneys of both mice and rats after oral dosing with 1000 mg/kg bw per day for 10 days. Greater effects were observed in mice than in rats (Goldsworthy & Popp, 1987).

Two metabolites of trichloroethylene, dichloroacetic acid and trichloroacetic acid (see monographs, this volume), have also been shown to induce peroxisome proliferation in mice and rats (Elcombe, 1985; Goldsworthy & Popp, 1987; DeAngelo *et al.*, 1989). Trichloroacetic acid induced peroxisome proliferation in the kidney of mice, but not rats (Goldsworthy & Popp, 1987).

Trichloroethylene has been reported to inhibit the activity of the natural immune system (natural killer, natural cytotoxic and natural P815 killer cells) in Sprague-Dawley rats and B6C3F1 mice (Wright *et al.*, 1991). The inhibition was particularly evident in the liver after administration *in vivo* and in both liver and spleen after exposure *in vitro*. The background activities of natural immune activities had previously been reported to be higher in species and strains with lower background incidences of liver tumours (Wright & Stacey, 1991). More recently, trichloroethylene has been shown to inhibit aspects of the natural immune system in cells isolated from human liver (Wright *et al.*, 1994). Inhibition of natural immunity may therefore enhance the likelihood of tumour development.

Nuclear magnetic resonance was used to show that trichloroethylene interacts non-specifically with lipid molecules and that, in phosphatidylcholine bilayers, interaction occurs predominantly with the interfacial region rather than the hydrocarbon interior (Bhakuni & Roy, 1994).

### 4.3 Reproductive and prenatal effects

#### 4.3.1 Humans

##### (a) Endocrine and gonadal effects

Out of a group of 99 metal workers in Aarhus (Denmark), 15 men who degreased parts with trichloroethylene for more than 20 h per week were asked to deliver a semen specimen (Rasmussen *et al.*, 1988). Twelve were included in the analysis and compared with 14 unexposed physicians. There was no difference between the two groups in terms of sperm count or morphology, but the exposed group had a small, non-significant increase in the prevalence of mature spermatozoa containing two fluorescent Y bodies, which may indicate Y-chromosomal nondisjunction.

##### (b) Fertility

Taskinen *et al.* (1989) conducted a nested case-control study of 120 cases of spontaneous abortion and 251 controls on the basis of a file of 6000 Finnish workers who had been biologically monitored for exposure to solvents. Information about their marriages and their wives' pregnancies and spontaneous abortions were obtained from national registries; data on paternal occupational exposure to solvents were collected by means of a questionnaire sent to workers and covered the period of spermatogenesis. The likelihood of exposure was defined in three categories: unexposed, potentially exposed (i.e. use of solvents was possible but no exposure was reported or measured) and probably exposed (i.e. exposure was measured or reported). No association was found between paternal occupational exposure to trichloroethylene and spontaneous abortion (crude odds ratio, 1.0; 95% CI, 0.6-2.0).

(c) *Pregnancy*

Pregnancies occurring among 3265 women biologically monitored for exposure to solvents in 1965–83 were identified from a Finnish database (Lindbohm *et al.*, 1990). Only one pregnancy per woman was included, resulting in a total of 120 cases of spontaneous abortion; 336 age-matched controls were randomly selected among women who had only normal births during the study period. Data on workplace, occupational exposure, medical history, alcohol and smoking habits were obtained from a postal questionnaire, to which 85.5% of subjects responded. For each potential exposure, women were classified, without knowledge of their case or control status, into one of three categories: unexposed, potentially exposed (i.e. work tasks might have involved use of solvents, but exposure was not reported or measured) or exposed (i.e. exposure was measured or reported). The analysis addressed 73 women who had had a spontaneous abortion and 167 controls who reported a pregnancy of interest and detailed information on occupational exposures during pregnancy. The odds ratio for spontaneous abortion, adjusted for previous spontaneous abortions, parity, smoking, use of alcohol and exposure to other solvents, was 0.6 (95% CI, 0.2–2.3) for exposure to trichloroethylene.

The 852 women for whom a spontaneous abortion was certified in one of the 11 hospital laboratories in Santa Clara County, CA (United States) were compared with 1618 controls randomly selected among County residents who had had a live birth and frequency matched by date of last menstrual period and hospital (Windham *et al.*, 1991). All participants were contacted by telephone and asked about occupational use of 18 solvents or products during the first 20 weeks of pregnancy. An excess risk for spontaneous abortion was observed for those women who reported exposure to trichloroethylene (crude odds ratio, 3.1; 95% CI, 0.92–10.4) [adjusted odds ratio not calculated]; four of the seven women who reported exposure to trichloroethylene had also used tetrachloroethylene. The odds ratio increased for women who reported more 'intense' exposure, primarily on the basis of detection of odour (odds ratio, 3.9;  $p = 0.04$ ). Odds ratios adjusted for maternal age, race, education, prior fetal loss, smoking, average number of hours worked and quality of response were nonsignificant when the whole group of halogenated solvents was considered (odds ratio for any use, 1.0; 95% CI, 0.65–1.6; odds ratio for use > 10 h per week, 1.5, 95% CI, 0.73–3.0).

Information on 7316 pregnancies was obtained from the hospital discharge register for 9186 women identified as working in Finnish laboratories (Taskinen *et al.*, 1994). The pregnancies resulted in 5663 births, 687 spontaneous abortions and 966 induced abortions, and a case-referent study was conducted within the cohort. Questionnaires were posted requesting confirmation of the study pregnancy and data on exposures; the response rate was 78%. The 206 women with only one registered spontaneous abortion and 329 controls randomly selected among women who had given birth to a normal infant were included in the analysis of spontaneous abortion. The analysis of congenital malformations involved 36 cases and 105 referents. Seven women who had had a spontaneous abortion and nine controls reported exposure to trichloroethylene, giving an odds ratio of 1.6 (95% CI, 0.5–4.8), adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control and febrile disease during pregnancy. The odds ratios associated with exposure to halogenated solvents as a group were 0.6 (0.4–1.1) for exposure on one to two days per week and 1.8 (0.9–3.7) for exposure on three to five days per week. The odds ratio for congenital malformations

associated with exposure to halogenated solvents was 0.8 (0.2–2.5), adjusted for alcohol consumption, parity, previous miscarriages and failed birth control.

In 1981, the groundwater in a small area in the southwestern part of the city of Tucson, Arizona (United States), was found to be contaminated with trichloroethylene and, to a lesser extent, with dichloroethylene and chromium (Goldberg *et al.*, 1990). The parents of 707 children with congenital heart disease who had conceived their child and spent the beginning of the pregnancy (one month before and the first trimester) in the Tucson valley between 1969 and 1987 were interviewed. The prevalence of congenital heart disease among children born to mothers who had been exposed (0.68%) was higher than that of mothers who lived outside the area (0.26%;  $p < 0.001$ ). The ratio decreased to near unity for new arrivals in the contaminated area after closure of the well.

#### 4.3.2 Experimental systems

Trichloroethylene and its metabolites appear to cross the placenta readily in many species (Helliwell & Hutton, 1949, 1950; Lanham, 1970; Withey & Karpinski, 1985; Ghantous *et al.*, 1986). In mice, inhalation of trichloroethylene resulted in accumulation of its metabolite, trichloroacetic acid (see also Land *et al.*, 1981), in amniotic fluid (Ghantous *et al.*, 1986).

A significant increase in the percentage of abnormal spermatozoa was observed in mice exposed to 0.2% trichloroethylene for 4 h per day for five days over that in controls and in mice exposed to 0.02% trichloroethylene (Land *et al.*, 1981). No sperm toxicity was induced in male Long-Evans rats exposed by gavage to up to 1000 mg/kg bw, trichloroethylene on five days per week for six weeks (Zenick *et al.*, 1984). Mating of untreated female NMRI mice with male mice that had been exposed to up to 450 ppm [2417 mg/m<sup>3</sup>] trichloroethylene by inhalation for 24 h did not influence fertilization or pre- or post-implantation rates and did not induce dominant lethal mutation (Slacik-Erben *et al.*, 1980). No modification of mating performance or female fertility was observed in groups of female Long-Evans rats exposed to trichloroethylene by gavage for two weeks before mating at doses up to 1000 mg/kg bw, which was a toxic dose (Manson *et al.*, 1984). Administration of trichloroethylene in the diet of mice and rats at concentrations equivalent to doses of up to 300 mg/kg bw per day for two generations resulted in marginal effects on testicular weight and on survival of pups of both the F<sub>1</sub> and F<sub>2</sub> generations at the highest dose. No other signs of reproductive toxicity were observed (United States National Toxicology Program, 1985, 1986).

Female Long-Evans rats were exposed by inhalation to 1800 ± 200 ppm [9666 ± 1074 mg/m<sup>3</sup>] trichloroethylene for two weeks before and/or during gestation. Post-natal body weight was decreased in the offspring of mothers that had been exposed before gestation. Significant increases in the incidence of skeletal and soft-tissue anomalies, indicative of developmental delay in maturation rather than teratogenesis, were observed in the group exposed during pregnancy alone (Dorfmueller *et al.*, 1979). A significant increase in the incidence of cardiac malformations was reported in newborn Sprague-Dawley rats after maternal exposure to trichloroethylene in drinking-water (1.5 or 1100 ppm [mg/L]) for seven days before and throughout gestation. [The actual dose could not be calculated from the available data.] No signs of maternal toxicity or other signs of fetal toxicity were observed (Dawson *et al.*, 1993). No increase in the frequency of birth defects has been reported in most other studies of rat or mouse dams exposed

by various routes to various concentrations of trichloroethylene, except for a predictable impairment of fetal growth associated with maternally toxic doses (Schwetz *et al.*, 1975; Leong *et al.*, 1975; Healy & Wilcox, 1978; Hardin *et al.*, 1981; Cosby & Dukelow, 1992).

The male offspring of female rats exposed to trichloroethylene in the drinking-water at up to 1250 mg/L before and during gestation and postpartum up to day 21 had enhanced locomotor activity and exploratory behaviour (Taylor *et al.*, 1985). Impairment of myelination of the central nervous system and decreased glucose uptake by whole brain and cerebellum were observed in the offspring of rats exposed to 312 or 625 mg/L trichloroethylene in the drinking-water before and during gestation and postpartum (Noland-Gerbee *et al.*, 1986; Isaacson & Taylor, 1989). The specific gravity of brain tissue was reduced in the offspring of mice exposed to 150 ppm [806 mg/m<sup>3</sup>] trichloroethylene by inhalation four weeks before and during gestation (Westergren *et al.*, 1984).

#### 4.4 Genetic and related effects

##### 4.4.1 Humans

*Cytogenetic damage in lymphocytes:* In a study of 28 male degreasers exposed to trichloroethylene, nine were reported to have > 13% hypodiploid cells in cultured peripheral lymphocytes (Konietzko *et al.*, 1978). These men had been exposed to a higher mean maximal concentration of trichloroethylene (206 ppm [1106 mg/m<sup>3</sup>]) than those considered to have normal rates of hypodiploidy (116 ppm [623 mg/m<sup>3</sup>]). A correlation ( $r = 0.46$ ;  $p < 0.05$ ) was also seen between the hypodiploidy rate and the average daily or average maximal exposure to trichloroethylene. The mean rate of hypodiploid cells was 10.9% (SD, 4.5;  $n = 27$ , excluding one man with karyotype 47, XY, +mar), in comparison with 6.5% (SD, 3.2) among 10 male controls. The exposed workers also had a fivefold higher mean rate of chromosomal breaks per 100 mitoses (3.1; SD, 3.7;  $n = 27$ ) than the controls (0.6; SD, 0.7;  $n = 10$ ), but these data were not commented upon. The effects of age and cigarette smoking could not be judged from the report. [The Working Group noted that the hypodiploidy rate among controls was very high.]

In a study of 22 workers who had constantly used trichloroethylene in their [unspecified] jobs for an average of 9.7 years (range, 0.7–34) and 22 controls matched for age, sex and smoking habits, no increase in the frequency of sister chromatid exchange was seen in peripheral lymphocyte (Nagaya *et al.*, 1989). Spot urine samples collected at the same time as the blood samples from the exposed workers showed a concentration of 19.1–1066.4 mg/L (mean, 183.6 mg/L) total trichloro compounds. Smoking increased the frequency of sister chromatid exchange.

A group of 15 workers involved in metal degreasing with trichloroethylene for more than 20 h per week in a half-open vapour plant had a significantly greater frequency of chromosomal aberrations, excluding gaps and hyperdiploid cells, in cultured lymphocytes than 669 controls; seven of the degreasers were also painters. The mean urinary concentration of trichloroacetate was fairly low: 3.7 mg/L (range, 0.02–26.9), and the mean number of cumulative working years was 4.6 (range, 0.8–22.0) (Rasmussen *et al.*, 1988). The effects of smoking and age could not be judged from the paper. The authors considered the reference group 'not ideal' but reported that the distribution of confounding factors was no different from that in the average population.

Sperm counts and the frequencies of abnormal sperm heads and of sperm with two fluorescent Y bodies were not significantly different in the 12 workers and 14 controls from whom semen samples containing sperm were taken.

Sister chromatid exchange was analysed in 22 male and 16 female workers in trichloroethylene synthesis and degreasing and in 26 control male and 25 female subjects who worked filling tanks with hydrogen, nitrogen and oxygen or as lathe operators (Seiji *et al.*, 1990). No effect of the occupational exposure was seen among nonsmokers, but the eight exposed smokers (all males) had a significantly higher mean frequency of sister chromatid exchange per cell (7.06) than seven male smoking controls (5.10). Sister chromatid exchange was also studied in nine male and 10 female tetrachloroethylene synthesis workers who had been exposed to an 8-h time-weighted geometric mean concentration of 8 ppm [43.0 mg/m<sup>3</sup>] trichloroethylene (75th percentile, 49 ppm [263 mg/m<sup>3</sup>]; maximum, 521 ppm [2798 mg/m<sup>3</sup>]) and 17 ppm [115 mg/m<sup>3</sup>] tetrachloroethylene (75th percentile, 28 ppm [190 mg/m<sup>3</sup>]; maximum, 567 ppm [3844 mg/m<sup>3</sup>]). They were compared with a control group of nine men and nine women and an extended control group consisting of 21 men and 23 women. Occupational exposure was reported to have affected the frequency of sister chromatid exchange in exposed male smokers, on the basis of a comparison of the frequency in these five men (7.33) with that in six nonsmoking male controls in the small (5.72;  $p < 0.05$ ) and nine controls in the extended (5.48;  $p < 0.01$ ) groups; the mean frequency of sister chromatid exchange in exposed male smokers was also higher than that in the 12 male smokers in the extended control group (5.7). No significant differences were reported between exposed and unexposed smokers. [Comparison of exposed smokers and unexposed nonsmokers may not be justified, especially as smoking usually induces sister chromatid exchange, although in this study such an effect could not be shown.]

#### 4.4.2 *Experimental systems* (see also Tables 12 and 13 and Appendices 1 and 2)

The genetic toxicology of trichloroethylene has been reviewed (Baden & Simmon, 1980; Fabricant & Chalmers, 1980; Vainio *et al.*, 1985; Crebelli & Carere, 1989; Candura & Faustman, 1991; Jackson *et al.*, 1993; European Centre for Ecotoxicology and Toxicology of Chemicals, 1994). The mechanisms of the possible genotoxicity of trichloroethylene were discussed by Henschler (1987).

##### (a) *DNA binding*

Trichloroethylene was reported to bind to DNA *in vitro* after metabolic activation; the binding was enhanced by the addition of glutathione and reduced by addition of SKF-525-A, an inhibitor of mixed-function oxidases. High-performance liquid chromatography indicated a possible DNA adduct, which could not be identified (Mazzullo *et al.*, 1992). DNA binding could not be demonstrated *in vivo* in several tissues of mice in one study (Bergman, 1983b) or in the liver of rats in another study (Parchman & Magee, 1982); however, the latter authors noted incorporation of label into normal nucleosides. A low level of covalent interaction was reported with the DNA of rat and mouse liver, kidney, lungs and stomach (estimated at 0.15 adducts per 10<sup>6</sup> nucleotides; Mazzullo *et al.*, 1992) and of mouse liver (maximum, 0.62 alkylations per 10<sup>6</sup> nucleotides; Stott *et al.*, 1982).

Table 12. Genetic and related effects of trichloroethylene without mutagenic stabilizers

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, <i>Escherichia coli</i> PQ37	-	-	7325 <sup>c</sup>	Mersch-Sundermann <i>et al.</i> (1989)
SAF, <i>Salmonella typhimurium</i> BAL13, forward mutation ( <i>ara</i> test)	-	-	190	Roldán-Arjona <i>et al.</i> (1991)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	(+)	160 vapour <sup>d</sup>	Simmon <i>et al.</i> (1977)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	160 vapour <sup>d</sup>	Baden <i>et al.</i> (1979)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	420 (8% vapour) 16h	Bartsch <i>et al.</i> (1979)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	+	18 vapour	Crebelli <i>et al.</i> (1982)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	260 vapour <sup>d</sup>	Shimada <i>et al.</i> (1985)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	167 <sup>e</sup>	Mortelmans <i>et al.</i> (1986)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	0	-	1050 vapour	McGregor <i>et al.</i> (1989)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	526 vapour <sup>d</sup>	Baden <i>et al.</i> (1979)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	(+)	0	50 <sup>f</sup>	Kringstad <i>et al.</i> (1981)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	(+)	-	50 vapour <sup>d</sup>	Shimada <i>et al.</i> (1985)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	167 <sup>e</sup>	Mortelmans <i>et al.</i> (1986)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	167 <sup>e</sup>	Mortelmans <i>et al.</i> (1986)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	-	167 <sup>e</sup>	Mortelmans <i>et al.</i> (1986)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	0	-	1050 vapour	McGregor <i>et al.</i> (1989)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	+	2600	Bronzetti <i>et al.</i> (1978)
SCG, <i>Saccharomyces cerevisiae</i> D7, gene conversion	-	+	1300	Bronzetti <i>et al.</i> (1978)
SCR, <i>Saccharomyces cerevisiae</i> D7, reverse mutation	-	+	3660	Crebelli <i>et al.</i> (1985)
ANG, <i>Aspergillus nidulans</i> , diploid yA2/+ strain 35x17, quiescent conidia, mitotic crossing-over	-	0	90 vapour	Crebelli <i>et al.</i> (1985)
ANG, <i>Aspergillus nidulans</i> , diploid yA2/+ strain 35x17, growth-mediated assay, mitotic crossing-over	-	0	90 vapour	Crebelli <i>et al.</i> (1985)
SZF, <i>Schizosaccharomyces pombe</i> P1, stationary phase, forward mutation	-	-	3280	Rossi <i>et al.</i> (1983)
SZF, <i>Schizosaccharomyces pombe</i> P1, growing cells, forward mutation	-	-	13 140	Rossi <i>et al.</i> (1983)
ANF, <i>Aspergillus nidulans</i> , haploid strain 35, quiescent conidia, forward mutation (methionine suppressor)	-	0	100 vapour	Crebelli <i>et al.</i> (1985)
ANF, <i>Aspergillus nidulans</i> , haploid strain 35, 'growth-mediated assay', forward mutation (methionine suppressor)	+	0	13 vapour	Crebelli <i>et al.</i> (1985)

Table 12 (contd)

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ANN, <i>Aspergillus nidulans</i> , diploid $\gamma A2/+$ strain 35 $\times$ 17, quiescent conidia, nondisjunctional diploids	-	0	3660	Crebelli <i>et al.</i> (1985)
ANN, <i>Aspergillus nidulans</i> , diploid $\gamma A2/+$ strain 35 $\times$ 17, quiescent conidia, haploids	-	0	3660	Crebelli <i>et al.</i> (1985)
ANN, <i>Aspergillus nidulans</i> , diploid $\gamma A2/+$ strain 35 $\times$ 17, 'growth-mediated assay', nondisjunctional diploids	+	0	40 vapour	Crebelli <i>et al.</i> (1985)
ANN, <i>Aspergillus nidulans</i> , diploid $\gamma A2/+$ strain 35 $\times$ 17, 'growth-mediated assay', haploids	+	0	90 vapour	Crebelli <i>et al.</i> (1985)
DMX, <i>Drosophila melanogaster</i> , sex-linked recessive lethal mutation	-		2500 <sup>c</sup> injection	Fourman <i>et al.</i> (1994)
DMX, <i>Drosophila melanogaster</i> , sex-linked recessive lethal mutation	?		5000 feeding <sup>d</sup>	Fourman <i>et al.</i> (1994)
URP, Unscheduled DNA synthesis, rat primary hepatocytes <i>in vitro</i>	-	0	130 vapour <sup>e</sup>	Shimada <i>et al.</i> (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, <i>tk</i> locus <i>in vitro</i>	-	+	146 <sup>f</sup>	Caspary <i>et al.</i> (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells <i>in vitro</i>	(+)	(+)	401 <sup>g</sup>	Galloway <i>et al.</i> (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells <i>in vitro</i>	-	-	14 900 <sup>h</sup>	Galloway <i>et al.</i> (1987)
TRR, Cell transformation, RL V/Fischer rat F1706 embryo cells <i>in vitro</i>	+	0	144	Price <i>et al.</i> (1978)
GIH, Gene mutation, human lymphoblastoid TK6 cells <i>in vitro</i>	-	-	600	Caspary <i>et al.</i> (1988)
ICR, Inhibition of intercellular communication, B6C3F1 mouse hepatocytes <i>in vitro</i>	+	0	1.3	Klaunig <i>et al.</i> (1989)
ICR, Inhibition of intercellular communication, F344 rat hepatocytes <i>in vitro</i>	-	0	13	Klaunig <i>et al.</i> (1989)
HMM, Host-mediated assay, gene conversion in <i>Saccharomyces cerevisiae</i> D4 recovered from CD-1 mouse liver, lungs and kidneys	+		400 po $\times$ 1 <sup>i</sup>	Bronzetti <i>et al.</i> (1978)
HMM, Host-mediated assay, gene conversion in <i>Saccharomyces cerevisiae</i> D7 recovered from CD-1 mouse liver and kidneys	+		400 po $\times$ 1	Bronzetti <i>et al.</i> (1978)
HMM, Host-mediated assay, gene conversion in <i>Saccharomyces cerevisiae</i> D7 recovered from CD-1 mouse lungs	-		400 po $\times$ 1	Bronzetti <i>et al.</i> (1978)
HMM, Host-mediated assay, reverse mutation in <i>Saccharomyces cerevisiae</i> D7 from CD-1 mouse liver, lungs and kidneys	+		400 po $\times$ 1	Bronzetti <i>et al.</i> (1978)
HMM, Host-mediated assay, forward mutation in <i>Schizosaccharomyces pombe</i> P1, CD-1 $\times$ C57Bl hybrid mouse	-		2000 iv or ip $\times$ 1	Rossi <i>et al.</i> (1983)
DVA, DNA single-strand breaks, mouse liver <i>in vivo</i>	-		2000 ip $\times$ 1	Parchman & Magee (1982)
DVA, DNA single-strand breaks (alkaline unwinding) in liver and kidney of male NMRI mice <i>in vivo</i>	+		790 ip $\times$ 1	Wallis (1986)

Table 12 (contd)

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DVA, DNA single-strand breaks (alkaline unwinding), mouse liver <i>in vivo</i>	+		1500 po x 1'	Nelson & Bull (1988)
DVA, DNA single-strand breaks (alkaline unwinding), rat liver <i>in vivo</i>	+		3000 po x 1'	Nelson & Bull (1988)
MST, Mouse spot test <i>in vivo</i>	-		350 ip x 1	Fahrig (1977)
UVM, Unscheduled DNA synthesis, CD-1 mouse primary hepatocytes <i>in vivo</i>	-		1000 po x 1	Doolittle <i>et al.</i> (1987)
MVM, Micronucleus induction, mouse bone-marrow erythrocytes <i>in vivo</i>	+		750 po x 2	Duprat & Gradiski (1980)
MVM, Micronucleus induction, B6C3F1 mouse bone-marrow erythrocytes <i>in vivo</i>	-		2500 ip x 3'	Shelby <i>et al.</i> (1993)
MVM, Micronucleus induction, mouse spermatocytes <i>in vivo</i> (spermatids examined)	-		565 inh 6 h/d x 5	Allen <i>et al.</i> (1994)
MVM, Micronucleus induction, mouse splenocytes <i>in vivo</i>	-		9800 inh 6 h	Kligerman <i>et al.</i> (1994)
MVR, Micronucleus induction, rat bone-marrow erythrocytes <i>in vivo</i>	+		5 inh 6 h	Kligerman <i>et al.</i> (1994)
MVR, Micronucleus induction, rat bone-marrow erythrocytes <i>in vivo</i>	-		960 inh 6 h x 4	Kligerman <i>et al.</i> (1994)
MVR, Micronucleus induction, rat peripheral lymphocytes <i>in vivo</i>	-		8800 inh 6 h	Kligerman <i>et al.</i> (1994)
MVR, Micronucleus induction, rat peripheral lymphocytes <i>in vivo</i>	-		960 inh 6 h x 4	Kligerman <i>et al.</i> (1994)
SVA, Sister chromatid exchange, rat peripheral lymphocytes <i>in vivo</i>	-		8800 inh 6 h	Kligerman <i>et al.</i> (1994)
SVA, Sister chromatid exchange, rat peripheral lymphocytes <i>in vivo</i>	-		960 inh 6 h x 4	Kligerman <i>et al.</i> (1994)
SVA, Sister chromatid exchange, mouse splenocytes <i>in vivo</i>	-		9800 inh 6 h	Kligerman <i>et al.</i> (1994)
CLA, Chromosomal aberrations, rat peripheral lymphocytes <i>in vivo</i>	-		8800 inh 6 h	Kligerman <i>et al.</i> (1994)
CLA, Chromosomal aberrations, rat peripheral lymphocytes <i>in vivo</i>	-		960 inh 6 h x 4	Kligerman <i>et al.</i> (1994)
CVA, Chromosomal aberrations, mouse splenocytes <i>in vivo</i>	-		9800 inh 6 h	Kligerman <i>et al.</i> (1994)
DLM, Dominant lethal mutation, male NMRI-Han/BGA mice <i>in vivo</i>	-		3400 inh 24 h'	Slacik-Erben <i>et al.</i> (1980)
BID, Binding (covalent) to salmon sperm DNA <i>in vitro</i>	-	+	270	Banerjee & Van Duuren (1978)
BID, Binding (covalent) to calf thymus DNA <i>in vitro</i>	-	+	340'	Bergman (1983b)
BID, Binding (covalent) to DNA of isolated rat hepatocytes <i>in vitro</i>	0	+	13	Miller & Guengerich (1983)
BID, Binding (covalent) to DNA of isolated mouse hepatocytes <i>in vitro</i>	+	0	13	Miller & Guengerich (1983)
BID, Binding (covalent) to calf thymus DNA <i>in vitro</i>	+	0	13	Miller & Guengerich (1983)
BVP, Binding (covalent) to RNA of NMRI mouse spleen, lung, liver, kidney, pancreas, testis and brain <i>in vivo</i>	0	+	131	DiRenzo <i>et al.</i> (1982)
	-		67 ip x 5'	Bergman (1983b)

Table 12 (contd)

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Binding (covalent) to DNA of NMRI mouse spleen, pancreas, lung, testis, kidney and brain <i>in vivo</i>	- <sup>c</sup>		67 ip x 5	Bergman (1983b)
BVD, Binding (covalent) to DNA of NMRI mouse liver <i>in vivo</i>	?		67 ip x 5	Bergman (1983b)
BVD, Binding (covalent) to DNA of B6C3F1 mouse liver <i>in vivo</i>	?		1200 po x 1	Stott <i>et al.</i> (1982)
BVD, Binding (covalent) to DNA of B6C3F1 mouse liver <i>in vivo</i>	?		250 ip x 1	Parchman & Magee (1982)
BVD, Binding (covalent) to DNA of rat liver <i>in vivo</i>	?		1000 ip x 1	Parchman & Magee (1982)
<b>Dichloroacetyl chloride</b>				
PRB, λ Prophage induction, <i>Escherichia coli</i> WP2	-	-	10 000	DeMarini <i>et al.</i> (1994)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	(+)	3	DeMarini <i>et al.</i> (1994)

<sup>a</sup> +, considered to be positive; (+), considered to be weakly positive in an inadequate study; -, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study); 0, not tested

<sup>b</sup> LED, lowest effective dose; HID, highest effective dose. In-vitro tests, µg/ml; in-vivo tests, mg/kg bw; ip, intraperitoneally; po, orally

<sup>c</sup> 99% purity or greater

<sup>d</sup> 0.001% stabilizers

<sup>e</sup> Also positive by gavage at 150 mg/kg for 5 days a week, 22 times with 400 mg/kg on the last day

<sup>f</sup> No DNA strand breaks in lungs of mice treated with 1300 mg/kg ip x 1

<sup>g</sup> Metabolic incorporation of <sup>14</sup>C into nucleotides was observed.

Table 13. Genetic and related effects of trichloroethylene containing mutagenic stabilizers or for which information on purity was not sufficiently clear

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, <i>Escherichia coli</i> PQ37	-	-	0.00	von der Hude <i>et al.</i> (1988)
***, Mutatox assay, derepression of luminescence operon, <i>Photobacterium phosphorium</i>	-	0	0.00	Elmore & Fitzgerald (1990)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	14 650	Henschler <i>et al.</i> (1977)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	525 vapour	Waskell (1978)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	+	260 vapour	Shimada <i>et al.</i> (1985)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	+	+	0.00	Milman <i>et al.</i> (1988)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	(+)	(+)	130 vapour	McGregor <i>et al.</i> (1989)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	+	+	50 vapour	Shimada <i>et al.</i> (1985)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	+	+	0.00	Milman <i>et al.</i> (1988)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	+	+	33 vapour	McGregor <i>et al.</i> (1989)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	-	0.00	Milman <i>et al.</i> (1988)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	525 vapour	Waskell (1978)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	0.00	Milman <i>et al.</i> (1988)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	65 vapour	McGregor <i>et al.</i> (1989)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	434	Greim <i>et al.</i> (1975)
ECK, <i>Escherichia coli</i> K12, forward mutation	-	-	434	Greim <i>et al.</i> (1975)
ECK, <i>Escherichia coli</i> K12, reverse mutation ( <i>arg</i> <sup>+</sup> )	-	+	434	Greim <i>et al.</i> (1975)
ECK, <i>Escherichia coli</i> K12, reverse mutation ( <i>gal</i> <sup>+</sup> )	-	-	434	Greim <i>et al.</i> (1975)
ECK, <i>Escherichia coli</i> K12, reverse mutation ( <i>nad</i> <sup>+</sup> )	-	-	434	Greim <i>et al.</i> (1975)
SCG, <i>Saccharomyces cerevisiae</i> D7, log-phase cultures, gene conversion	0	+	1970	Callen <i>et al.</i> (1980)
SCG, <i>Saccharomyces cerevisiae</i> D7, log-phase and stationary cultures, gene conversion	-	-	2900	Koch <i>et al.</i> (1988)
SCG, <i>Saccharomyces cerevisiae</i> XV185-14C, reverse mutation ( <i>lys1-1, his1-7, hom3-10</i> )	0	+	1460	Shahin & Von Borstel (1977)
SCR, <i>Saccharomyces cerevisiae</i> D7, log-phase cultures, reverse mutation	0	+	1970	Callen <i>et al.</i> (1980)
SCH, <i>Saccharomyces cerevisiae</i> D7, log-phase cultures, mitotic recombinants or otherwise genetically altered colonies ( <i>ade2</i> )	0	+	1970	Callen <i>et al.</i> (1980)

Table 13 (contd)

Test system	Result*	Dose <sup>b</sup> (LED/HID)	Reference
SCR, <i>Saccharomyces cerevisiae</i> D7, log-phase and stationary cultures, reverse mutation	-	2900	Koch <i>et al.</i> (1988)
SZF, <i>Schizosaccharomyces pombe</i> P1, stationary phase, forward mutation	-	3280	Rossi <i>et al.</i> (1983)
SZF, <i>Schizosaccharomyces pombe</i> P1, growing cells, forward mutation	-	13 140	Rossi <i>et al.</i> (1983)
SCN, <i>Saccharomyces cerevisiae</i> D61.M, growing cells, aneuploidy	0	725	Koch <i>et al.</i> (1988)
TSM, <i>Tradescantia</i> species, mutation	+	0.0003	Schraier & Sautkulis (1982)
URP, Unscheduled DNA synthesis, rat primary hepatocytes <i>in vitro</i>	-	130 vapour	Shimada <i>et al.</i> (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes <i>in vitro</i>	-	0.00	Millman <i>et al.</i> (1988)
URP, Unscheduled DNA synthesis, rat primary hepatocytes <i>in vitro</i>	+	1445	Williams <i>et al.</i> (1989)
UIA, Unscheduled DNA synthesis, B6C3F1 mouse primary hepatocytes <i>in vitro</i>	+	0.00	Millman <i>et al.</i> (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells <i>in vitro</i>	0	9	White <i>et al.</i> (1979)
CIC, Chromosomal aberrations, Chinese hamster lung (CHL) cells <i>in vitro</i>	-	1000	Sofuni <i>et al.</i> (1985)
TBM, BALB/c-3T3 mouse cells, cell transformation <i>in vitro</i>	(+)	250	Tu <i>et al.</i> (1985)
TFS, Syrian hamster embryo cells, morphological transformation <i>in vitro</i>	(+)	25	Amacher & Zelljadt (1983)
SHL, Sister chromatid exchange, human lymphocytes <i>in vitro</i>	(+)	178	Gu <i>et al.</i> (1981)
HMM, Host-mediated assay, forward mutation in <i>Schizosaccharomyces pombe</i> P1 recovered from CD-1 mouse kidneys and lungs	-	2000 po x 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, forward mutation in <i>Schizosaccharomyces pombe</i> P1 recovered from CD-1 mouse liver	(+)	2000 po x 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, <i>Schizosaccharomyces pombe</i> P1, forward mutation, in CD-1 mouse peritoneum	(+)	1000 po x 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, <i>Schizosaccharomyces pombe</i> P1, forward mutation, in Sprague-Dawley rat peritoneum	-	1000 po x 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, forward mutation in <i>Schizosaccharomyces pombe</i> P1, CD-1 x 7BL hybrid mouse	-	2000 iv or ip x 1	Rossi <i>et al.</i> (1983)
UPR, Unscheduled DNA synthesis, Fischer-344 male rat hepatocytes <i>in vivo</i>	-	1000 po x 1	Mirsalis <i>et al.</i> (1989)
UVM, Unscheduled DNA synthesis, male and female B6C3F1 mouse hepatocytes <i>in vivo</i>	-	1000 po x 1	Mirsalis <i>et al.</i> (1989)

Table 13 (contd)

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CBA, Chromosomal aberrations, CD-1 mouse bone marrow cells <i>in vivo</i>	-		1000 po x 1	Loprieno & Abbondandolo (1980)
CBA, Chromosomal aberrations, mouse bone marrow cells <i>in vivo</i>	-		1200 po x 1	Sbrana <i>et al.</i> (1985) (abstract)
CBA, Chromosomal aberrations, mouse bone marrow cells <i>in vivo</i>	-		795 inh 7 h x 50 <sup>c</sup>	Sbrana <i>et al.</i> (1985) (abstract)
MVM, Micronucleus induction, mouse bone marrow erythrocytes <i>in vivo</i>	+		1200 po x 1	Sbrana <i>et al.</i> (1985) (abstract)
MVM, Micronucleus induction, mouse bone marrow erythrocytes <i>in vivo</i>	+		460 ip x 1	Hrelia <i>et al.</i> (1995)
SLH, Sister chromatid exchange, human lymphocytes <i>in vivo</i>	(+)		0.00	Gu <i>et al.</i> (1981)
BID, Binding (covalent) to calf thymus DNA <i>in vitro</i>	0	+	3.2	Mazzullo <i>et al.</i> (1992)
BVD, Binding (covalent) to DNA of BALB/c mouse liver, kidney, lung and stomach <i>in vivo</i>	(+)		0.76 ip x 1	Mazzullo <i>et al.</i> (1992)
BVD, Binding (covalent) to DNA of Wistar rat liver, kidney, lung and stomach <i>in vivo</i>	(+)		0.76 ip x 1	Mazzullo <i>et al.</i> (1992)
***, Enzyme-altered foci in male Osborne-Mendel rat liver <i>in vivo</i> , promotion protocol, with and without NDEA as an initiator	-		1300 mg/kg, 5 d/week, 7 weeks	Milman <i>et al.</i> (1988)
***, Enzyme-altered foci in male Osborne-Mendel rat liver <i>in vivo</i> , initiation protocol, phenobarbital as promoter	-		1300 mg/kg	Milman <i>et al.</i> (1988)
***, S-Phase induction, male and female B6C3F1 mouse hepatocytes <i>in vivo</i>	+		200 mg/kg	Mirsalis <i>et al.</i> (1989)

NDEA, *N*-nitrosodiethylamine

<sup>a</sup>+, considered to be positive; (+), considered to be weakly positive in an inadequate study; -, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study); 0, not tested

<sup>b</sup>LED, lowest effective dose; HID, highest effective dose. In-vitro tests, mg/ml; in-vivo tests, mg/kg bw; 0.00, dose not reported; ip, intraperitoneally; po, orally

<sup>c</sup>5 days/week, 10 weeks

\*\*\*, Not included on profile

(b) *Mutation and allied effects*

The stabilizers often used in commercial preparations of trichloroethylene, such as epichlorohydrin and 1,2-epoxybutane, are mutagenic, rendering problematic the interpretation of positive results in assays for the mutagenicity of trichloroethylene *per se* (McGregor *et al.*, 1989). Humans are exposed mostly, if not exclusively, to preparations containing stabilizers.

Apart from two reports in which trichloroethylene weakly induced mutation in *Salmonella typhimurium* TA1535, purified trichloroethylene did not induce gene mutation in various strains of *Salmonella* in the absence of metabolic activation; however, trichloroethylene containing directly mutagenic epoxide stabilizers did. Purified trichloroethylene also did not usually induce mutation in *Salmonella* in the presence of exogenous metabolic activation systems, except in two tests with *S. typhimurium* TA100.

Trichloroethylene (pure or of unspecified purity) gave negative results in the SOS chromotest in *Escherichia coli* with and without metabolic activation and in the Mutatox assay in the absence of metabolic activation. In the presence of metabolic activation, analytical-grade trichloroethylene induced *arg*<sup>+</sup> reverse mutations, but not forward mutations or *gal*<sup>+</sup> or *nad*<sup>+</sup> reversions, in *E. coli*.

Trichloroethylene (pure or of unspecified purity) induced gene conversion in *Saccharomyces cerevisiae* in two of three studies and induced reverse mutation in all four studies available in the presence of a metabolic activation system. In a single study, pure trichloroethylene or trichloroethylene containing stabilizers did not induce forward mutation in *Schizosaccharomyces pombe*. Pure trichloroethylene induced forward mutation in one study of growing cultures of *Aspergillus nidulans*, which are capable of some metabolic activation reactions, whereas no such effect was seen in quiescent conidia. Trichloroethylene (of unspecified purity) induced aneuploidy in *S. cerevisiae* in the presence of growth-mediated metabolic activation, and the pure compound induced aneuploidy in *A. nidulans*. In a single study, trichloroethylene (of unspecified purity) induced gene mutation in *Tradescantia*. Pure trichloroethylene did not cause recessive lethal mutations in *Drosophila melanogaster* after injection, and equivocal results were obtained after feeding.

Unscheduled DNA synthesis *in vitro* was reported in four studies, one with mouse and three with rat hepatocytes. Positive results were obtained with trichloroethylene (of unspecified purity) in mouse cells and in one study of rat cells, while negative results were obtained in the other two studies of rat primary hepatocytes, in one of which trichloroethylene of high and of unspecified purity were compared. Pure trichloroethylene induced gene mutation in mouse lymphoma L5178Y cells in the presence of exogenous metabolic activation. In a single study, pure trichloroethylene weakly induced sister chromatid exchange in Chinese hamster cells *in vitro* with and without metabolic activation. Pure trichloroethylene did not increase the frequency of chromosomal aberrations in Chinese hamster cells *in vitro*. In three different assays, trichloroethylene (of unspecified purity) weakly induced cell transformation in mouse, Syrian hamster and (pure trichloroethylene) rat cells *in vitro*, without exogenous metabolic activation. Pure trichloroethylene inhibited intercellular communication in mouse hepatocytes but not in rat hepatocytes *in vitro*.

A 95% pure formulation weakly induced sister chromatid exchange in the absence of metabolic activation in one study. No induction of gene mutation was seen in human lymphoblastoid cells exposed to pure trichloroethylene.

In a host-mediated assay, gene conversion and reverse mutation were induced in *S. cerevisiae* recovered from the liver, lungs and kidneys of mice treated orally with pure trichloroethylene. Forward mutation was weakly induced by trichloroethylene of unspecified purity in *Schizosaccharomyces pombe* cells injected into the peritoneum of mice in one of two studies; no effect was seen in the only study available in rats. *S. pombe* cells recovered from mice after intravenous injection showed no forward mutation in one study; a positive result was seen in another study in mouse liver, but not in kidneys or lungs, after treatment with trichloroethylene of unspecified purity.

Pure trichloroethylene induced DNA single-strand breaks/alkaline-labile sites *in vivo* in mouse liver and kidney and in rat liver. Unscheduled DNA synthesis was not augmented in mouse or rat hepatocytes after treatment with trichloroethylene (pure or of unspecified purity) *in vivo*, and pure trichloroethylene did not induce a significant response in a mouse spot test. Trichloroethylene did not induce chromosomal aberrations in mouse bone marrow *in vivo*. Micronuclei were reported to be induced by trichloroethylene (pure or of unknown purity) in mouse bone-marrow polychromatic erythrocytes in two studies (one was reported in an abstract), while two other studies showed no such effect. A significant increase ( $p = 0.028$ ) observed in one of the latter studies was considered to be due to an exceptionally low control value. Micronuclei were not induced in mouse spermatocytes. In a study in which mice and rats were exposed by inhalation to reagent-grade trichloroethylene (purity, > 99%), micronuclei were induced in the bone-marrow cells of rats but not of mice; neither micronuclei, chromosomal aberrations nor sister chromatid exchange were induced in the peripheral lymphocytes of rats or the splenocytes of mice (Kligerman *et al.*, 1994). In a single study, pure trichloroethylene did not induce dominant lethal mutation in mice. Trichloroethylene increased the frequency of S-phase in mouse hepatocytes *in vivo* but did not produce enzyme-altered foci in rat liver.

### (c) Genetic effects of trichloroethylene metabolites

The genetic toxicology of dichloroacetic and trichloroacetic acids is reviewed in the relevant monographs in this volume. Dichloroacetyl chloride, a presumed metabolite of trichloroethylene, did not induce prophage in *E. coli*, but was weakly mutagenic in *S. typhimurium* TA100 in the absence of metabolic activation in one study.

The minor urinary metabolite, *N*-acetyl-*S*-(1,2-dichlorovinyl)-*L*-cysteine, was mutagenic in *S. typhimurium* TA2638 in the presence of kidney cytosol, which allows deacetylation to the corresponding cysteine conjugate (Vamvakas *et al.*, 1987). The presumed intermediate metabolite, *S*-(1,2-dichlorovinyl)-*L*-cysteine, was mutagenic to *S. typhimurium* TA100 and TA2638 in the presence and absence of metabolic activation (Green & Odum, 1985; Dekant *et al.*, 1986c). *S*-(1,2-Dichlorovinyl)glutathione, the precursor of the cysteine conjugate, was also mutagenic to *S. typhimurium* TA2638 in the presence of rat kidney microsomes, which allow degradation to the cysteine conjugate (Vamvakas *et al.*, 1988). Both the cysteine and the glutathione conjugate induced a low rate of unscheduled DNA synthesis in a cultured pig kidney cell line (Vamvakas *et al.*, 1989). In the same cell line, *S*-(1,2-dichlorovinyl)-*L*-cysteine induced

DNA double-strand breaks and expression of the proto-oncogenes *c-fos* and *c-myc* (Vamvakas *et al.*, 1992; Vamvakas & Köster, 1993; Vamvakas *et al.*, 1993). DNA single-strand breaks were observed in mouse kidney and double-strand breaks in rat kidney after intraperitoneal injection of *S*-(1,2-dichlorovinyl)-L-cysteine (Jaffe *et al.*, 1985; McLaren *et al.*, 1994).

<sup>35</sup>*S*-(1,2-Dichlorovinyl)-L-cysteine metabolites bound to isolated DNA *in vitro* (Bhattacharya & Schulze, 1972).

(d) *Mutations in proto-oncogenes in tumours from trichloroethylene-treated animals*

A group of 110 male B6C3F1 mice, eight weeks of age, were given trichloroethylene in corn oil orally by gavage at a dose of 1700 mg/kg bw per day on five days per week for up to 76 weeks. There were two concurrent control groups, each consisting of 50 male mice: one was untreated and the other received corn oil at a dose of 10 ml/kg bw. Ten control mice in each group were killed at 76 weeks, and the remainder were killed at 96, 103 and 134 weeks [numbers not stated]. At death, liver tumours 0.5 cm in diameter were taken for histological examination and for analysis of oncogenes. At the time of the terminal kill, there were 24 untreated controls, 32 vehicle controls and 75 animals treated with trichloroethylene. The numbers of hepatocellular adenomas per mouse in animals in these three groups were  $0.9 \pm 0.06$  (8%),  $0.13 \pm 0.06$  (13%) and  $1.27 \pm 0.14$  (67%); the corresponding numbers of hepatocellular carcinomas were  $0.09 \pm 0.06$  (8%),  $0.12 \pm 0.06$  (12%) and  $0.57 \pm 0.10$  (39%), respectively. The authors noted numerous foci of cellular alteration (presumed preneoplastic lesions) in the livers of treated mice but only rare foci in the livers of controls. No neoplasms related to treatment were found at other sites. The frequency of mutations in codon 61 of *H-ras* was not significantly different in 76 hepatocellular tumours from trichloroethylene-treated mice and in those from the 74 combined historical and concurrent controls (51% versus 69%). The spectra of these mutations, however, showed a significant decrease in AAA and an increase in CTA in the tumours from treated mice in comparison with those from controls. Other *H-ras* and *K-ras* mutations each contributed 4% to the total in the treated mice, whereas their frequency appeared to be very low in the concurrent controls and none were seen in the historical controls. The authors interpreted these findings as suggesting that exposure to trichloroethylene provides the environment for a selective growth advantage for spontaneous CTA mutations in codon 61 of *H-ras* (Anna *et al.*, 1994).

## 5. Summary and Evaluation

### 5.1 Exposure data

Trichloroethylene, a chlorinated solvent, has been produced commercially since the 1920s in many countries by chlorination of ethylene or acetylene. Its use in vapour degreasing began in the 1920s. In the 1930s, it was introduced for use in dry cleaning, but it has had limited use in that way since the 1950s. Currently, 80–90% of trichloroethylene worldwide is used for degreasing metals. Use for all applications in western Europe, Japan and the United States in 1990 was about 225 thousand tonnes.

Trichloroethylene has been detected in air, water, soil, food and animal tissues. The most heavily exposed people are those working in the degreasing of metals, who are exposed by inhalation.

## 5.2 Human carcinogenicity data

Three cohort studies were considered to be particularly relevant for the evaluation of trichloroethylene. Two of these studies, conducted in Sweden and Finland, involved people who had been monitored for exposure to trichloroethylene by measurement of trichloroacetic acid in urine. The levels in samples from most of the people in the two cohorts indicated relatively low levels of exposure. The third study, from the United States, covered workers exposed to trichloroethylene during maintenance of military aircraft and missiles, some of whom were also exposed to other solvents.

A fourth cohort study included all workers in an aircraft manufacturing company in the United States. This study was considered less relevant, as only one-third of the jobs in the plant entailed exposure to trichloroethylene and the exposures of the workers could not be classified.

In none of the available cohort studies was it possible to control for potential confounding factors, such as those associated with social class with regard to cervical cancer and smoking in respect of urinary bladder cancer.

Case-control studies have been conducted to investigate a number of cancer sites, including a multisite study from Montréal, Canada, in which other cancer cases were used as controls. Most of these studies do not provide risk estimates for exposure to trichloroethylene separately but only for groups of chemicals.

The results of the three most informative cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected. The risk for these cancers was not elevated in the fourth, less informative cohort study. Results for liver cancer were given separately in the study from Finland and for the maintenance workers in the study in the United States. A total of seven cases were observed, whereas 4.00 were expected. Three case-control studies of primary liver cancer indicated elevated relative risks for people exposed to solvents, but only a few of the subjects in each study reported exposure to trichloroethylene.

With regard to non-Hodgkin's lymphoma, the results of the three most informative cohort studies were consistent; the data indicated a modest excess relative risk, with 27 cases observed and 18.9 expected. The risk for non-Hodgkin's lymphoma was not increased in the fourth, less informative study. In a case-control study covering all malignant lymphomas, an elevated odds ratio for exposure to trichloroethylene was indicated on the basis of seven exposed cases. The risk for non-Hodgkin's lymphoma was not increased among people assumed to have been exposed to trichloroethylene in the study in Montréal.

A twofold risk for cervical cancer was observed in two cohort studies.

The occurrence of cancer of the kidney was not elevated in the cohort studies; however, a study of German workers exposed to trichloroethylene revealed five cases of renal cancer whereas no case was found in an unexposed comparison group. The study may, however, have been initiated after the observation of a cluster. A case-control study and the multisite cancer

study, both from Montréal, Canada, provided discordant results with regard to cancer of the kidney.

The incidence of urinary bladder cancer was not increased in the two cohort studies from Sweden and Finland, whereas slightly increased numbers of deaths were seen in the two United States cohorts. The incidence of urinary bladder cancer was not increased in people assumed to be exposed to trichloroethylene in the Montréal study.

Data on cancer incidence or mortality have been reported from five areas in which groundwater was contaminated with trichloroethylene. A weak association between contamination and the incidence of leukaemia was indicated in two of these studies, from Massachusetts and New Jersey, United States. The cohort studies of trichloroethylene-exposed workers did not indicate an association with the occurrence of leukaemia. Two studies, from Finland and New Jersey, suggested a marginal increase in the occurrence of non-Hodgkin's lymphoma in areas with contaminated groundwater.

Overall, the most important observations are the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for non-Hodgkin's lymphoma in all three of the most informative cohort studies. Two of these studies reported data for primary liver cancer separately. Finally, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated groundwater is noted.

### **5.3 Animal carcinogenicity data**

Trichloroethylene, with and without stabilizers, was tested for carcinogenicity by oral administration in two adequate experiments in mice. The studies showed significant increases in the incidences of benign and malignant liver tumours. Of seven studies in which trichloroethylene was given orally to rats, most were inconclusive because of reduced survival or a too short treatment. In two of the studies, the incidence of uncommonly occurring renal-cell tumours was significantly increased in male rats, and in one study an increased incidence of interstitial-cell testicular tumours was seen.

Trichloroethylene was tested for carcinogenicity by inhalation in four experiments in mice. One study showed an increased incidence of lymphomas, one study showed increased incidences of liver tumours, and three studies showed increased incidences of lung tumours. One of three experiments in which rats were exposed by inhalation showed an increased incidence of interstitial testicular tumours and a marginal increase in that of renal-cell tumours in males. No increase in tumour incidence was observed in one study in hamsters exposed by inhalation.

In limited studies, trichloroethylene and its proposed metabolite trichloroethylene oxide did not increase the incidence of skin tumours or local sarcomas in mice when administered by topical application or subcutaneous injection.

### **5.4 Other relevant data**

In rodents, trichloroethylene is rapidly absorbed from the gastrointestinal tract and through the lungs, whereas absorption of the vapour through the skin is negligible. The major pathway is oxidative metabolism leading to the formation of chloroacetic acids. Mice showed consistently

higher rates of oxidative biotransformation than rats. A minor pathway in rodents and humans involves the formation of mercapturic acids.

The acute toxicity of trichloroethylene in rodents and humans is low. After high doses of trichloroethylene are administered repeatedly to rodents, damage is seen in liver and kidney (in mice and rats) and in lung (in mice only). Repeated exposure of humans in the workplace appears to have no marked toxic effects on the kidney or liver. Trichloroethylene is a more potent peroxisome proliferator in the livers of mice than of rats.

The available studies show no consistent effect of trichloroethylene on the human reproductive system. Trichloroethylene is metabolized to trichloroacetic acid in the placenta or fetus of many species. There is little evidence of toxic effects in developing rats or mice.

Studies of structural chromosomal aberrations, aneuploidy and sister chromatid exchange in peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive.

Pure trichloroethylene did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange or unscheduled DNA synthesis in rodents, whereas an increased induction of micronuclei and DNA single-strand breaks/alkaline labile sites was observed.

In single studies with human cells *in vitro*, trichloroethylene of low purity slightly increased the frequencies of sister chromatid exchange and unscheduled DNA synthesis. Pure trichloroethylene did not induce gene mutation in human cells. In mammalian cells *in vitro*, pure trichloroethylene induced cell transformation, sister chromatid exchange and gene mutation, but not chromosomal aberrations. In fungi, trichloroethylene (pure or of unspecified purity) induced aneuploidy, gene mutation and mitotic recombination and induced gene conversion in the presence of metabolic activation.

Gene mutation or DNA damage was usually not induced in prokaryotes by pure trichloroethylene, while preparations containing epoxide stabilizers were mutagenic. Sulfur-containing metabolites formed by a minor trichloroethylene biotransformation pathway were genotoxic in bacteria and cultured renal cells.

## 5.5 Evaluation<sup>1</sup>

There is *limited evidence* in humans for the carcinogenicity of trichloroethylene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of trichloroethylene.

### Overall evaluation<sup>2</sup>

Trichloroethylene is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group considered the following evidence:

- (i) Although the hypothesis linking the formation of mouse liver tumours with peroxisome proliferation is plausible, trichloroethylene also induced tumours at other sites in mice and rats.

<sup>1</sup> For definition of the italicized terms, see Preamble, pp. 22-26.

<sup>2</sup> Dr N.H. Stacey disassociated himself from the overall evaluation.

(ii) Several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin's lymphoma.

## 6. References

- Abrahamsson, K., Ekdahl, A., Collén, J., Fahlström, E., Sporrang, N. & Pedersén, M. (1995) Marine algae— a source of trichloroethylene and perchloroethylene. *Limnol. Oceanogr.* (in press)
- Ahlmark, A., Gerhardsson, G. & Holm, A. (1963) Trichloroethylene exposure in Swedish engineering workshops. In: *Proceedings of the 14th International Congress on Occupational Health*, London, Permanent Commission and International Association on Occupational Health, pp. 448–450
- Aitio, A., Luotamo, M. & Kiilunen, M., eds (1995) *Kemikaalialtistumisen Biomonitorointi* [Biological Monitoring of Exposure to Chemicals], Helsinki, Finnish Institute of Occupational Health, pp. 292–294 (in Finnish)
- Allen, B.C. & Fisher, J.W. (1993) Pharmacokinetic modeling of trichloroethylene and trichloroacetic acid in humans. *Risk Anal.*, **13**, 71–86
- Allen, J.W., Collins, B.W. & Evansky, P.A. (1994) Spermatid micronucleus analyses of trichloroethylene and chloral hydrate effects in mice. *Mutat. Res.*, **323**, 81–88
- Almaguer, D., Kramkowski, R.S. & Orris, P. (1984) *Johnson Controls, Inc., Watertown, WI* (Health Hazard Evaluation Report No. 83-296-1491), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Amacher, D.E. & Zelljadt, I. (1983) The morphological transformation of Syrian hamster embryo cells by chemicals reportedly nonmutagenic to *Salmonella typhimurium*. *Carcinogenesis*, **4**, 291–295
- American Conference of Governmental Industrial Hygienists (1994) *1994–1995 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, pp. 34, 62
- Andelman, J.B. (1985) Inhalation exposure in the home to volatile organic contaminants of drinking water. *Sci. total Environ.*, **47**, 443–460
- Andersen, M.E., Gargas, M.L., Clewell, H.J., III & Severyn, K.M. (1987) Quantitative evaluation of the metabolic interactions between trichloroethylene and 1,1-dichloroethylene *in vivo* using gas uptake methods. *Toxicol. appl. Pharmacol.*, **89**, 149–157
- Anna, C.H., Maronpot, R.R., Pereira, M.A., Foley, J.F., Malarkey, D.E. & Anderson, M.W. (1994) *ras* Proto-oncogene activation in dichloroacetic-, trichloroethylene- and tetrachloroethylene-induced liver tumors in B6C3F1 mice. *Carcinogenesis*, **15**, 2255–2261
- Anttila, A., Pukkala, E., Sallmén, M., Hernberg, S. & Hemminki, K. (1995) Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. *J. occup. Med.* (in press)
- Arbeidsinspectie (1994) *De Nationale MAC-lijst 1994* [The national MAC list 1994], The Hague, p. 40
- Arizona Department of Health Services (1990) *The Incidence of Childhood Leukemia and Testicular Cancer in Pima County: 1970–1986*, Tucson
- Aviado, D.M., Zakhari, S., Simaan, J. & Ulsamer, A.G. (1976) *Methyl Chloroform and Trichloroethylene in the Environment*, Cleveland, OH, CRC Press
- Axelsson, O., Andersson, K., Hogstedt, C., Holmberg, B., Molina, G. & de Verdier, A. (1978) A cohort study on trichloroethylene exposure and cancer mortality. *J. occup. Med.*, **20**, 194–196

- Axelsson, O., Andersson, K., Seldén, A. & Hogstedt, C. (1984) Cancer morbidity and exposure to trichloroethylene (Abstract). *Arb. Hälsa*, **29**, 126
- Axelsson, O., Seldén, A., Andersson, K. & Hogstedt, C. (1994) Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J. occup. Med.*, **36**, 556-562
- Baden, J.M. & Simmon, V.F. (1980) Mutagenic effects of inhalational anesthetics. *Mutat. Res.*, **75**, 169-189
- Baden, J.M., Kelley, M., Mazze, R.I. & Simmon, V.F. (1979) Mutagenicity of inhalation anaesthetics: trichloroethylene, divinyl ether, nitrous oxide and cyclopropane. *Br. J. Anaesthesiol.*, **51**, 417-421
- Bai, C.-L. & Stacey, N.H. (1993) Mechanism of trichloroethylene-induced elevation of individual serum bile acids. II. In vitro and in vivo interference by trichloroethylene with bile acid transport in isolated rat hepatocytes. *Toxicol. appl. Pharmacol.*, **121**, 296-302
- Banerjee, S. & Van Duuren, B.L. (1978) Covalent binding of the carcinogen trichloroethylene to hepatic microsomal proteins and to exogenous DNA *in vitro*. *Cancer Res.*, **38**, 776-780
- Barret, L., Faure, J. & Danel, V. (1984) Epidemiological study of cancer in a community of workers occupationally exposed to trichloroethylene and cutting oils (Abstract no. 34). Stockholm, Association Européenne des Centres Anti-poison
- Bartsch, H., Malaveille, C., Barbin, A. & Planche, G. (1979) Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. *Arch. Toxicol.*, **41**, 249-277
- Bauer, U. (1981a) Human exposure to environmental chemicals. Investigations on volatile organic halogenated compounds in water, air, food, and human tissues. I. Properties, distribution and effects of volatile organic halogenated compounds. Analytical methods. *Zbl. Bakt. Hyg. I. Abt. B*, **174**, 15-56 (in German)
- Bauer, U. (1981b) Human exposure to environmental chemicals. Investigations on volatile organic halogenated compounds in water, air, food, and human tissues. IV. Calculation of human exposure to organic halogenated compounds from the environment. *Zbl. Bakt. Hyg. I. Abt. B*, **174**, 556-583 (in German)
- Belanger, P.L. & Coye, M.J. (1984) *Basic Tool and Supply*, Oakland, CA (Health Hazard Evaluation Report No. 84-196-1527), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Bergman, K. (1983a) Application and results of whole-body autoradiography in distribution studies of organic solvents. *Arch. Toxicol.*, **12**, 59-118
- Bergman, K. (1983b) Interactions of trichloroethylene with DNA *in vitro* and with RNA and DNA of various mouse tissues *in vivo*. *Arch. Toxicol.*, **54**, 181-193
- Besemer, A.C., Eggels, P.G., van Esch, G.J., Hollander, J.C.T., Huldy, H.J. & Maas, R.J.M. (1984) *Criteria Document over Trichloetheen* [Criteria for Trichloroethylene] (Publication No. 33), The Hague, Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer
- Bhakuni, V. & Roy, R. (1994) Interaction of trichloroethylene with phosphatidylcholine and its localization in the phosphatidylcholine vesicles: a <sup>1</sup>H-NMR study. *Biochem. Pharmacol.*, **47**, 1461-1464
- Bhattacharya, R.K. & Schulze, M.O. (1972) Properties of DNA treated with S-(1,2-dichlorovinyl)-L-cysteine and a lyase. *Arch. Biochem. Biophys.*, **153**, 105-115

- Birner, G., Vamvakas, S., Dekant, W. & Henschler, D. (1993) Nephrotoxic and genotoxic *N*-acetyl-S-dichlorovinyl-L-cysteine is a urinary metabolite after occupational 1,1,2-trichloroethene exposure in humans: implications for the risk of trichloroethene exposure. *Environ. Health Perspectives*, **99**, 281-284
- Blair, A. (1980) Mortality among workers in the metal polishing and plating industry, 1951-1969. *J. occup. Med.*, **22**, 158-162
- Blair, A. & Mason, T.J. (1980) Cancer mortality in United States counties with metal electroplating industries. *Arch. environ. Health*, **35**, 92-94
- Bloom, T.F., Kramkowski, R.S. & Cromer, J.W. (1974) *Essex Wire Corp., Kenton, OH* (Health Hazard Evaluation Determination Report No. 73-151-141), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Bogen, K.T., Hall, L.C., Perry, L., Fish, R., McKone, T.E., Dowd, P., Patton, S.E. & Mallon, B. (1988) *Health Risk Assessment of Trichloroethylene (TCE) in California Drinking Water* (DE88-005364), Livermore, CA, Lawrence Livermore National Laboratory, Environmental Sciences Division
- Bonse, G. & Henschler, D. (1976) Chemical reactivity, biotransformation, and toxicity of polychlorinated aliphatic compounds. *Crit. Rev. Toxicol.*, **4**, 395-409
- Bonse, G., Urban, T., Reichert, D. & Henschler, D. (1975) Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. *Biochem. Pharmacol.*, **24**, 1829-1834
- Brandt-Rauf, P.W. & Hathaway, J.A. (1986) Biliary tract cancer in the chemical industry: a proportional mortality study. *Br. J. ind. Med.*, **43**, 716-717
- Brandt-Rauf, P.W., Pincus, M.R. & Adelson, S. (1982) Cancer of the gallbladder: a review of forty-three cases. *Hum. Pathol.*, **13**, 48-53
- Brandt-Rauf, P.W., Pincus, M.R. & Adelson, S. (1986) Carcinoma of the ampulla of Vater. *Dig. Dis.*, **4**, 43-48
- Brodzinsky, R. & Singh, H.B. (1983) *Volatile Organic Chemicals in the Atmosphere: An Assessment of Available Data (Final Report)*, Menlo Park, CA, SRI International, pp. 107-108
- Bronzetti, G., Zeiger, E. & Frezza, D. (1978) Genetic activity of trichloroethylene in yeast. *J. environ. Pathol. Toxicol.*, **1**, 411-418
- Bruckner, J.V., Davis, B.D. & Blancato, J.N. (1989) Metabolism, toxicity, and carcinogenicity of trichloroethylene. *Crit. Rev. Toxicol.*, **20**, 31-50
- Buben, J.A. & O'Flaherty, E.J. (1985) Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. *Toxicol. appl. Pharmacol.*, **78**, 105-122
- Budavari, S., ed. (1989) *The Merck Index*, 11th Ed., Rahway, NJ, Merck & Co., pp. 1516-1517
- Burgess, W.A. (1981) *Recognition of Health Hazards in Industry. A Review of Materials and Processes*, New York, John Wiley & Sons, pp. 20-32
- Burmaster, D.E. (1982) The new pollution—groundwater contamination. *Environment*, **24**, 6-36
- Burroughs, G.E. (1980) *Protective Coatings Corporation, Fort Wayne, IN* (Health Hazard Evaluation Report No. 79-96-729), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Burroughs, G.E. & Moody, P.L. (1982) *Industrial Plastics, Valley City, OH* (Health Hazard Evaluation Report No. 81-029-1088), Cincinnati, OH, United States National Institute for Occupational Safety and Health

- Butler, T.C. (1949) Metabolic transformations of trichloroethylene. *J. Pharmacol. exp. Ther.*, **97**, 84-92
- Byington, K.H. & Leibman, K.C. (1965) Metabolism of trichloroethylene in liver microsomes. II. Identification of the reaction product as chloral hydrate. *Mol. Pharmacol.*, **1**, 247-254
- Callen, D.F., Wolf, C.R. & Philpot, R.M. (1980) Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in *Saccharomyces cerevisiae*. *Mutat. Res.*, **77**, 55-63
- Candura, S.M. & Faustman, E.M. (1991) Trichloroethylene: toxicology and health hazards. *Med. Lav.*, **13**, 17-25
- Caspary, W.J., Langenbach, R., Penman, B.W., Crespi, C., Myhr, B.C. & Mitchell, A.D. (1988) The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells. *Mutat. Res.*, **196**, 61-81
- Chakrabarti, S.K. & Tuchweber, B. (1988) Studies of acute nephrotoxic potential of trichloroethylene in Fischer 344 rats. *J. Toxicol. environ. Health*, **23**, 147-158
- Chemical Information Services, Ltd (1994) *Directory of World Chemical Producers 1995/96 Standard Edition*, Dallas, TX, p. 678
- Christensen, J.M. & Rasmussen, K. (1990) Exposure of Danish workers to trichloroethylene 1947-1987. *Ugeskr. Laeg.*, **152**, 464-466 (in Danish)
- Cohn, P., Klotz, J., Bove, F., Berkowitz, M. & Fagliano, J. (1994) Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma. *Environ. Health Perspectives*, **102**, 556-561
- Cole, W.J., Mitchell, R.G. & Salamonsen, R.F. (1975) Isolation, characterization and quantitation of chloral hydrate as a transient metabolite of trichloroethylene in man using electron capture gas chromatography and mass fragmentography. *J. Pharm. Pharmacol.*, **27**, 167-171
- Comba, M.E., Palabrica, V.S. & Kaiser, K.L.E. (1994) Volatile halocarbons as tracers of pulp mill effluent plumes. *Environ. Toxicol. Chem.*, **13**, 1065-1074
- Commandeur, J.N.M. & Vermeulen, N.P.E. (1990) Identification of *N*-acetyl(2,2-dichlorovinyl)- and *N*-acetyl(1,2-dichlorovinyl)-L-cysteine as two regioisomeric mercapturic acids of trichloroethylene in the rat. *Chem. Res. Toxicol.*, **3**, 212-218
- Cook, W.A. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 89, 111, 126, 155, 220
- Cosby, N.C. & Dukelow, W.R. (1992) Toxicology of maternally ingested trichloroethylene (TCE) on embryonal and fetal development in mice and of TCE metabolites on in vitro fertilization. *Fundam. appl. Toxicol.*, **19**, 268-274
- Costa, A.K., Katz, I.D. & Ivanetich, K.M. (1980) Trichloroethylene: its interaction with hepatic microsomal cytochrome P-450 in vitro. *Biochem. Pharmacol.*, **29**, 433-439
- Crebelli, R. & Carere, A. (1989) Genetic toxicology of 1,1,2-trichloroethylene. *Mutat. Res.*, **221**, 11-37
- Crebelli, R., Bignami, M., Conti, L. & Carere, A. (1982) Mutagenicity of trichloroethylene in *Salmonella typhimurium* TA100. *Ann. Ist. super. Sanità*, **18**, 117-122
- Crebelli, R., Conti, G., Conti, L. & Carere, A. (1985) Mutagenicity of trichloroethylene, trichloroethanol and chloral hydrate in *Aspergillus nidulans*. *Mutat. Res.*, **155**, 105-111
- Daft, J.L. (1989) Determination of fumigants and related chemicals in fatty and non-fatty foods. *J. agric. Food Chem.*, **37**, 560-564
- Dallas, C.E., Gallo, J.M., Ramanathan, R., Muralidhara, S. & Bruckner, J.V. (1991) Physiological pharmacokinetic modeling of inhaled trichloroethylene in rats. *Toxicol. appl. Pharmacol.*, **110**, 303-314

- Daniel, J.W. (1963) The metabolism of <sup>36</sup>Cl-labelled trichloroethylene and tetrachloroethylene in the rat. *Biochem. Pharmacol.*, **12**, 795–802
- Davidson, I.W.F. & Beliles, R.P. (1991) Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab. Rev.*, **23**, 493–599
- Dawson, B.V., Johnson, P.D., Goldberg, S.J. & Ulreich, J.B. (1993) Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. *J. Am. Coll. Cardiol.*, **21**, 1466–1472
- DeAngelo, A.B., Daniel, F.B., McMillan, L., Wernsing, P. & Savage, R.E., Jr (1989) Species and strain sensitivity to the induction of peroxisome proliferation by chloroacetic acids. *Toxicol. appl. Pharmacol.*, **101**, 285–298
- Dees, C. & Travis, C. (1993) The mitogenic potential of trichloroethylene in B6C3F1 mice. *Toxicol. Lett.*, **69**, 129–137
- Dekant, W. (1986) Metabolic conversions of tri- and tetrachloroethylene: formation and deactivation of genotoxic intermediates. In: Chambers, P.L., Gehring, P. & Sakai, F., eds, *New Concepts and Developments in Toxicology*, Amsterdam, Elsevier Science Publishers, pp. 211–221
- Dekant, W., Metzler, M. & Henschler, D. (1984) Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. *Biochem. Pharmacol.*, **33**, 2021–2027
- Dekant, W., Metzler, M. & Henschler, D. (1986a) Identification of *S*-1,2-dichlorovinyl-*N*-acetylcysteine as a urinary metabolite of trichloroethylene: a possible explanation for its nephrocarcinogenicity in male rats. *Biochem. Pharmacol.*, **35**, 2455–2458
- Dekant, W., Schulz, A., Metzler, M. & Henschler, D. (1986b) Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. *Xenobiotica*, **16**, 143–152
- Dekant, W., Vamvakas, S., Berthold, K., Schmidt, S., Wild, D. & Henschler, D. (1986c) Bacterial  $\beta$ -lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. *Chem.-biol. Interactions*, **60**, 31–45
- Dekant, W., Berthold, K., Vamvakas, S., Henschler, D. & Anders, M.W. (1988) Thioacylating intermediates as metabolites of *S*-(1,2-dichlorovinyl)-L-cysteine and *S*-(1,2,2-trichlorovinyl)-L-cysteine formed by cysteine conjugate  $\beta$ -lyase. *Chem. Res. Toxicol.*, **1**, 175–178
- Dekant, W., Koob, M. & Henschler, D. (1990) Metabolism of trichloroethene—in vivo and in vitro evidence for activation by glutathione conjugation. *Chem.-Biol. Interactions*, **73**, 89–101
- DeMarini, D.M., Perry, E. & Shelton, M.L. (1994) Dichloroacetic acid and related compounds: induction of prophage in *E. coli* and mutagenicity and mutation spectra in *Salmonella* TA100. *Mutagenesis*, **9**, 429–437
- Deutsche Forschungsgemeinschaft (1993) *MAK- und BAT Werte Liste 1993* [MAK and BAT value list 1993] (Report No. 29), Weinheim, VCH Verlagsgesellschaft, pp. 75, 129
- Dickson, A.G. & Riley, J.P. (1976) The distribution of short-chain halogenated aliphatic hydrocarbons in some marine organisms. *Mar. Pollut. Bull.*, **7**, 167–169
- DiRenzo, A.B., Gandolfi, A.J. & Sipes, I.G. (1982) Microsomal bioactivation and covalent binding of aliphatic halides to DNA. *Toxicol. Lett.*, **11**, 243–252
- Doolittle, D.J., Muller, G. & Scribner, H.E. (1987) The *in vivo*–*in vitro* hepatocyte assay for assessing DNA repair and DNA replication: studies in the CD-1 mouse. *Food chem. Toxicol.*, **25**, 399–405
- Dorfmueller, M.A., Henne, S.P., York, R.G., Bornschein, R.L. & Manson, J.M. (1979) Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. *Toxicology*, **14**, 153–166

- Droz, P.O. & Fernández, J.G. (1978) Trichloroethylene exposure. Biological monitoring by breath and urine analysis. *Br. J. ind. Med.*, **35**, 35-42
- Dubrow, R. & Gute, D.M. (1987) Cause-specific mortality among Rhode Island jewelry workers. *Am. J. ind. Med.*, **12**, 579-593
- Duprat, P. & Gradiski, D. (1980) Cytogenetic effect of trichloroethylene in the mouse as evaluated by the micronucleus test. *IRCS med. Sci.*, **8**, 182
- von Düszein, J., Lahl, U., Bätjer, K., Cetinkaya, M., Stachel, B. & Thiemann, W. (1982) Occurrence of volatile halogenated hydrocarbons in air, water and food in East Germany. *Dtsch. Lebensm. Rundsch.*, **78**, 253-356 (in German)
- Elcombe, C.R. (1985) Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: a biochemical human hazard assessment. *Arch. Toxicol.*, **Suppl. 8**, 6-17
- Elcombe, C.R., Rose, M.S. & Pratt, I.S. (1985) Biochemical, histological, and ultrastructural changes in rat and mouse liver following the administration of trichloroethylene: possible relevance to species differences in hepatocarcinogenicity. *Toxicol. appl. Pharmacol.*, **79**, 365-376
- Eller, P.M., ed. (1994) *NIOSH Manual of Analytical Methods*, 4th Ed., Vol. 3 (DHHS (NIOSH) Publ. No. 94-113), Washington DC, United States Government Printing Office, Methods 1022 and 3701
- Elmore, E. & Fitzgerald, M.P. (1990) Evaluation of the bioluminescence assays as screens for genotoxic chemicals. *Progr. clin. biol. Res.*, **340D**, 379-387
- Entz, R.C. & Diachenko, G.W. (1988) Residues of volatile halocarbons in margarines. *Food Addit. Contam.*, **5**, 267-276
- Ertle, T., Henschler, D., Müller, G. & Spassowski, M. (1972) Metabolism of trichloroethylene in man. I. The significance of trichloroethanol in long-term exposure conditions. *Arch. Toxicol.*, **29**, 171-188
- European Centre for Ecotoxicology and Toxicology of Chemicals (1994) *Trichloroethylene: Assessment of Human Carcinogenic Hazard* (ECETOC Technical Report No. 60), Brussels
- Fabricant, J.D. & Chalmers, J.H., Jr (1980) Evidence of the mutagenicity of ethylene dichloride and structurally related compounds. In: Ames, B., Infante, P. & Reitz, R., eds, *Ethylene Dichloride: A Potential Health Risk* (Banbury Report 5), Cold Spring Harbor, NY, CSH Press, pp. 309-329
- Fagliano, J., Berry, M., Bove, F. & Burke, T. (1990) Drinking water contamination and the incidence of leukemia: an ecologic study. *Am. J. public Health*, **80**, 1209-1212
- Fahrig, R. (1977) The mammalian spot test (Fallfleckentest) with mice. *Arch. Toxicol.*, **38**, 87-98
- Fazio, T. (1990) Food additives: direct. In: Helrich, K., ed., *Official Methods of Analysis of the Association of Official Analytical Chemists*, 15th Ed., Vol. 2, Arlington, VA, Association of Official Analytical Chemists, p. 1175
- Fielding, M., Gibson, T.M. & James, H.A. (1981) Levels of trichloroethylene, tetrachloroethylene and p-dichlorobenzene in groundwaters. *Environ. Technol. Lett.*, **2**, 545-550
- Filser, J.G. & Bolt, H.M. (1979) Pharmacokinetics of halogenated ethylenes in rats. *Arch. Toxicol.*, **42**, 123-136
- Fishbein, L. (1976) Industrial mutagens and potential mutagens. I. Halogenated aliphatic derivatives. *Mutat. Res.*, **32**, 267-308
- Fisher, J.W., Whittaker, T.A., Taylor, D.H., Clewell, H.J., III & Andersen, M.E. (1989) Physiologically based pharmacokinetic modeling of the pregnant rat: a multiroute exposure model for trichloroethylene and its metabolite, trichloroacetic acid. *Toxicol. appl. Pharmacol.*, **99**, 395-414

- Fisher, J.W., Gargas, M.L., Allen, B.C. & Andersen, M.E. (1991) Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse. *Toxicol. appl. Pharmacol.*, **109**, 183-195
- Flood, T.J., Aickin, M., Lucier, J.L. & Petersen, N.J. (1990) *Incidence Study of Childhood Cancer in Maricopa County: 1965-1986* (Final Report), Phoenix, Arizona Department of Health Services
- Forkert, P.G. & Birch, D.W. (1989) Pulmonary toxicity of trichloroethylene in mice. Covalent binding and morphological manifestations. *Drug Metab. Disposition*, **17**, 106-113
- Foureman, P., Mason, J.M., Valencia, R. & Zimmering, S. (1994) Chemical mutagenesis testing in *Drosophila*: IX. Results of 50 coded compounds tested for the National Toxicology Program. *Environ. mol. Mutag.*, **23**, 51-63
- Fredriksson, M., Bengtsson, N.-O., Hardell, L. & Axelson, O. (1989) Colon cancer, physical activity, and occupational exposures. A case-control study. *Cancer*, **63**, 1838-1842
- Fukuda, K., Takemoto, K. & Tsuruta, H. (1983) Inhalation carcinogenicity of trichloroethylene in mice and rats. *Ind. Health*, **21**, 243-254
- Fytianos, K., Vasilikiotis, G. & Weil, L. (1985) Identification and determination of some trace organic compounds in coastal seawater of northern Greece. *Bull. environ. Contam. Toxicol.*, **34**, 390-395
- Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B. & Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ. mol. Mutag.*, **10** (Suppl. 10), 1-175
- Garabrant, D.H., Held, J., Langholz, B. & Bernstein, L. (1988) Mortality of aircraft manufacturing workers in southern California. *Am. J. ind. Med.*, **13**, 683-693
- Ghantous, H., Danielsson, B.R.G., Dencker, L., Gorczak, J. & Vesterberg, O. (1986) Trichloroacetic acid accumulates in murine amniotic fluid after tri- and tetrachloroethylene inhalation. *Acta pharmacol. toxicol.*, **58**, 105-114
- Gilles, D. & Philbin, E. (1976) *TRW Inc., Philadelphia, PA* (Health Hazard Evaluation Determination Report No. 76-61-337), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Goldberg, S.J., Lebowitz, M.D., Graver, E.J. & Hicks, S. (1990) An association of human congenital cardiac malformations and drinking water contaminants. *J. Am. Coll. Cardiol.*, **16**, 155-164
- Goldsworthy, T.L. & Popp, J.A. (1987) Chlorinated hydrocarbon-induced peroxisomal enzyme activity in relation to species and organ carcinogenicity. *Toxicol. appl. Pharmacol.*, **88**, 225-233
- Gorman, R., Rinsky, R., Stein, G. & Anderson, K. (1984) *Pratt & Whitney Aircraft, West Palm Beach, FL* (HETA Report No. 82-075-1545), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Gossett, R.W., Brown, D.A. & Young, D.R. (1983) Predicting the bioaccumulation of organic compounds in marine organisms using octanol/water partition coefficients. *Mar. Pollut. Bull.*, **14**, 387-392
- Grandjean, E., Münchinger, R., Turrian, V., Haas, P.A., Knoepfel, H.-K. & Rosenmund, H. (1955) Investigations into the effects of exposure to trichloroethylene in mechanical engineering. *Br. J. ind. Med.*, **12**, 131-142
- Green, T. & Odum, J. (1985) Structure/activity studies of the nephrotoxic and mutagenic action of cysteine conjugates of chloro- and fluoroalkenes. *Chem.-biol. Interactions*, **54**, 15-31

- Green, T. & Prout, M.S. (1985) Species differences in response to trichloroethylene. II. Biotransformation in rats and mice. *Toxicol. appl. Pharmacol.*, **79**, 401-411
- Greenberg, A.E., Clesceri, L.S. & Eaton, A.D., eds (1992) *Standard Methods for the Examination of Water and Wastewater*, 18th Ed., Washington DC, American Public Health Association/American Water Works Association/Water Environment Federation, pp. 6-17-6-36, 6-42-6-57
- Greim, H., Bonse, G., Radwan, Z., Reichert, D. & Henschler, D. (1975) Mutagenicity *in vitro* and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. *Biochem. Pharmacol.*, **24**, 2013-2017
- Gu, Z.W., Sele, B., Chmara, D., Jalbert, P., Vincent, M., Vincent, F., Marka, C. & Faure, J. (1981) Effects of trichloroethylene and some of its metabolites on the rate of sister chromatid exchange. Study *in vivo* and *in vitro* on human lymphocytes. *Ann. Génét.*, **24**, 105-106 (in French)
- Guengerich, F.R., Kim, D.-H. & Iwasaki, M. (1991) Role of human cytochrome P-450 II E1 in the oxidation of many low molecular weight cancer suspects. *Chem. Res. Toxicol.*, **4**, 168-179
- Gunter, B.J. (1977) *FMC Corp., Bloomfield, CO* (Health Hazard Evaluation Determination Report No. 76-101-376), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Hajimiragha, H., Ewers, U., Jansen-Rosseck, R. & Brockhaus, A. (1986) Human exposure to volatile halogenated hydrocarbons from the general environment. *Int. Arch. occup. environ. Health*, **58**, 141-150
- Hamdan, H. & Stacey, N.H. (1993) Mechanism of trichloroethylene-induced elevation of individual serum bile acids. 1. Correlation of trichloroethylene concentrations to bile acids in rat serum. *Toxicol. appl. Pharmacol.*, **121**, 291-295
- Hansch, C., Leo, A. & Hoekman, D.H. (1995) *Exploring QSAR*, Washington, DC, American Chemical Society
- Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br. J. Cancer*, **43**, 169-176
- Hardell, L., Bengtsson, N.O., Jonsson, U., Eriksson, S. & Larsson, L.G. (1984) Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria—an epidemiological investigation. *Br. J. Cancer*, **50**, 389-397
- Hardie, D.W.F. (1964) Chlorocarbons and chlorohydrocarbons. Trichloroethylene. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 2nd Ed., Vol. 5, New York, John Wiley & Sons, pp. 183-195
- Hardin, B.D., Bond, G.P., Sikov, M.R., Andrew, F.D., Beliles, R.P. & Niemeier, R.W. (1981) Testing of selected workplace chemicals for teratogenic potential. *Scand. J. Work Environ. Health*, **7** (Suppl. 4), 66-75
- Hargarten, J.J., Hetrick, G.H. & Fleming, A.J. (1961) Industrial safety experience with trichloroethylene: its use as a vapor degreasing solvent, 1948-1957. *Arch. environ. Health*, **3**, 461-467
- Hathway, D.E. (1980) Consideration of the evidence for mechanisms of 1,1,2-trichloroethylene metabolism, including new identification of its dichloroacetic acid and trichloroacetic acid metabolites in mice. *Cancer Lett.*, **8**, 263-269
- Healy, T.E.J. & Wilcox, A. (1978) Chronic exposures of rats to inhalational anaesthetic agents. *J. Physiol.*, **276**, 24P-25P
- Heikes, D.L. (1987) Purge and trap method for determination of volatile halocarbons and carbon disulfide in table-ready foods. *J. Assoc. off. anal. Chem.*, **70**, 215-226

- Heikes, D.L. & Hopper, M.L. (1986) Purge and trap method for determination of fumigants in whole grains, milled grain products, and intermediate grain-based foods. *J. Assoc. off. anal. Chem.*, **69**, 990-998
- Heineman, E.F., Cocco, P., Gómez, M.R., Dosemeci, M., Stewart, P.A., Hayes, R.B., Hoar Zahm, S., Thomas, T.L. & Blair, A. (1994) Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. *Am. J. ind. Med.*, **26**, 155-169
- Helliwell, P.J. & Hutton, A.M. (1949) Analgesia in obstetrics. *Anaesthesia*, **4**, 18-21
- Helliwell, P.J. & Hutton, A.M. (1950) Trichloroethylene anaesthesia. 1. Distribution in the foetal and maternal circulation of pregnant sheep and goats. *Anaesthesia*, **5**, 4-13
- Hellmann, H. (1984) Volatile organochlorine hydrocarbons in water in East Germany. *Haustech. Bauphys. Umwelttech. Gesund. Ing.*, **105**, 269-278 (in German)
- Henschler, D. (1977) Metabolism and mutagenicity of halogenated olefins—a comparison of structure and activity. *Environ. Health Perspectives*, **21**, 61-64
- Henschler, D. (1987) Mechanisms of genotoxicity of chlorinated aliphatic hydrocarbons. In: De Matteis, F. & Lock, E.A., eds, *Selectivity and Molecular Mechanisms of Toxicity*, New York, MacMillan, pp.153-181
- Henschler, D. & Bonse, G. (1977) Metabolic activation of chlorinated ethylenes: dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides. *Arch. Toxicol.*, **39**, 7-12
- Henschler, D., Eder, E., Neudecker, T. & Metzler, M. (1977) Carcinogenicity of trichloroethylene: fact or artifact. *Arch. Toxicol.*, **37**, 233-236
- Henschler, D., Romen, W., Elsässer, H.M., Reichert, D., Eder, E. & Radwan, Z. (1980) Carcinogenicity study of trichloroethylene by longterm inhalation in three animal species. *Arch. Toxicol.*, **43**, 237-248
- Henschler, D., Elsässer, H., Romen, W. & Eder, E. (1984) Carcinogenicity study of trichloroethylene, with and without epoxide stabilizers, in mice. *J. Cancer Res. clin. Oncol.*, **107**, 149-156
- Henschler, D., Vamvakas, S., Lammert, M., Dekant, W., Kraus, B., Thomas, B. & Ulm, K. (1995) Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethylene. *Arch. Toxicol.* (in press)
- Herbert, P., Charbonnier, P., Rivolta, L., Servais, M., Van Mensch, F. & Campbell, I. (1986) The occurrence of chlorinated solvents in the environment. *Chem. Ind.*, **December**, 861-869
- Hernberg, S., Korkala, M.-L., Asikainen, U. & Riala, R. (1984) Primary liver cancer and exposure to solvents. *Int. Arch. occup. environ. Health*, **54**, 147-153
- Hernberg, S., Kauppinen, T., Riala, R., Korkala, M.-L. & Asikainen, U. (1988) Increased risk for primary liver cancer among women exposed to solvents. *Scand. J. Work Environ. Health*, **14**, 356-365
- Herren-Freund, S.L., Pereira, M.A., Khoury, M.D. & Olson, G. (1987) The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. *Toxicol. appl. Pharmacol.*, **90**, 183-189
- Hirata, T., Nakasugi, O., Yoshioka, M. & Sumi, K. (1992) Groundwater pollution by volatile organochlorines in Japan and related phenomena in the subsurface environment. *Water Sci. Technol.*, **2**, 9-16

- Hrelia, P., Maffei, F., Vivagni, F., Flori, P., Stanzani, R. & Cantelli Forti, G. (1995) Interactive effects between trichloroethylene and pesticides at metabolic and genetic level in mice. *Environ. Health Perspectives* (in press)
- von der Hude, W., Behm, C., Gürtler, R. & Basler, A. (1988) Evaluation of SOS chromotest. *Mutat. Res.*, **203**, 81-94
- IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 20, *Some Halogenated Hydrocarbons*, Lyon, pp. 545-572
- IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 364-366
- IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 99-100
- IARC (1987c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 202-203
- IARC (1987d) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 201
- IARC (1987e) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 143-144
- IARC (1987f) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 152-154
- IARC (1987g) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 62
- IARC (1987h) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 69
- IARC (1987i) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 72
- IARC (1987j) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 72
- IARC (1987k) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, p. 73
- IARC (1987l) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42*, Lyon, pp. 120-122
- IARC (1989a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 199-213
- IARC (1989b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 217-228

- IARC (1989c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 263–287
- IARC (1991) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 52, *Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds*, Lyon, pp. 337–359
- IARC (1994a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 73–159
- IARC (1994b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 181–213
- IARC (1994c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 321–346
- Ikeda, M. (1977) Metabolism of trichloroethylene and tetrachloroethylene in human subjects. *Environ. Health Perspectives*, **21**, 239–245
- Ikeda, M. & Imamura, T. (1973) Biological half-life of trichloroethylene and tetrachloroethylene in human subjects. *Int. Arch. Arbeitsmed.*, **31**, 209–224
- ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 396–397
- Inoue, O., Seiji, K., Kawai, T., Jin, C., Liu, Y.-T., Chen, Z., Cai, S.-X., Yin, S.-N., Li, G.-L., Nakatsuka, H., Watanabe, T. & Ikeda, M. (1989) Relationship between vapor exposure and urinary metabolite excretion among workers exposed to trichloroethylene. *Am. J. ind. Med.*, **15**, 103–110
- Isaacson, L.G. & Taylor, D.H. (1989) Maternal exposure to 1,1,2-trichloroethylene affects myelin in the hippocampal formation of the developing rat. *Brain Res.*, **488**, 403–407
- Isacson, P., Bean, J.A., Splinter, R., Olson, D.B. & Kohler, J. (1985) Drinking water and cancer incidence in Iowa. III. Association of cancer with indices of contamination. *Am. J. Epidemiol.*, **121**, 856–869
- Jackson, M.A., Stack, H.F. & Waters, M.D. (1993) The genetic toxicology of putative nongenotoxic carcinogens. *Mutat. Res.*, **296**, 241–277
- Jaffe, D.R., Hassall, C.D., Gandolfi, A.J. & Brendel, K. (1985) Production of DNA single strand breaks in rabbit renal tissue after exposure to 1,2-dichlorovinylcysteine. *Toxicology*, **35**, 25–33
- Jalihal, S.S. & Barlow, A.M. (1984) Leukaemia in dry cleaners (Letter to the Editor). *J. R. Soc. Health*, **104**, 42
- Johnson, P. (1980) *Miami Carey, Inc., Monroe, OH* (Health Hazard Evaluation Report No. 80-48-689), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Kim, C., Manning, R.O., Brown, R.P. & Bruckner, J.V. (1994) A comprehensive evaluation of the vial equilibration method for quantification of the metabolism of volatile organic chemicals. Trichloroethylene. *Drug Metab. Disposition*, **22**, 858–865
- Kimbrough, R.D., Mitchell, F.L. & Houk, V.N. (1985) Trichloroethylene: an update. *J. Toxicol. environ. Health*, **15**, 369–383
- Kimmerle, G. & Eben, A. (1973) Metabolism, excretion and toxicology of trichloroethylene after inhalation. 1. Experimental exposure on rats. *Arch. Toxicol.*, **30**, 115–126
- Kjellstrand, P., Bjerkemo, M., Mortensen, I., Månsson, L., Lanke, J. & Holmquist, B. (1981a) Effects of long-term exposure to trichloroethylene on the behavior of Mongolian gerbils (*Meriones unguiculatus*). *J. Toxicol. environ. Health*, **8**, 787–793

- Kjellstrand, P., Kanje, M., Månsson, L., Bjerkemo, M., Mortensen, I., Lanke, J. & Holmquist, B. (1981b) Trichloroethylene: effects on body and organ weights in mice, rats and gerbils. *Toxicology*, **21**, 105-115
- Kjellstrand, P., Holmquist, B., Alm, P., Kanje, M., Romare, S., Jonsson, I., Månsson, L. & Bjerkemo, M. (1983a) Trichloroethylene: further studies on the effects on body and organ weights and plasma butyrylcholinesterase activity in mice. *Acta pharmacol. toxicol.*, **53**, 375-384
- Kjellstrand, P., Holmquist, B., Mandahl, N. & Bjerkemo, M. (1983b) Effects of continuous trichloroethylene inhalation on different strains of mice. *Acta pharmacol. toxicol.*, **53**, 369-374
- Klaunig, J.E., Ruch, R. & Lin, E.L.C. (1989) Effects of trichloroethylene and its metabolites on rodent hepatocyte intercellular communication. *Toxicol. appl. Pharmacol.*, **99**, 454-465
- Kligerman, A.D., Bryant, M.F., Doerr, C.L., Erexson, G.L., Evansky, P.A., Kwanyuen, P. & McGee, J.K. (1994) Inhalation studies of the genotoxicity of trichloroethylene to rodents. *Mutat. Res.*, **322**, 87-96
- Koch, R., Schlegelmilch, R. & Wolf, H.U. (1988) Genetic effects of chlorinated ethylenes in the yeast *Saccharomyces cerevisiae*. *Mutat. Res.*, **206**, 209-216
- Kominsky, J.R. (1978) *Dana Corp., Tipton, IN* (Health Hazard Evaluation Report No. 76-24-350; US NTIS PB-273716), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Konietzko, H., Haberlandt, W., Heilbronner, H., Reill, G. & Weichardt, H. (1978) Chromosome studies on trichloroethylene workers. *Arch. Toxicol.*, **40**, 201-206 (in German)
- Krain, L.S. (1972) Gallbladder and extrahepatic bile duct carcinoma. Analysis of 1,808 cases. *Geriatrics*, **27**, 111-117
- Kringstad, K.P., Ljungquist, P.O., de Sousa, F. & Strömberg, L.M. (1981) Identification and mutagenic properties of some chlorinated aliphatic compounds in the spent liquor from kraft pulp chlorination. *Environ. Sci. Technol.*, **15**, 562-566
- Kromhout, H., Swuste, P. & Boleij, J.S.M. (1994) Empirical modelling of chemical exposure in the rubber-manufacturing industry. *Ann. occup. Hyg.*, **38**, 3-22
- Kronoveter, K.J. & Boiano, J.L. (1984) *Charlies' Taxidermy and Gifts, Fleetwood, PA* (Health Hazard Evaluation Report No. 83-276-1499), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Lagakos, S.W., Wessen, B.J. & Zelen, M. (1986) An analysis of contaminated well water and health effects in Woburn, Massachusetts. *J. Am. stat. Assoc.*, **81**, 583-596
- Land, P.C., Owen, E.L. & Linde, H.W. (1981) Morphologic changes in mouse spermatozoa after exposure to inhalational anesthetics during early spermatogenesis. *Anesthesiology*, **54**, 53-56
- Landrigan, P.J., Stein, G.F., Kominsky, J.R., Ruhe, R.L. & Watanabe, A.S. (1987) Common-source community and industrial exposure to trichloroethylene. *Arch. environ. Health*, **42**, 327-332
- Lanham, S. (1970) Studies on placental transfer. *Ind. Med.*, **39**, 46-49
- Larson, J.L. & Bull, R.J. (1992a) Species differences in the metabolism of trichloroethylene to the carcinogenic metabolites trichloroacetate and dichloroacetate. *Toxicol. appl. Pharmacol.*, **115**, 278-285
- Larson, J.L. & Bull, R.J. (1992b) Metabolism and lipoperoxidative activity of trichloroacetate and dichloroacetate in rats and mice. *Toxicol. appl. Pharmacol.*, **115**, 268-277
- Lee, S. & Parkinson, D. (1982) *Rola-Esmark Co., Dubois, PA* (Health Hazard Evaluation Report No. 80-168-1204), Cincinnati, OH, United States National Institute for Occupational Safety and Health

- Leibman, K.C. (1968) On the metabolism of trichloroethylene (Letter to the Editor). *Anesthesiology*, **29**, 1066–1067
- Leibman, K.C. & McAllister, W.J., Jr (1967) Metabolism of trichloroethylene in liver microsomes. III. Induction of the enzymic activity and its effect on excretion of metabolites. *J. Pharmacol. exp. Ther.*, **157**, 574–580
- Leong, B.K.J., Schwetz, B.A. & Gehring, P.J. (1975) Embryo- and fetotoxicity of inhaled trichloroethylene, perchloroethylene, methylchloroform, and methylene chloride in mice and rats (Abstract No. 34). *Toxicol. appl. Pharmacol.*, **33**, 136
- Lesage, S., Jackson, R.E., Priddle, M.W. & Reiemann, P. (1990) Occurrence and fate of organic solvent residues in anoxic ground-water at the Gloucester landfill, Canada. *Environ. Sci. Technol.*, **24**, 559–566
- Lide, D.R., ed. (1993) *CRC Handbook of Chemistry and Physics*, 74th Ed., Boca Raton, FL, CRC Press, pp. 3–242, D-197
- Liebler, D.C. & Guengerich, F.P. (1983) Olefin oxidation by cytochrome P-450: evidence for group migration in catalytic intermediates formed with vinylidene chloride and *trans*-1-phenyl-1-butene. *Biochemistry*, **22**, 5482–5489
- Ligocki, M.P., Leuenberger, C. & Pankow, J.F. (1985) Trace organic compounds in rain—II. Gas scavenging of neutral organic compounds. *Atmos. Environ.*, **19**, 1609–1617
- Lillian, D., Singh, H.B., Appleby, A., Lobban, L., Arnts, R., Gumpert, R., Hague, R., Toomey, J., Kazazis, J., Antell, M., Hansen, D. & Scott, B. (1975) Atmosphere fates of halogenated compounds. *Environ. Sci. Technol.*, **9**, 1042–1048
- Linak, E., Leder, A. & Yoshida, Y. (1992) C<sub>2</sub> Chlorinated solvents. In: *Chemical Economics Handbook*, Menlo Park, CA, SRI International, pp. 632.3000–632.3001
- Lindbohm, M.-L., Taskinen, H., Sallmén, M. & Hemminki, K. (1990) Spontaneous abortions among women exposed to organic solvents. *Am. J. ind. Med.*, **17**, 449–463
- Loprieno, N. & Abbondandolo, A. (1980) Comparative mutagenic evaluation of some industrial compounds. In: Norpoth, K.H. & Garner, R.C., eds, *Short-term Test Systems for Detecting Carcinogens*, Berlin, Springer-Verlag, pp. 333–356
- Love, J.R. & Kern, M. (1981) *Metro Bus Maintenance Shop, Washington, DC* (Health Hazard Evaluation Report No. 81-065-938), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Lovelock, J.E. (1974) Atmospheric halocarbons and stratospheric ozone. *Nature*, **252**, 292–294
- Lowengart, R.A., Peters, J.M., Cicioni, C., Buckley, J., Bernstein, L., Preston-Martin, S. & Rappaport, E. (1987) Childhood leukemia and parents' occupational and home exposures. *J. natl Cancer Inst.*, **79**, 39–46
- Málek, B., Krcmářová, B. & Rodová, O. (1979) An epidemiological study of hepatic tumour incidence in subjects working with trichloroethylene. II. Negative result of retrospective investigations in dry cleaners. *Prac. Léč*, **31**, 124–126 (in Czech)
- Malker, H.S.R., McLaughlin, J.K., Malker, B.K., Stone, B.J., Weiner, J.A., Ericsson, J.L.E. & Blot, W.J. (1986) Biliary tract cancer and occupation in Sweden. *Br. J. ind. Med.*, **43**, 257–262
- Maltoni, C., Lefemine, G. & Cotti, G. (1986) Experimental research on trichloroethylene carcinogenesis. In: Maltoni, C. & Mehlman, M.A., eds, *Archives of Research on Industrial Carcinogenesis*, Vol. V, Princeton, NJ, Princeton Scientific Publishing Co., pp. 1–393

- Maltoni, C., Lefemine, G., Cotti, G. & Perino, G. (1988) Long-term carcinogenic bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. *Ann. N.Y. Acad. Sci.*, **534**, 316-351
- Manson, J.M., Murphy, M., Richdale, N. & Smith, M.K. (1984) Effects of oral exposure to trichloroethylene on female reproductive function. *Toxicology*, **32**, 229-242
- Mazzullo, M., Bartoli, S., Bonora, B., Colacci, A., Lattanzi, G., Niero, A., Silingardi, P. & Grilli, S. (1992) In vivo and in vitro interaction of trichloroethylene with macromolecules from various organs of rat and mouse. *Res. Commun. chem. Pathol. Pharmacol.*, **76**, 192-208
- McCarthy, T.B. & Jones, R.D. (1983) Industrial gassing poisonings due to trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane, 1961-80. *Br. J. ind. Med.*, **40**, 450-455
- McConnell, G., Ferguson, D.M. & Pearson, C.R. (1975) Chlorinated hydrocarbons and the environment. *Endeavor*, **34**, 13-18
- McGregor, D.B., Reynolds, D.M. & Zeiger, E. (1989) Conditions affecting the mutagenicity of trichloroethylene in *Salmonella*. *Environ. mol. Mutag.*, **13**, 197-202
- McLaren, J., Boulikas, T. & Vamvakas, S. (1994) Induction of poly(ADP-ribosylation) in the kidney after in vivo application of renal carcinogens. *Toxicology*, **88**, 101-112
- Meadows, S.D., Gandolfi, A.J., Nagle, R.B. & Shively, J.W. (1988) Enhancement of DMN-induced kidney tumors by 1,2-dichlorovinylcysteine in Swiss-Webster mice. *Drug chem. Toxicol.*, **11**, 307-318
- Melnick, R.L., Jameson, C.W., Goehl, T.J., Maronpot, R.R., Collins, B.J., Greenwell, A., Harrington, F.W., Wilson, R.E., Tomaszewski, K.E. & Agarwal, D.K. (1987) Application of microencapsulation for toxicology studies. II. Toxicity of microencapsulated trichloroethylene in Fischer 344 rats. *Fundam. appl. Toxicol.*, **8**, 432-442
- Mersch-Sundermann, V., Müller, G. & Hofmeister, A. (1989) Examination of mutagenicity of organic microcontaminations of the environment. IV. Communication: the mutagenicity of halogenated aliphatic hydrocarbons with the SOS-chromotest. *Zbl. Hyg.*, **189**, 266-271 (in German)
- Mertens, J.A. (1993) Chlorocarbons and chlorohydrocarbons. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 6, New York, John Wiley & Sons, pp. 40-50
- Miller, R.E. & Guengerich, F.P. (1982) Oxidation of trichloroethylene by liver microsomal cytochrome P-450: evidence for chlorine migration in a transition state not involving trichloroethylene oxide. *Biochemistry*, **21**, 1090-1097
- Miller, R.E. & Guengerich, F.P. (1983) Metabolism of trichloroethylene in isolated hepatocytes, microsomes and reconstituted enzyme systems containing cytochrome P-450. *Cancer Res.*, **43**, 1145-1152
- Milman, H.A., Story, D.L., Riccio, E.S., Sivak, A., Tu, A.S., Williams, G.M., Tong, C. & Tyson, C.A. (1988) Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. *Ann. N.Y. Acad. Sci.*, **534**, 521-530
- Mirsalis, J.C., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P. & Spalding, J.W. (1989) Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. *Environ. mol. Mutag.*, **14**, 155-164
- Monster, A.C. (1984) Trichloroethylene. In: Aitio, A., Riihimaki, V. & Vainio, H., eds, *Biological Monitoring and Surveillance of Workers Exposed to Chemicals*, Washington, DC, Hemisphere Publishing Corp., pp. 111-130

- Monster, A.C., Boersma, G. & Duba, W.C. (1976) Pharmacokinetics of trichloroethylene in volunteers, influence of workload and exposure concentration. *Int. Arch. occup. environ. Health*, **38**, 87-102
- Monster, A.C., Boersma, G. & Duba, W.C. (1979) Kinetics of trichloroethylene in repeated exposure of volunteers. *Int. Arch. occup. environ. Health*, **42**, 283-292
- Moore, D.R.J., Walker, S.L. & Ansari, R. (1991) *Canadian Water Quality Guidelines for Trichloroethylene* (Scientific Series No. 183), Ottawa, Inland Waters Directorate, Water Quality Branch
- Morse, K.M. & Goldberg, L. (1943) Chlorinated solvent exposures at degreasing operations. *Ind. Med.*, **12**, 706-713
- Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutag.*, **8** (Suppl. 7), 1-119
- Mroueh, U.-M. (1993) *Orgaanisten Liuotteiden Käyttö Suomessa* [Solvent use in Finland], Helsinki, National Board of Waters and the Environment
- Müller, G., Spassovski, M. & Henschler, D. (1972) Trichloroethylene exposure and trichloroethylene metabolites in urine and blood. *Arch. Toxicol.*, **29**, 335-340
- Müller, G., Spassovski, M. & Henschler, D. (1974) Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. *Arch. Toxicol.*, **32**, 283-295
- Müller, W.F., Coulston, F. & Korte, F. (1982) Comparative metabolism of [<sup>14</sup>C]trichloroethylene in chimpanzees, baboons, and rhesus monkeys. *Chemosphere*, **11**, 215-218
- Nagaya, T., Ishikawa, N. & Hata, H. (1989) Sister-chromatid exchanges in lymphocytes of workers exposed to trichloroethylene. *Mutat. Res.*, **222**, 279-282
- Nakajima, T., Wang, R.-S., Murayama, N. & Sato, A. (1990) Three forms of trichloroethylene-metabolizing enzymes in rat liver induced by ethanol, phenobarbital, and 3-methylcholanthrene. *Toxicol. appl. Pharmacol.*, **102**, 546-552
- Nakajima, T., Wang, R.-S., Elovaara, E., Park, S.S., Gelboin, H.V. & Vainio, H. (1992) A comparative study on the contribution of cytochrome P450 isoenzymes to metabolism of benzene, toluene, and trichloroethylene in rat liver. *Biochem. Pharmacol.*, **43**, 251-257
- Nelson, M.A. & Bull, R.J. (1988) Induction of strand breaks in DNA by trichloroethylene and metabolites in rat and mouse liver *in vivo*. *Toxicol. appl. Pharmacol.*, **94**, 45-54
- Noland-Gerbee, E.A., Pfohl, R.J., Taylor, D.H. & Bull, R.J. (1986) 2-Deoxyglucose uptake in developing rat brain upon pre- and postnatal exposure to trichloroethylene. *Neurotoxicology*, **7**, 157-164
- Nomiyama, K. (1971) Estimation of trichloroethylene exposure by biological material. *Int. Arch. Arbeitsmed.*, **27**, 281-292
- Nomiyama, K. & Nomiyama, H. (1977) Dose-response relationship for trichloroethylene in man. *Int. Arch. occup. environ. Health*, **39**, 237-248
- Nomiyama, K., Nomiyama, H. & Arai, H. (1986) Reevaluation of subchronic toxicity of trichloroethylene (Abstract No. P16-4). *Toxicol. Lett.*, **31**, 225
- Novotná, E., David, A. & Málek, B. (1979) An epidemiological study on hepatic tumour incidence in subjects working with trichloroethylene: I. Negative result of retrospective investigations in subjects with primary liver carcinoma. *Prac. Léč.*, **31**, 121-123 (in Czech)
- Odum, J., Foster, J.R. & Green, T. (1992) A mechanism for the development of Clara cell lesions in the mouse lung after exposure to trichloroethylene. *Chem.-biol. Interactions*, **83**, 135-153
- Ogata, M., Takatsuka, Y. & Tomokuni, K. (1971) Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. *Br. J. ind. Med.*, **28**, 386-391

- Okawa, M.T., Blejer, H.P. & Solomon, R.M. (1978) *Trans World Airlines Corp., Los Angeles, CA* (Health Hazard Evaluation Determination Report No. 78-38-312), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Olsson, H. & Brandt, L. (1980) Occupational exposure to organic solvents and Hodgkin's disease in men. A case-referent study. *Scand. J. Work Environ. Health*, **6**, 302-305
- Paddle, G.M. (1983) Incidence of liver cancer and trichloroethylene manufacture: joint study by industry and a cancer registry. *Br. med. J.*, **286**, 846
- Papdullo, R.F., Shareef, S.A., Kincaid, L.E. & Murphy, P.V. (1985) *Survey of Trichloroethylene Emission Sources* (EPA-450/3-85-021; PB86-107943), Research Triangle Park, NC, Office of Air Quality Planning and Standards, Environmental Protection Agency
- Paraf, F., Paraf, A. & Barge, J. (1990) Is industrial exposure a risk factor in gallbladder cancer? *Gastroenterol. clin. Biol.*, **14**, 877-880 (in French)
- Parchman, L.G. & Magee, P.N. (1982) Metabolism of [<sup>14</sup>C]trichloroethylene to <sup>14</sup>CO<sub>2</sub> and interaction of a metabolite with liver DNA in rats and mice. *J. Toxicol. environ. Health*, **9**, 797-813
- Peters, J.M., Preston-Martin, S. & Yu, M.C. (1981) Brain tumors in children and occupational exposure of parents. *Science*, **213**, 235-237
- Peters, J.M., Garabrant, D.H., Preston-Martin, S. & Yu, M.C. (1984) Is trichloroethylene a human carcinogen? (Abstract). *Scand. J. Work Environ. Health*, **13**, 180
- Pfaffenberger, C.D., Peoples, A.J. & Briggie, T.V. (1984) Blood plasma levels of volatile chlorinated solvents and metabolites in occupationally exposed workers. In: Veziroglu, T.N., ed., *The Biosphere: Problems and Solutions*, Amsterdam, Elsevier Science Publishers, pp. 559-569
- PPG Industries, Inc. (1994) *Product Information Sheet, Trichloroethylene*, Pittsburgh, PA
- Price, P.J., Hassett, C.M. & Mansfield, J.I. (1978) Transforming activities of trichloroethylene and proposed industrial alternatives. *In Vitro*, **14**, 290-293
- Prout, M.S., Provan, W.M. & Green, T. (1985) Species differences in response to trichloroethylene. I. Pharmacokinetics in rats and mice. *Toxicol. appl. Pharmacol.*, **79**, 389-400
- Rantala, K., Riipinen, H. & Anttila, A. (1992) *Altisteettyössä, 22—Halogeenihiitivedyt* [Exposure at work—halogenated hydrocarbons], Helsinki, Finnish Institute of Occupational Health—Finnish Work Environment Fund
- Rasmussen, K., Sabroe, S., Wohler, M., Ingerslev, H.J., Kappel, B. & Nielsen, J. (1988) A genotoxic study of metal workers exposed to trichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. *Int. Arch. occup. environ. Health*, **60**, 419-423
- Roldán-Arjona, T., García-Pedrajas, M.D., Luque-Romero, F.L., Hera, C. & Pueyo, C. (1991) An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis*, **6**, 199-205
- Rossi, A.M., Migliore, L., Barale, R. & Loprieno, N. (1983) In vivo and in vitro mutagenicity studies of a possible carcinogen, trichloroethylene, and its two stabilizers, epichlorohydrin and 1,2-epoxybutane. *Teratog. Carcinog. Mutag.*, **3**, 75-87
- Ruhe, R.L. (1982) *Synthes Ltd, Monument, CO* (Health Hazard Evaluation Report No. 82-040-1119), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Ruhe, R.L. & Donohue, M. (1980) *Duralectra, Inc., Natick, MA* (Health Hazard Evaluation Report No. 79-147-702), Cincinnati, OH, United States National Institute for Occupational Safety and Health

- Ruhe, R.L., Watanabe, A. & Stein, G. (1981) *Superior Tube Company, Collegetown, PA* (Health Hazard Evaluation Report No. 80-49-808), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Sabel, G.V. & Clark, T.P. (1984) Volatile organic compounds as indicators of municipal solid waste leachate contamination. *Waste Manage. Res.*, **2**, 119-130
- Sack, T.M., Steele, D.H., Hammerstrom, K. & Remmers, J. (1992) A survey of household products for volatile organic compounds. *Atmos. Environ.*, **26A**, 1063-1070
- Sadtler Research Laboratories (1980) *1980 Cumulative Index*, Philadelphia, PA
- Sawyer, L.D., McMahon, B.M., Newsome, W.H. & Parker, G.A., eds (1990) Pesticide and industrial chemical residues. In: Helrich, K., ed., *Official Methods of Analysis of the Association of Official Analytical Chemists*, 15th Ed., Vol. 1, Arlington, VA, Association of Official Analytical Chemists, pp. 290-291
- Sax, N.I. & Lewis, R.J. (1987) *Hawley's Condensed Chemical Dictionary*, 11th Ed., New York, Van Nostrand Reinhold Company, p. 1176
- Sbrana, I., Lascialfari, D. & Loprieno, N. (1985) Trichloroethylene induces micronuclei but not chromosomal aberrations in mouse bone marrow cells (Abstract). In: Ramel, C., ed., *Fourth International Conference on Environmental Mutagens, Stockholm, June 24-28, 1985*, New York, Alan R. Liss, p. 163
- Schairer, L.A. & Sautkulis, R.C. (1982) Detection of ambient levels of mutagenic atmospheric pollutants with the higher plant *Tradescantia*. *Environ. Mutag. Carcinog. Plant Biol.*, **2**, 154-194
- Schweizerische Unfallversicherungsanstalt [Swiss Accident Insurance Company] (1994) *Grenzwerte am Arbeitsplatz* [Limit values at the workplace], Lucerne, pp. 101, 131
- Schwetz, B.A., Leong, B.K.J. & Gehring, P.J. (1975) The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. *Toxicol. appl. Pharmacol.*, **32**, 84-96
- Scott, J.E., Forkert, P.G., Oulton, M., Rasmusson, M.-G., Temple, S., Fraser, M.O. & Whitefield, S. (1988) Pulmonary toxicity of trichloroethylene: induction of changes in surfactant phospholipids and phospholipase A2 activity in the mouse lung. *Exp. mol. Pharmacol.*, **49**, 141-150
- Seiji, K., Jin, C., Watanabe, T., Nakatsuka, H. & Ikeda, M. (1990) Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits. *Int. Arch. occup. environ. Health*, **62**, 171-176
- Seldén, A., Hultberg, B., Ulander, A. & Ahlberg, G., Jr (1993) Trichloroethylene exposure in vapour degreasing and the urinary excretion of *N*-acetyl- $\beta$ -D-glucosaminidase. *Arch. Toxicol.*, **67**, 224-226
- Shahin, M.M. & Von Borstel, R.C. (1977) Mutagenic and lethal effects of  $\alpha$ -benzene hexachloride, dibutyl phthalate and trichloroethylene in *Saccharomyces cerevisiae*. *Mutat. Res.*, **48**, 173-180
- Sharpe, C.R., Rochon, J.E., Adam, J.M. & Suissa, S. (1989) Case-control study of hydrocarbon exposures in patients with renal cell carcinoma. *Can. med. Assoc. J.*, **140**, 1309-1318
- Shelby, M.D., Erexson, G.L., Hook, G.J. & Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. *Environ. mol. Mutag.*, **21**, 160-179
- Sherwood, R.J. (1976) Ostwald solubility coefficients of some industrially important substances. *Br. J. ind. Med.*, **33**, 106-107
- Shimada, T., Swanson, A.F., Leber, P. & Williams, G.M. (1985) Activities of chlorinated ethane and ethylene compounds in the *Salmonella*/rat microsome mutagenesis and rat hepatocyte/DNA repair assays under vapor phase exposure conditions. *Cell Biol. Toxicol.*, **1**, 159-179

- Shindell, S. & Ulrich, S. (1985) A cohort study of employees of a manufacturing plant using trichloroethylene. *J. occup. Med.*, **27**, 577-579
- Shipman, A.J. & Whim, B.P. (1980) Occupational exposure to trichloroethylene in metal cleaning processes and to tetrachloroethylene in the drycleaning industry in the UK. *Ann. occup. Hyg.*, **23**, 197-204
- Siegel, J., Jones, R.A., Coon, R.A. & Lyon, J.P. (1971) Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. *Toxicol. appl. Pharmacol.*, **18**, 168-174
- Siemiatycki, J. (1991) *Risk Factors for Cancer in the Workplace*, Boca Raton, FL, CRC Press
- Simmon, V.F., Kauhanen, K. & Tardiff, R.G. (1977) Mutagenic activity of chemicals identified in drinking water. In: Scott, D., Bridges, B.A. & Sobels, F.H., eds, *Progress in Genetic Toxicology*, Amsterdam, Elsevier/North-Holland, pp. 249-258
- Singh, H.B., Salas, L.J., Smith, A.J. & Shigeishi, H. (1981) Measurement of some potentially hazardous organic chemicals in urban environments. *Atmos. Environ.*, **15**, 601-612
- Singh, H.B., Salas, L.J. & Stiles, R.E. (1983) Selected man-made halogenated chemicals in the air and oceanic environment. *J. geophys. Res.*, **88**, 3675-3683
- Skender, L.J., Karacic, V. & Prpic-Majic, D. (1991) A comparative study of human levels of trichloroethylene and tetrachloroethylene after occupational exposure. *Arch. environ. Health*, **46**, 174-178
- Skender, L., Karacic, V., Bosner, B. & Prpic-Majic, D. (1993) Assessment of exposure to trichloroethylene and tetrachloroethylene in the population of Zagreb, Croatia. *Int. Arch. occup. environ. Health*, **65**, S163-S165
- Slacik-Erben, R., Roll, R., Franke, G. & Uehleke, H. (1980) Trichloroethylene vapours do not produce dominant lethal mutations in male mice. *Arch. Toxicol.*, **45**, 37-44
- Smith, G.F. (1966) Trichloroethylene: a review. *Br. J. ind. Med.*, **23**, 249-262
- Smyth, H.F., Jr, Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A. & Nycum, J.S. (1969) Range-finding toxicity data. List VII. *Am. ind. Hyg. Assoc. J.*, **30**, 470-476
- Sofuni, T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M. & Ishidate, M., Jr (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds. II. Chromosome aberration tests in cultured mammalian cells. *Bull. natl Inst. Hyg. Sci. (Tokyo)*, **103**, 64-75
- Spirtas, R., Stewart, P.A., Lee, J.S., Marano, D.E., Forbes, C.D., Grauman, D.J., Pettigrew, H.M., Blair, A., Hoover, R.N. & Cohen, J.L. (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br. J. ind. Med.*, **48**, 515-530
- Staples, C.A., Werner, A.F. & Hoogheem, T.J. (1985) Assessment of priority pollutant concentrations in the United States using STORET database. *Environ. Toxicol. Chem.*, **4**, 131-142
- Steward, A., Allott, P.R., Cowles, A.L. & Mapleson, W.W. (1973) Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *Br. J. Anaesthesiol.*, **45**, 282-293
- Stewart, P.A., Lee, J.S., Marano, D.E., Spirtas, R., Forbes, C.D. & Blair, A. (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility. II. Exposures and their assessment. *Br. J. ind. Med.*, **48**, 531-537
- Stott, W.T., Quast, J.F. & Watanabe, P.G. (1982) The pharmacokinetics and macromolecular interactions of trichloroethylene in mice and rats. *Toxicol. appl. Pharmacol.*, **62**, 137-151

- Su, C. & Goldberg, E.D. (1976) Environmental concentrations and fluxes of some halocarbons. In: Windom, H.L. & Duce, R.A., eds, *Marine Pollutant Transfer*, Lexington, MA, Lexington Books, pp. 353-374
- Sullivan, D.A., Jones, A.D. & Williams, J.G. (1985) Results of the United States Environmental Protection Agency's air toxics analysis in Philadelphia. In: *Proceedings of the 78th Annual Meeting of the Air Pollution Control Association*, Vol. 2, Detroit, MI, Air Pollution Control Association, Paper 85-17.5
- Taskinen, H., Anttila, A., Lindbohm, M.-L., Sallmén, M. & Hemminki, K. (1989) Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work Environ. Health*, **15**, 345-352
- Taskinen, H., Kyyrönen, P., Hemminki, K., Hoikkala, M., Lajunen, K. & Lindbohm, M.-L. (1994) Laboratory work and pregnancy outcome. *J. occup. Med.*, **36**, 311-319
- Taylor, D.H., Lagory, K.E., Zaccaro, D.J., Pfohl, R.J. & Laurie, R.D. (1985) Effect of trichloroethylene on the exploratory and locomotor activity of rats exposed during development. *Sci. total Environ.*, **47**, 415-420
- Thomas, R.D. (1989) Epidemiology and toxicology of volatile organic chemical contaminants in water absorbed through the skin. *J. Am. Coll. Toxicol.*, **8**, 779-795
- Tola, S., Vilhunen, R., Järvinen, E. & Korkala, M.-L. (1980) A cohort study on workers exposed to trichloroethylene. *J. occup. Med.*, **22**, 737-740
- Trouwborst, T. (1981) Groundwater pollution by volatile halogenated hydrocarbons: source of pollution and methods to estimate their relevance. *Sci. total Environ.*, **21**, 41-46
- Trussell, A.R., Cromer, J.L., Umphres, M.D., Kelly, P.E. & Moncur, J.G. (1980) Monitoring of volatile halogenated organics: a survey of twelve drinking waters from various parts of the world. In: Jolley, R.L., Brungs, W.A., Cumming, R.B. & Jacobs, V.A., eds, *Water Chlorination. Environment Impact and Health Effects*, Vol. 3, Ann Arbor, MI, Ann Arbor Science, pp. 39-53
- Tu, A.S., Murray, T.A., Hatch, K.M., Sivak, A. & Milman, H.A. (1985) In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. *Cancer Lett.*, **28**, 85-92
- Tucker, A.N., Sanders, V.M., Barnes, D.W., Bradshaw, T.J., White, K.L., Jr, Sain, L.E., Borzelleca, J.F. & Munson, A.E. (1982) Toxicology of trichloroethylene in the mouse. *Toxicol. appl. Pharmacol.*, **62**, 351-357
- Työministeriö [Ministry of Labour] (1993) *HTP-Arvot 1993* [Limit values 1993], Tampere, p. 19
- Uhler, A.D. & Diachenko, G.W. (1987) Volatile halocarbon compounds in process water and processed foods. *Bull. environ. Contam. Toxicol.*, **39**, 601-607
- Ulander, A., Seldén, A. & Ahlberg, G., Jr (1992) Assessment of intermittent trichloroethylene exposure in vapor degreasing. *Am. ind. Hyg. Assoc. J.*, **53**, 742-743
- United Kingdom Health and Safety Executive (1994) *Occupational Exposure Limits 1994* (Guidance Note EH 40/94), London, Her Majesty's Stationary Office, p. 26
- United States Agency for Toxic Substances and Disease Registry (1989) *Toxicology Profile for Trichloroethylene* (ATSDR/TP-88-24), Oak Ridge, TN, Oak Ridge National Laboratory
- United States Environmental Protection Agency (1985) *Health Assessment Document for Trichloroethylene (Final Report)* (EPA-600/8-82006F; US NTIS PB85-249696), Washington DC
- United States Environmental Protection Agency (1986a) Method 8010. Halogenated volatile organics. In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods* (US EPA No. SW-846), 3rd Ed., Vol. 1A, Washington DC, Office of Solid Waste and Emergency Response, pp. 1-13

- United States Environmental Protection Agency (1986b) Method 8240. Gas chromatography/mass spectrometry for volatile organics. In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods* (US EPA No. SW-846), 3rd Ed., Vol. 1A, Washington DC, Office of Solid Waste and Emergency Response, pp. 1–43
- United States Environmental Protection Agency (1988a) *Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air* (EPA-600/4-89-017; US NTIS PB90-116989), Research Triangle Park, NC, Office of Research and Development, pp. TO1-1–TO1-38; TO3-1–TO3-22; TO14-1–TO14-94
- United States Environmental Protection Agency (1988b) *Methods for the Determination of Organic Compounds in Drinking Water* (EPA-600/4-88-039; US NTIS PB89-220461), Cincinnati, OH, Environmental Monitoring Systems Laboratory, pp. 5–87, 255–323 (Methods 502.1, 502.2, 503.1, 524.1, 524.2)
- United States Environmental Protection Agency (1989) *Contract Laboratory Program Statistical Database*, Washington DC
- United States Environmental Protection Agency (1993) *1991 Toxic Release Inventory* (EPA 745-R-93-003), Washington DC, Office of Pollution Prevention and Toxics, p. 250
- United States Environmental Protection Agency (1994) Protection of the environment. *US Code fed. Regul.*, **Title 40**, Part 136, Appendix A, pp. 400–413, 559–573, 602–614 (Methods 601, 624, 1624)
- United States Food and Drug Administration (1977) Trichloroethylene. Removal from food additive use. *Fed. Regist.*, **42**, 49465–49471
- United States Food and Drug Administration (1983) Trichloroethylene. In: Warner, C., Modderman, J., Fazio, T., Beroza, M., Schwartzman, G., Fominaya, K. & Sherma, J., eds, *Food Additives Analytical Manual*, Vol. 1, *A Collection of Analytical Methods for Selected Food Additives*, Washington DC/Arlington VA, Bureau of Foods/Association of Official Analytical Chemists, pp. 176–185, 224–232, 317
- United States National Cancer Institute (1976) *Carcinogenesis Bioassay of Trichloroethylene* (CAS No. 79-01-6) (Tech. Rep. Ser. No. 2), Bethesda, MD
- United States National Institute for Occupational Safety and Health (1994a) *NIOSH Pocket Guide to Chemical Hazards* (DHHS (NIOSH) Publ. No. 94-116), Cincinnati, OH, pp. 316–317, 350
- United States National Institute for Occupational Safety and Health (1994b) *National Occupational Exposure Survey, 1981–1983*, Cincinnati, OH
- United States National Institute for Occupational Safety and Health (1994c) *RTECS Chem-Bank*, Cincinnati, OH
- United States National Toxicology Program (1985) *Trichloroethylene: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Feed* (NTP-86-068), Bethesda, MD, Department of Health and Human Services, National Institutes of Health
- United States National Toxicology Program (1986) *Trichloroethylene: Reproduction and Fertility Assessment in F344 Rats When Administered in the Feed, Final Report* (NTP-86-085), Bethesda, MD, Department of Health and Human Services, National Institutes of Health
- United States National Toxicology Program (1988) *Toxicology and Carcinogenesis Studies of Trichloroethylene* (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (*Gavage Studies*) (Tech. Rep. Ser. No. 273), Research Triangle Park, NC
- United States National Toxicology Program (1990) *Carcinogenesis Studies of Trichloroethylene* (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F<sub>1</sub> Mice (*Gavage Studies*) (Tech. Rep. Ser. No. 243), Research Triangle Park, NC

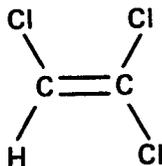
- United States Occupational Safety and Health Administration (1990) *OSHA Analytical Methods Manual*, 2nd Ed., Part 1, Vol. 1, Salt Lake City, UT, Method 7
- United States Occupational Safety and Health Administration (1994) Air contaminants. *US Code fed. Regul.*, **Title 29**, Part 1910.1000, p. 18
- Urano, K., Kawamoto, K., Abe, Y. & Otake, M. (1988) Chlorinated organic compounds in urban air in Japan. *Sci. total Environ.*, **74**, 121-131
- Vainio, H., Waters, M.D. & Norppa, H. (1985) Mutagenicity of selected organic solvents. *Scand. J. Work Environ. Health*, **11** (Suppl. 1), 75-82
- Vamvakas, S. & Köster, U. (1993) The nephrotoxin dichlorovinylcysteine induces expression of the protooncogenes *c-fos* and *c-myc* in LLC-PK<sub>1</sub> cells. A comparative investigation with growth factors and 12-*O*-tetradecanoylphorbolacetate. *Cell Biol. Toxicol.*, **9**, 1-13
- Vamvakas, S., Dekant, W., Berthold, K., Schmidt, S., Wild, D. & Henschler, D. (1987) Enzymatic transformation of mercapturic acids derived from halogenated alkenes to reactive and mutagenic intermediates. *Biochem. Pharmacol.*, **36**, 2741-2748
- Vamvakas, S., Elfarra, A.A., Dekant, W., Henschler, D. & Anders, M.W. (1988) Mutagenicity of amino acid and glutathione *S*-conjugates in the Ames test. *Mutat. Res.*, **206**, 83-90
- Vamvakas, S., Dekant, W. & Henschler, D. (1989) Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine *S*-conjugates of haloalkenes and haloalkanes. *Mutat. Res.*, **222**, 329-335
- Vamvakas, S., Bittner, D., Dekant, W. & Anders, M.W. (1992) Events that precede and that follow *S*-(1,2-dichlorovinyl)-*L*-cysteine-induced release of mitochondrial Ca<sup>2+</sup> and their association with cytotoxicity to renal cells. *Biochem. Pharmacol.*, **44**, 1131-1138
- Vamvakas, S., Bittner, D. & Köster, U. (1993) Enhanced expression of the protooncogenes *c-myc* and *c-fos* in normal and malignant renal growth. *Toxicol. Lett.*, **67**, 161-172
- Vandervort, R. & Polakoff, A. (1973) *Dunham-Bush, Inc., West Hartford, CN* (Health Hazard Evaluation/Toxicity Determination Report No. 72-84-31; US NTIS PB-229-627), Cincinnati, OH, United States National Institute for Occupational Safety and Health
- Van Duuren, B.L., Goldschmidt, B.M., Loewengart, G., Smith, A.C., Melchionne, S., Seidman, I. & Roth, D. (1979) Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J. natl Cancer Inst.*, **63**, 1433-1439
- Van Duuren, B.L., Kline, S.A., Melchionne, S. & Seidman, I. (1983) Chemical structure and carcinogenicity relationships of some chloroalkene oxides and their parent olefins. *Cancer Res.*, **43**, 159-162
- Vartiainen, T., Pukkala, E., Rienoja, T., Strandman, T. & Kaksonen, K. (1993) Population exposure to tri- and tetrachloroethene and cancer risk: two cases of drinking water pollution. *Chemosphere*, **27**, 1171-1181
- Vernot, E.H., MacEwen, J.D., Haun, C.C. & Kinkead, E.R. (1977) Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. appl. Pharmacol.*, **42**, 417-423
- Wallis, S.A.S. (1986) Induction of single-strand breaks in DNA of mice by trichloroethylene and tetrachloroethylene. *Toxicol. Lett.*, **31**, 31-35
- Waskell, L. (1978) A study of the mutagenicity of anesthetics and their metabolites. *Mutat. Res.*, **57**, 141-153
- Weast, R.C. & Astle, M.J. (1985) *CRC Handbook of Data on Organic Compounds*, Vols I & II, Boca Raton, FL, CRC Press Inc., pp. 627(I), 592(II)

- Westergren, I., Kjellstrand, P., Linder, L.E. & Johansson, B.B. (1984) Reduction of brain specific gravity in mice prenatally exposed to trichloroethylene. *Toxicol. Lett.*, **23**, 223-226
- White, A.E., Takehisa, S., Eger, E.I., II, Wolff, S. & Sterens, W.C. (1979) Sister chromatid exchanges induced by inhaled anesthetics. *Anesthesiology*, **50**, 426-430
- WHO (1985) *Trichloroethylene* (Environmental Health Criteria 50), Geneva
- WHO (1993) *Guidelines for Drinking-water Quality*, Vol. 1, *Recommendations*, 2nd Ed., Geneva, pp. 62-63, 175
- Williams, G.M., Mori, H. & McQueen, C.A. (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. *Mutat. Res.*, **221**, 263-286
- Windham, G.C., Shusterman, D., Swan, S.H., Fenster, L. & Eskenazi, B. (1991) Exposure to organic solvents and adverse pregnancy outcome. *Am. J. ind. Med.*, **20**, 241-259
- Withey, J.R. & Karpinski, K. (1985) The fetal distribution of some aliphatic chlorinated hydrocarbons in the rat after vapor phase exposure. *Biol. Res. Pregnancy Perinatol.*, **6**, 79-88
- Wright, P.F.A. & Stacey, N.H. (1991) A species/strain comparison of hepatic natural lymphocytotoxic activities in rats and mice. *Carcinogenesis*, **12**, 1365-1370
- Wright, P.F.A., Thomas, W.D. & Stacey, N.H. (1991) Effects of trichloroethylene on hepatic and splenic lymphocytotoxic activities in rodents. *Toxicology*, **70**, 231-242
- Wright, P.F.A., Schlichting, L.M. & Stacey, N.H. (1994) Effects of chlorinated solvents on the natural lymphocytotoxic activities of human liver immune cells. *Toxicol. in vitro*, **8**, 1037-1039
- Zenick, H., Blackburn, K., Hope, E., Richdale, N. & Smith, M.K. (1984) Effects of trichloroethylene exposure on male reproductive function in rats. *Toxicology*, **31**, 237-250
- Ziglio, G., Fara, G.M., Beltramelli, G. & Pregliasco, F. (1983) Human environmental exposure to trichloro- and tetrachloroethylene from water and air in Milan, Italy. *Arch. environ. Contam. Toxicol.*, **12**, 57-64
- Ziglio, G., Beltramelli, G., Pregliasco, F., Arosio, D. & De Donato, S. (1984a) Ambient exposure to chlorinated solvents of the student population of a commune in northern Italy. *Ig. Mod.*, **82**, 133-161 (in Italian)
- Ziglio, G., Beltramelli, G. & Giovanardi, A. (1984b) Occurrence of halogenated organic compounds in drinking-water of some cities of northern Italy. *Ig. Mod.*, **82**, 419-435 (in Italian)
- Ziglio, G., Beltramelli, G., Pregliasco, F. & Mazzocchi, M.A. (1984c) Exposure to trichloroethylene through drinking-water of some families of Porto Mantovano (Mn). *Ig. Mod.*, **82**, 591-605 (in Italian)
- Zoeteman, B.C.J., Harmsen, K., Linders, J.B.H.J., Morra, C.F.H. & Slooff, W. (1980) Persistent organic pollutants in river water and ground water of the Netherlands. *Chemosphere*, **9**, 231-249

## **APPENDIX B**

**Excerpts from the 1990 NTP Technical Report  
Toxicology and Carcinogenesis Studies of Trichloroethylene  
(Without Epichlorohydrin) [CAS No. 79-01-6] in  
F344/N Rats and B6C3F1 Mice (Gavage Studies)  
pp. 7-8, 34-39, 46-51**

# CARCINOGENESIS STUDIES OF TRICHLOROETHYLENE



## TRICHLOROETHYLENE

CAS NO. 79-01-6  
C2HCl3 Mol. Wt. 131.40

### ABSTRACT

Carcinogenesis studies of epichlorohydrin-free trichloroethylene (TCE) were conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats and B6C3F<sub>1</sub> mice. Dosage levels were 500 and 1,000 mg/kg for rats and 1,000 mg/kg for mice. Trichloroethylene was administered five times per week for 103 weeks, and surviving animals were killed between weeks 103 and 107. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls. Groups of 50 male and 50 female rats were used as untreated controls.

The dosage levels selected for the 2-year study were based on the results of the 13-week studies. Groups of 10 male and 10 female rats received TCE by gavage at doses of 125 to 2,000 mg/kg (males) and 62.5 to 1,000 mg/kg (females) for 13 weeks. Groups of 10 male and 10 female mice received gavage doses of 375 to 6,000 mg/kg of TCE for 13 weeks. Survival, body weight gains, and previous experience with TCE were used to select doses for the 2-year study. All rats survived the 13-week study, but males receiving 2,000 mg/kg exhibited a 24% difference in final body weight. At the 1,000 mg/kg dose, final body weights for males (-3%) and for females (-2%) were similar to those of controls. The doses selected for the 2-year study in rats were 500 and 1,000 mg/kg for both sexes. The initial doses used in the earlier bioassay in Osborne-Mendel rats were 549 and 1,097 mg/kg for both sexes. A total of 8/10 male mice and 10/10 female mice receiving doses of TCE as high as 1,500 mg/kg survived the 13-week experimental period. The single dosage level selected for the 2-year study in mice was 1,000 mg/kg for both sexes. This dose was less than the high dose used in the earlier bioassay in B6C3F<sub>1</sub> mice (2,339 mg/kg for males and 1,739 for females) and was similar to the previous low doses (1,169 mg/kg for males and 869 for females).

In the 2-year study, the survival of both low and high dose male rats and dosed male mice was less ( $P \leq 0.005$ ) than that of the vehicle controls. Mean body weights of dosed rats of each sex were lower than those of the vehicle controls, and after week 65, the decrements in body weight gains were dose related. The mean body weight of dosed male mice was lower than that of the vehicle controls throughout the study, while those of dosed and vehicle control female mice were comparable.

Cytomegaly (toxic nephrosis) of the kidney was observed in 96/98 male and in 97/97 female rats given TCE, with none being found in male or female vehicle control rats. This lesion was more severe in males, particularly in the high dose group. Cytomegaly was observed in 45/50 male mice and in 48/49 female mice administered TCE, and in none of the vehicle controls. Renal tubular cell adenocarcinomas were found in three high dose male rats; these neoplasms were observed in those male rats killed at the end of the study (0/33, 0/20, and 3/16, 19%). The incidence in the high dose male rats at the end of the study was greater ( $P < 0.05$ ) than that in the controls. Renal tubular cell adenocarcinomas are considered uncommon occurrences in F344/N rats, with 3/748 (0.4%) being observed in historical vehicle gavage controls. Additional renal tumors in dosed male rats included one transitional cell carcinoma of the renal pelvis and two tubular cell adenomas in low dose animals and one carcinoma of the renal pelvis in a high dose animal. No renal neoplasms were found in vehicle control rats; one untreated control male rat had a transitional cell papilloma of the renal pelvis. In female rats, one tubular cell adenocarcinoma was found in the high dose group.

An increased incidence ( $P < 0.05$ , life table) of peritoneal mesotheliomas was detected in low dose male rats (control, 1/50; low dose, 5/50; high dose, 1/49). Mesotheliomas have been diagnosed in 16/752 (2.1%) historical vehicle control male F344/N rats, and the increased incidence in the present study may have been related to the administration of TCE.

The results in male F344/N rats were considered equivocal for detecting a carcinogenic response because both groups receiving TCE showed significantly reduced survival compared to vehicle controls (35/50, 70%; 20/50, 40%; 16/50, 32%) and because 20% of the animals in the high dose group were killed accidentally by gavage error.

Negative trends were observed for chromophobe adenomas of the pituitary gland and for endometrial stromal polyps in female rats. These decreases were not considered to be related to the administration of TCE.

The administration of TCE to mice caused increased incidences of hepatocellular carcinoma in males (control, 8/48; dosed, 31/50;  $P < 0.001$ ) and in females (control, 2/48; dosed, 13/49;  $P < 0.005$ ). Hepatocellular carcinomas metastasized to the lungs in five dosed male mice and one control male mouse, and none was observed in females. The incidence of hepatocellular adenomas was increased in male mice (control, 7/48; dosed 14/50) and in female mice (control, 4/48; dosed, 16/49;  $P < 0.05$ ).

Under the conditions of these studies, epichlorohydrin-free trichloroethylene caused renal tubular-cell neoplasms in male F344/N rats, produced toxic nephrosis in both sexes, and shortened the survival time of males. This experiment in male F344/N rats was considered to be inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene. For female F344/N rats receiving trichloroethylene, containing no epichlorohydrin, there was no evidence of carcinogenicity. Trichloroethylene (without epichlorohydrin) was carcinogenic for B6C3F<sub>1</sub> mice, causing increased incidences of hepatocellular carcinomas in males and females and of hepatocellular adenomas in females.

TABLE 4. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a)

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Subcutaneous Tissue: Fibroma</b>				
Tumor Rates				
Overall (b)	3/50 (6%)	4/50 (8%)	1/50 (2%)	0/49 (0%)
Adjusted (c)		10.2%	5.0%	0.0%
Terminal (d)		2/35 (6%)	1/20 (5%)	0/16 (0%)
Statistical Tests (e)				
Life Table		P=0.108N	P=0.356N	P=0.208N
Incidental Tumor Test		P=0.064N	P=0.216N	P=0.141N
Cochran-Armitage Trend Test		P=0.027N		
Fisher Exact Test			P=0.181N	P=0.061N
<b>Skin or Subcutaneous Tissue: Fibroma</b>				
Tumor Rates				
Overall (b)	3/50 (6%)	4/50 (8%)	1/50 (2%)	1/49 (2%)
Adjusted (c)		10.2%	5.0%	6.3%
Terminal (d)		2/35 (6%)	1/20 (5%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.318N	P=0.356N	P=0.475N
Incidental Tumor Test		P=0.238N	P=0.216N	P=0.373N
Cochran-Armitage Trend Test		P=0.104N		
Fisher Exact Test			P=0.181N	P=0.187N
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>				
Tumor Rates				
Overall (b)	1/49 (2%)	3/50 (6%)	2/50 (4%)	2/49 (4%)
Adjusted (c)		7.6%	9.5%	10.9%
Terminal (d)		2/35 (6%)	1/20 (5%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.461	P=0.656	P=0.568
Incidental Tumor Test		P=0.583N	P=0.494N	P=0.639N
Cochran-Armitage Trend Test		P=0.415N		
Fisher Exact Test			P=0.500N	P=0.510N
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>				
Tumor Rates				
Overall (b)	1/49 (2%)	4/50 (8%)	2/50 (4%)	2/49 (4%)
Adjusted (c)		10.4%	9.5%	10.9%
Terminal (d)		3/35 (9%)	1/20 (5%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.584N	P=0.570N	P=0.669
Incidental Tumor Test		P=0.439N	P=0.368N	P=0.516N
Cochran-Armitage Trend Test		P=0.259N		
Fisher Exact Test			P=0.339N	P=0.349
<b>Hematopoietic System: Leukemia</b>				
Tumor Rates				
Overall (b)	11/50 (22%)	5/50 (10%)	5/50 (10%)	1/49 (2%)
Adjusted (c)		13.6%	17.9%	5.9%
Terminal (d)		4/35 (11%)	2/20 (10%)	0/16 (0%)
Statistical Tests (e)				
Life Table		P=0.394N	P=0.336	P=0.368N
Incidental Tumor Test		P=0.255N	P=0.548	P=0.309N
Cochran-Armitage Trend Test		P=0.094N		
Fisher Exact Test			P=0.630	P=0.107N

TABLE 4. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Hematopoietic System: Leukemia or Lymphoma</b>				
Tumor Rates				
Overall (b)	12/50 (24%)	6/50 (12%)	5/50 (10%)	1/49 (2%)
Adjusted (c)		15.4%	17.9%	5.9%
Terminal (d)		4/35 (11%)	2/20 (10%)	0/16 (0%)
Statistical Tests (e)				
Life Table		P=0.287N	P=0.455	P=0.270N
Incidental Tumor Test		P=0.121N	P=0.512N	P=0.126N
Cochran-Armitage Trend Test		P=0.051N		
Fisher Exact Test			P=0.500N	P=0.059N
<b>Kidney: Tubular-Cell Adenocarcinoma</b>				
Tumor Rates				
Overall (b)	0/49 (0%)	0/48 (0%)	0/49 (0%)	3/49 (6%)
Adjusted (c)		0.0%	0.0%	18.8%
Terminal (d)		0/33 (0%)	0/20 (0%)	3/16 (19%)
Statistical Tests (e)				
Life Table		P=0.009	(f)	P=0.028
Incidental Tumor Test		P=0.009	(f)	P=0.028
Cochran-Armitage Trend Test		P=0.038		
Fisher Exact Test			(f)	P=0.125
<b>Kidney: Tubular-Cell Adenoma or Adenocarcinoma</b>				
Tumor Rates				
Overall (b)	0/49 (0%)	0/48 (0%)	2/49 (4%)	3/49 (6%)
Adjusted (c)		0.0%	5.6%	18.8%
Terminal (d)		0/33 (0%)	0/20 (0%)	3/16 (19%)
Statistical Tests (e)				
Life Table		P=0.019	P=0.194	P=0.028
Incidental Tumor Test		P=0.030	P=0.327	P=0.028
Cochran-Armitage Trend Test		P=0.084		
Fisher Exact Test			P=0.253	P=0.125
<b>Pituitary: Chromophobe Adenoma</b>				
Tumor Rates				
Overall (b)	4/39 (10%) (g)	7/42 (17%) (h)	2/35 (6%) (i)	1/26 (4%)
Adjusted (c)		21.2%	8.2%	7.7%
Terminal (d)		7/33 (21%)	1/18 (6%)	1/13 (8%)
Statistical Tests (e)				
Life Table		P=0.147N	P=0.285N	P=0.258N
Incidental Tumor Test		P=0.125N	P=0.250N	P=0.258N
Cochran-Armitage Trend Test		P=0.150N		
Fisher Exact Test			P=0.128N	P=0.111N
<b>Adrenal: All Pheochromocytomas</b>				
Tumor Rates				
Overall (b)	8/45 (18%)	4/45 (9%)	3/42 (7%)	1/44 (2%)
Adjusted (c)		13.3%	15.8%	3.2%
Terminal (d)		4/30 (13%)	3/19 (16%)	0/16 (0%)
Statistical Tests (e)				
Life Table		P=0.348N	P=0.571	P=0.393N
Incidental Tumor Test		P=0.270N	P=0.571	P=0.254N
Cochran-Armitage Trend Test		P=0.140N		
Fisher Exact Test			P=0.539N	P=0.187N

TABLE 4. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Thyroid: C-Cell Carcinoma</b>				
Tumor Rates				
Overall (b)	0/44 (0%)	2/44 (5%)	3/43 (7%)	0/39 (0%)
Adjusted (c)		6.5%	15.9%	0.0%
Terminal (d)		2/31 (6%)	2/15 (13%)	0/14 (0%)
Statistical Tests (e)				
Life Table		P=0.470N	P=0.231	P=0.425N
Incidental Tumor Test		P=0.429N	P=0.281	P=0.425N
Cochran-Armitage Trend Test		P=0.232N		
Fisher Exact Test			P=0.489	P=0.278N
<b>Thyroid: C-Cell Adenoma or Carcinoma</b>				
Tumor Rates				
Overall (b)	5/44 (11%)	4/44 (9%)	3/43 (7%)	0/39 (0%)
Adjusted (c)		12.9%	15.9%	0.0%
Terminal (d)		4/31 (13%)	2/15 (13%)	0/14 (0%)
Statistical Tests (e)				
Life Table		P=0.224N	P=0.464	P=0.202N
Incidental Tumor Test		P=0.197N	P=0.519	P=0.202N
Cochran-Armitage Trend Test		P=0.061N		
Fisher Exact Test			P=0.513N	P=0.074N
<b>Preputial Gland: Adenoma</b>				
Tumor Rates				
Overall (b)	4/50 (8%)	4/50 (8%)	0/50 (0%)	1/49 (2%)
Adjusted (c)		11.4%	0.0%	6.2%
Terminal (d)		4/35 (11%)	0/20 (0%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.253N	P=0.154N	P=0.473N
Incidental Tumor Test		P=0.253N	P=0.154N	P=0.473N
Cochran-Armitage Trend Test		P=0.084N		
Fisher Exact Test			P=0.059N	P=0.187N
<b>Preputial Gland: Adenoma or Adenocarcinoma</b>				
Tumor Rates				
Overall (b)	4/50 (8%)	5/50 (10%)	1/50 (2%)	3/49 (6%)
Adjusted (c)		13.5%	5.0%	13.4%
Terminal (d)		4/35 (11%)	1/20 (5%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.553	P=0.254	P=0.536
Incidental Tumor Test		P=0.457N	P=0.211N	P=0.541N
Cochran-Armitage Trend Test		P=0.272N		
Fisher Exact Test			P=0.102N	P=0.369N
<b>Testis: Interstitial-Cell Tumor</b>				
Tumor Rates				
Overall (b)	44/47 (94%)	47/49 (96%)	47/49 (96%)	32/46 (70%)
Adjusted (c)		100.0%	100.0%	96.8%
Terminal (d)		35/35 (100%)	20/20 (100%)	14/15 (93%)
Statistical Tests (e)				
Life Table		P=0.004	P<0.001	P=0.008
Incidental Tumor Test		P=0.252N	P=0.190	P=0.594N
Cochran-Armitage Trend Test	P<0.001N			
Fisher Exact Test			P=0.691	P=0.001N

**TABLE 4. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)**

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Peritoneum: Malignant Mesothelioma</b>				
Tumor Rates				
Overall (b)	1/50 (2%)	1/50 (2%)	5/50 (10%)	0/49 (0%)
Adjusted (c)		2.9%	16.1%	0.0%
Terminal (d)		1/35 (3%)	0/20 (0%)	0/16 (0%)
Statistical Tests (e)				
Life Table		P=0.518	P=0.042	P=0.656N
Incidental Tumor Test		P=0.348N	P=0.274	P=0.656N
Cochran-Armitage Trend Test		P=0.407N		
Fisher Exact Test			P=0.102	P=0.505N
<b>Peritoneum: All Mesotheliomas</b>				
Tumor Rates				
Overall (b)	1/50 (2%)	1/50 (2%)	5/50 (10%)	1/49 (2%)
Adjusted (c)		2.9%	15.6%	6.3%
Terminal (d)		1/35 (3%)	0/20 (0%)	1/16 (6%)
Statistical Tests (e)				
Life Table		P=0.286	P=0.042	P=0.578
Incidental Tumor Test		P=0.583	P=0.274	P=0.578
Cochran-Armitage Trend Test		P=0.585		
Fisher Exact Test			P=0.102	P=0.747

(a) Dosed groups received doses of 500 or 1,000 mg/kg of trichloroethylene by gavage.

(b) Number of tumor bearing animals/number of animals examined at the site.

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill.

(e) Beneath the control incidence are the P values associated with the trend test. Beneath each dosed group incidence is the P value corresponding to the pairwise comparison between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

(f) Not significant; no tumors were observed in dosed or control groups.

(g) Two chromophobe carcinomas, one adenoma, NOS, and one carcinoma, NOS, were also observed.

(h) One chromophobe carcinoma was also observed.

(i) One adenoma, NOS, was also observed.

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (a)

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>				
Tumor Rates				
Overall (b)	0/49 (0%)	1/50 (2%)	1/49 (2%)	3/50 (6%)
Adjusted (c)		2.7%	3.0%	7.5%
Terminal (d)		1/37 (3%)	1/33 (3%)	0/26 (0%)
Statistical Tests (e)				
Life Table		P=0.151	P=0.736	P=0.246
Incidental Tumor Test		P=0.326	P=0.736	P=0.541
Cochran-Armitage Trend Test		P=0.202		
Fisher Exact Test			P=0.747	P=0.309
<b>Hematopoietic System: Leukemia</b>				
Tumor Rates				
Overall (b)	10/49 (20%) (f)	14/50 (28%)	4/50 (8%)	9/50 (18%)
Adjusted (c)		33.8%	10.7%	29.1%
Terminal (d)		10/37 (27%)	2/33 (6%)	6/26 (23%)
Statistical Tests (e)				
Life Table		P=0.316N	P=0.019N	P=0.446N
Incidental Tumor Test		P=0.110N	P=0.004N	P=0.182N
Cochran-Armitage Trend Test		P=0.121N		
Fisher Exact Test			P=0.009N	P=0.171N
<b>Pituitary: Chromophobe Adenoma</b>				
Tumor Rates				
Overall (b)	18/43 (42%)	13/37 (35%)	6/34 (18%)	6/41 (15%)
Adjusted (c)		37.5%	24.0%	22.0%
Terminal (d)		9/29 (31%)	5/23 (22%)	3/22 (14%)
Statistical Tests (e)				
Life Table		P=0.131N	P=0.135N	P=0.191N
Incidental Tumor Test		P=0.036N	P=0.075N	P=0.040N
Cochran-Armitage Trend Test		P=0.022N		
Fisher Exact Test			P=0.081N	P=0.032N
<b>Pituitary: All Adenomas or Carcinomas</b>				
Tumor Rates				
Overall (b)	19/43 (44%)	13/37 (35%)	8/34 (24%)	6/41 (15%)
Adjusted (c)		37.5%	30.3%	22.0%
Terminal (d)		9/29 (31%)	6/23 (26%)	3/22 (14%)
Statistical Tests (e)				
Life Table		P=0.151N	P=0.297N	P=0.191N
Incidental Tumor Test		P=0.038N	P=0.188N	P=0.040N
Cochran-Armitage Trend Test		P=0.024N		
Fisher Exact Test			P=0.209N	P=0.032N
<b>Adrenal: Cortical Adenoma</b>				
Tumor Rates				
Overall (b)	2/45 (4%)	1/46 (2%)	2/48 (4%)	3/47 (6%)
Adjusted (c)		3.0%	6.1%	12.0%
Terminal (d)		1/33 (3%)	2/33 (6%)	3/25 (12%)
Statistical Tests (e)				
Life Table		P=0.142	P=0.500	P=0.210
Incidental Tumor Test		P=0.142	P=0.500	P=0.210
Cochran-Armitage Trend Test	P=0.227			
Fisher Exact Test		P=0.516	P=0.317	

**TABLE 5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (a) (Continued)**

	Untreated Control	Vehicle Control	Low Dose	High Dose
<b>Thyroid: C-Cell Adenoma</b>				
Tumor Rates				
Overall (b)	2/36 (6%) (g)	4/41 (10%)	1/45 (2%)	1/44 (2%)
Adjusted (c)		10.9%	3.3%	4.2%
Terminal (d)		3/34 (9%)	1/30 (3%)	1/24 (4%)
Statistical Tests (e)				
Life Table		P=0.168N	P=0.214N	P=0.290N
Incidental Tumor Test		P=0.127N	P=0.168N	P=0.210N
Cochran-Armitage Trend Test		P=0.086N		
Fisher Exact Test			P=0.152N	P=0.159N
<b>Mammary Gland: Fibroadenoma</b>				
Tumor Rates				
Overall (b)	10/49 (20%)	9/50 (18%)	12/50 (24%)	4/50 (8%)
Adjusted (c)		22.9%	32.6%	14.5%
Terminal (d)		7/37 (19%)	9/33 (27%)	3/26 (12%)
Statistical Tests (e)				
Life Table		P=0.307N	P=0.240	P=0.285N
Incidental Tumor Test		P=0.169N	P=0.353	P=0.177N
Cochran-Armitage Trend Test		P=0.114N		
Fisher Exact Test			P=0.312	P=0.117N
<b>Uterus: Endometrial Stromal Polyp</b>				
Tumor Rates				
Overall (b)	10/45 (22%)	15/48(31%)	8/48 (17%)	6/46 (13%)
Adjusted (c)		40.1%	23.1%	21.0%
Terminal (d)		13/35(37%)	7/33 (21%)	4/25 (16%)
Statistical Tests (e)				
Life Table		P=0.074N	P=0.098N	P=0.120N
Incidental Tumor Test		P=0.035N	P=0.069N	P=0.056N
Cochran-Armitage Trend Test		P=0.019N		
Fisher Exact Test			P=0.075N	P=0.030N
<b>Uterus: Endometrial Stromal Polyp or Sarcoma</b>				
Tumor Rates				
Overall (b)	10/45 (22%)	15/48 (31%)	8/48 (17%)	7/46(15%)
Adjusted (c)		40.1%	23.1%	23.5%
Terminal (d)		13/35 (37%)	7/33 (21%)	4/25(16%)
Statistical Tests (e)				
Life Table		P=0.127N	P=0.098N	P=0.193N
Incidental Tumor Test		P=0.060N	P=0.069N	P=0.086N
Cochran-Armitage Trend Test		P=0.037N		
Fisher Exact Test			P=0.075N	P=0.055N

(a) Dosed groups received doses of 500 or 1,000 mg/kg of trichloroethylene by gavage.

(b) Number of tumor bearing animals/number of animals examined at the site.

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill.

(e) Beneath the control incidence are the P values associated with the trend test. Beneath each dosed group incidence is the P value corresponding to the pairwise comparison between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

(f) One malignant lymphoma, histiocytic type, was also observed.

(g) One C-cell carcinoma was also observed.

**TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (a)**

	Vehicle Control	Dosed
<b>Lung: Alveolar/Bronchiolar Adenoma</b>		
Tumor Rates		
Overall (b)	4/49 (8%)	5/50 (10%)
Adjusted (c)	10.5%	27.1%
Terminal (d)	2/33 (6%)	4/16 (25%)
Statistical Tests (e)		
Life Table		P=0.197
Incidental Tumor Test		P=0.375
Fisher Exact Test		P=0.513
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>		
Tumor Rates		
Overall (b)	3/49 (6%)	1/50 (2%)
Adjusted (c)	9.1%	4.0%
Terminal (d)	3/33 (9%)	0/16 (0%)
Statistical Tests (e)		
Life Table		P=0.553N
Incidental Tumor Test		P=0.407N
Fisher Exact Test		P=0.301N
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>		
Tumor Rates		
Overall (b)	7/49 (14%)	6/50 (12%)
Adjusted (c)	19.2%	30.0%
Terminal (d)	5/33 (15%)	4/16 (25%)
Statistical Tests (e)		
Life Table		P=0.310
Incidental Tumor Test		P=0.575
Fisher Exact Test		P=0.484N
<b>Hematopoietic System: Malignant Lymphoma, Undifferentiated Type</b>		
Tumor Rates		
Overall (b)	3/50 (6%)	5/50 (10%)
Adjusted (c)	6.7%	17.4%
Terminal (d)	0/33 (0%)	1/16 (6%)
Statistical Tests (e)		
Life Table		P=0.258
Incidental Tumor Test		P=0.590
Fisher Exact Test		P=0.357
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>		
Tumor Rates		
Overall (b)	3/50 (6%)	3/50 (6%)
Adjusted (c)	8.8%	14.6%
Terminal (d)	2/33 (6%)	1/16 (6%)
Statistical Tests (e)		
Life Table		P=0.34F
Incidental Tumor Test		P=0.663N
Fisher Exact Test		P=0.661

**TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (a) (Continued)**

	Vehicle Control	Dosed
<b>Hematopoietic System: Lymphoma, All Malignant</b>		
Tumor Rates		
Overall(b)	11/50 (22%)	13/50 (26%)
Adjusted (c)	25.2%	45.7%
Terminal (d)	3/33 (9%)	3/16 (19%)
Statistical Tests (e)		
Life Table		P=0.116
Incidental Tumor Test		P=0.398N
Fisher Exact Test		P=0.408
<b>Liver: Adenoma</b>		
Tumor Rates		
Overall(b)	7/48 (15%)	14/50 (28%)
Adjusted (c)	20.6%	53.1%
Terminal (d)	6/33 (18%)	6/16 (37%)
Statistical Tests (e)		
Life Table		P=0.002
Incidental Tumor Test		P=0.048
Fisher Exact Test		P=0.084
<b>Liver: Carcinoma</b>		
Tumor Rates		
Overall(b)	8/48 (17%)	31/50 (62%)
Adjusted (c)	22.1%	92.9%
Terminal (d)	6/33 (18%)	14/16 (88%)
Statistical Tests (e)		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
<b>Liver: Adenoma or Carcinoma</b>		
Tumor Rates		
Overall(b)	14/48 (29%)	39/50 (78%)
Adjusted (c)	38.4%	100%
Terminal (d)	11/33 (33%)	16/16 (100%)
Statistical Tests (e)		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
<b>Harderian Gland: All Adenomas</b>		
Tumor Rates		
Overall(b)	0/50 (0%)	4/50 (8%)
Adjusted (c)	0.0%	12.0%
Terminal (d)	0/33 (0%)	0/16 (0%)
Statistical Tests (e)		
Life Table		P=0.044
Incidental Tumor Test		P=0.216
Fisher Exact Test		P=0.059

**TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (a) (Continued)**

---

- (a) The dosed group received doses of 1,000 mg/kg of trichloroethylene by gavage.
- (b) Number of tumor bearing animals/number of animals examined at the site.
- (c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
- (d) Observed tumor incidence at terminal kill.
- (e) Beneath the dosed group incidence is the P value corresponding to the pairwise comparison between the dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Fisher exact test compares directly the overall incidence rates. A negative trend or lower incidence is indicated by N.

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (a)

	Vehicle Control	Dosed
<b>Lung: Alveolar/Bronchiolar Adenoma</b>		
Tumor Rates		
Overall (b)	0/48 (0%)	4/48 (8%)
Adjusted (c)	0.0%	14.3%
Terminal (d)	0/32 (0%)	2/22 (9%)
Statistical Tests (e)		
Life Table		P=0.040
Incidental Tumor Test		P=0.064
Fisher Exact Test		P=0.059
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>		
Tumor Rates		
Overall (b)	1/48 (2%)	4/48 (8%)
Adjusted (c)	2.5%	14.3%
Terminal (d)	0/32 (0%)	2/22 (9%)
Statistical Tests (e)		
Life Table		P=0.132
Incidental Tumor Test		P=0.184
Fisher Exact Test		P=0.181
<b>Hematopoietic System: Malignant Lymphoma, Undifferentiated Type</b>		
Tumor Rates		
Overall (b)	1/48 (2%)	3/49 (6%)
Adjusted (c)	2.2%	10.1%
Terminal (d)	0/32 (0%)	0/23 (0%)
Statistical Tests (e)		
Life Table		P=0.252
Incidental Tumor Test		P=0.476
Fisher Exact Test		P=0.316
<b>Hematopoietic System: Malignant Lymphoma, Lymphocytic Type</b>		
Tumor Rates		
Overall (b)	0/48 (0%)	3/49 (6%)
Adjusted (c)	0.0%	9.6%
Terminal (d)	0/32 (0%)	0/23 (0%)
Statistical Tests (e)		
Life Table		P=0.096
Incidental Tumor Test		P=0.324
Fisher Exact Test		P=0.125
<b>Hematopoietic System: Malignant Lymphoma, Histiocytic Type</b>		
Tumor Rates		
Overall (b)	1/48 (2%)	3/49 (6%)
Adjusted (c)	2.8%	10.9%
Terminal (d)	0/32 (0%)	2/23 (9%)
Statistical Tests (e)		
Life Table		P=0.228
Incidental Tumor Test		P=0.323
Fisher Exact Test		P=0.316

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (a) (Continued)

	Vehicle Control	Dosed
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>		
Tumor Rates		
Overall(b)	3/48 (6%)	2/49 (4%)
Adjusted (c)	9.1%	7.5%
Terminal (d)	2/32 (6%)	1/23 (4%)
Statistical Tests (e)		
Life Table		P=0.636N
Incidental Tumor Test		P=0.424N
Fisher Exact Test		P=0.490N
<b>Hematopoietic System: Lymphoma, All Malignant</b>		
Tumor Rates		
Overall(b)	7/48 (15%)	13/49 (27%)
Adjusted (c)	18.8%	38.0%
Terminal (d)	3/32 (9%)	3/23 (13%)
Statistical Tests (e)		
Life Table		P=0.047
Incidental Tumor Test		P=0.331
Fisher Exact Test		P=0.114
<b>Hematopoietic System: Lymphoma or Leukemia</b>		
Tumor Rates		
Overall(b)	7/48 (15%)	14/49 (29%)
Adjusted (c)	18.8%	39.3%
Terminal (d)	3/32 (9%)	3/23 (13%)
Statistical Tests (e)		
Life Table		P=0.032
Incidental Tumor Test		P=0.287
Fisher Exact Test		P=0.076
<b>Liver: Adenoma</b>		
Tumor Rates		
Overall(b)	4/48 (8%)	16/49 (33%)
Adjusted (c)	12.5%	55.6%
Terminal (d)	4/32 (13%)	11/23 (48%)
Statistical Tests (e)		
Life Table		P<0.001
Incidental Tumor Test		P=0.001
Fisher Exact Test		P=0.003
<b>Liver: Carcinoma</b>		
Tumor Rates		
Overall(b)	2/48 (4%)	13/49 (27%)
Adjusted (c)	6.2%	43.9%
Terminal (d)	2/32 (6%)	8/23 (35%)
Statistical Tests (e)		
Life Table		P<0.001
Incidental Tumor Test		P=0.002
Fisher Exact Test		P=0.002

**TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (a) (Continued)**

	Vehicle Control	Dosed
<b>Liver: Adenoma or Carcinoma</b>		
Tumor Rates		
Overall(b)	6/48 (13%)	22/49 (45%)
Adjusted (c)	18.7%	69.7%
Terminal (d)	6/32 (19%)	4/23 (61%)
Statistical Tests (e)		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
<b>Stomach: Squamous Cell Papilloma or Carcinoma</b>		
Tumor Rates		
Overall(b)	0/47 (0%)	3/47 (6%)
Adjusted (c)	0.0%	8.1%
Terminal (d)	0/32 (0%)	0/22 (0%)
Statistical Tests (e)		
Life Table		P=0.112
Incidental Tumor Test		P=0.261
Fisher Exact Test		P=0.121
<b>Pituitary: Chromophobe Adenoma</b>		
Tumor Rates		
Overall(b)	3/27 (11%)	0/28 (0%)
Adjusted (c)	13.1%	0.0%
Terminal (d)	2/19 (11%)	0/14 (0%)
Statistical Tests (e)		
Life Table		P=0.183N
Incidental Tumor Test		P=0.081N
Fisher Exact Test		P=0.111N
<b>Harderian Gland: Adenoma</b>		
Tumor Rates		
Overall(b)	0/48 (0%)	3/49 (6%)
Adjusted (c)	0.0%	8.3%
Terminal (d)	0/32 (0%)	0/23 (0%)
Statistical Tests (e)		
Life Table		P=0.114
Incidental Tumor Test		P=0.171
Fisher Exact Test		P=0.125

(a) The dosed groups received doses of 1,000 mg/kg of trichloroethylene by gavage.

(b) Number of tumor-bearing animals/number of animals examined at the site.

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill.

(e) Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to the pairwise comparison between the dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Fisher exact test compares directly the overall incidence rates. A negative trend or lower incidence is indicated by N.

## **APPENDIX C**

### **DESCRIPTION OF ONLINE SEARCHES FOR TRICHLOROETHYLENE**

## DESCRIPTION OF ONLINE SEARCHES FOR TRICHLOROETHYLENE

Searches were limited to 1989 [the year before the NTP bioassay (NTP, 1990) which has an extensive literature review] through September 1997.

Online searches for trichloroethylene [CASRN 79-01-6] were performed in databases on the systems of the National Library of Medicine, STN International, DIALOG, and the Chemical Information System from 1989 to date. Toxicology information was sought in EMIC, EMICBACK, RTECS, and TOXLINE. Occupational safety and health information was obtained from NIOSHTIC. Environmental information was obtained from TRI95 (Toxic Chemical Release Inventory for 1995, online availability 1997) and the Chemical Abstracts file, which was searched by appropriate section codes (59, air pollution and industrial hygiene; 60, waste treatment and disposal; and 61, water). The Chemical Abstracts Service Registry file and SANSS provided chemical identification information.

Market information was sought in The Chemical Economics Handbook.

Regulatory information was obtained from the online database CHEMLIST and the in-house FESA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FDA), 29 (OSHA), and 40 (EPA).

Also, the review of 1200 life sciences journals for current awareness was accomplished using Current Contents on Diskette® (and cumulative issues on CD-ROM).

**APPENDIX D**  
**REPORT ON CARCINOGENS (ROC), 9<sup>TH</sup> EDITION**  
**REVIEW SUMMARY**

**Report on Carcinogens (RoC), 9<sup>th</sup> Edition  
Review Summary**

**Trichloroethylene**

**NOMINATION**

Review based on results of an NTP Bioassay of Trichloroethylene (1990), reporting clear evidence of carcinogenicity in experimental animals.

**DISCUSSION**

Trichloroethylene is used as an industrial solvent for vapor degreasing and cold cleaning of fabricated metal parts. It has also been used as a carrier solvent for the active ingredients of insecticides and fungicides, as a solvent for waxes and oils, as an anesthetic for medical and dental use, and as an extractant for spice oleoresins and for caffeine from coffee. There is clear evidence that trichloroethylene causes malignant tumor formation in multiple species of experimental animals. Epidemiological data are limited for evaluating the carcinogenicity of trichloroethylene in humans although studies have suggested that occupational exposure to trichloroethylene causes cancer of the liver and biliary tract, and also non-Hodgkin's lymphoma. A recently published epidemiology study has indicated that occupational exposure to trichloroethylene has also been associated with renal cancer in workers. The recommendations from the three NTP reviews of this nomination are as follows:

<u>Review Committee</u>	<u>Recommendation</u>	<u>Vote</u>
NIEHS (RG1)	list as a reasonably anticipated human carcinogen	6 yes/2 no*
NTP EC Working Group (RG2)	list as a reasonably anticipated human carcinogen	7 yes/ 1 no*
NTP Board RoC Subcommittee	list as a reasonably anticipated human carcinogen	7 yes/0 no

\* No votes cast by reviewers because they felt relevant data supported listing as a *known to be human carcinogen*

**Public Comments Received**

A total of 3 public comments were received:

- 1 against listing in the RoC in any category
- 2 recommended deferring action until the US EPA had completed its review of the carcinogenic potential of this compound