Hazard Assessment Report

Ver. 1.1

No. 3

1,2-Dichloroethane

Cabinet order number in the gazetted list

(Law for PRTR and Promotion of Chemical Management): 1-116

CAS registry number: 107-06-2

New Energy and Industrial Technology Development Organization

(NEDO)

Outsourcer:

Chemicals Evaluation and Research Institute (CERI)

National Institute of Technology and Evaluation (NITE)

Contents

1. Chemical substance identification information

1.1 Material name: 1,2-Dichloroethane

1.2 Class reference number in the gazetted list (Chemical Substance Control Law)

: 2-54

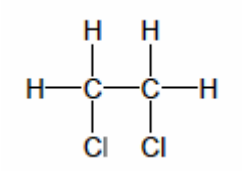
1.3 Cabinet order number in the gazetted list (Law for PRTR and Promotion of Chemical Management)

: 1-116

1.4 CAS registry number

: 107-06-2

1.5 Structural formula



1.6 Chemical formula: $C_2H_4Cl^2$

1.7 Molecular weight: 98.96

2. General information

2.1 Synonyms

Ethylene dichloride

2.2 Purity

>99.5% (General products)

(NITE, 2002)

2.3 Impurity

Nonvolatile component (<0.002%) (General products)

(NITE, 2002)

2.4 Additives/Stabilizers

No additives/stabilizers (General products)

(NITE, 2002)

2.5 Current regulations in Japan

Law for PRTR and Promotion of Chemical Management: Class I PRTR Chemicals

Chemical Substance Control Law: Designated Chemical Substance (Type II Monitored Chemical Substance)

Fire defense law: Class 1 Petroleum in Hazard Category 4

Industrial Safety and Health Law:

Class-1 organic solvents

Dangerous substances (Inflammable Substances)

Harmful substances whose names, etc., are to be indicated

Harmful substances whose name, etc., are to be noticed

Chemical substances made public

Control concentration: 10 ppm

Basic Environment Low:

Environmental criteria related to water pollution: 0.004 mg/L

Environmental criteria related to water pollution of groundwater: 0.004 mg/L

Environmental criteria related to soil pollution: 0.004 mg/L (Concentration of test solutions in dissolution test)

Sewerage Law:

Water quality standard: 0.04 mg/L

Water pollution control law: Harmful substances

Effluent standards: 0.04 mg/L

Air Pollution Control Law: Harmful air pollutant (Substances Requiring Priority Action)

Soil Contamination Countermeasures Law: Specified chemical substances (Substances Requiring Priority Action)

Law on the Prevention of Marine Pollution and Maritime Disaster: Harmful liquid substances, Group B

Ship Safety Law: Inflammable liquid

Civil Aeronautics Law: Inflammable liquid

Port Regulation Law: Inflammable liquid

Waste Management Law: Special Management Industrial Waste

Criteria: 0.4 mg/L (waste acid/base, content), 0.04 mg/L (Sludge, etc., elution volume)

3. Physical-Chemical Properties

Appearance: Colorless liquid (U.S. NLM: HSDB, 2001)

Melting point: -35.7℃ (IPCS, 1999)

Boiling point: 83-84℃ (Merck, 2001)

Flash point: 13℃ (direct vent type) (IPCS, 1999; Merck, 2001)

18℃ (unvented type) (Merck, 2001)

Ignition point: 413℃ (IPCS, 1999)

Explosion limit: 6.2-16 vol% (in air) (IPCS, 1999)

Specific gravity: 1.2569 (20℃/4℃) (Merck, 2001)

Vapor density: 3.42 (Air=1)

Vapor pressure: 5.3 kPa (10℃), 8.1 kPa (20℃), 14.0 kPa (30℃) (Verschueren, 2001)

Partition coefficient: Octanol/water Partition coefficient log Kow=1.48 (measured), 1.83 (caluculated) (SRC: KowWin, 2002)

Dissociation constant: No dissociation group

Spectrum: Major MS fragment

m/z 62 (base peak= 1.0), 2.7 (0.91) , 49 (0.40), 64 (0.32), 63 (0.19) (U.S. NIST, 1998)

Adsorption/Desorption properties: Soil sorption coefficient Koc=44 (estimated) (SRC: KowWin, 2002)

Solubility:

Water: 8.6 g/L (25℃) (U.S. NLM: HSDB, 2001)

Ethanol, chloroform and ether: Voluntarily soluble (Merck, 2001)

Henry's Constant: 120 Pa·m^3/mol (1.18 x 10^{-4} atm·m^3/mol) (23℃, measured) (SRC: KowWin, 2002)

Conversion factor: (Air, 20℃) 1 ppm=4.11 mg/m^3, 1 mg=0.243 ppm

4. Source information

4.1 Production and import, etc.

Table 4-1 shows the production and import, etc. of 1,2-dichloroethane for the five years from 1997 to 2001 (Production: Ministry of Economy, Trade and Industry, 2002; Import and export: Ministry of Finance, 2003). The production and import of 1,2-dichloroethane have been on the decline, while export has increased remarkably since 2000.

Table 4-1 Production and import, etc. of 1,2-dichloroethane (ton)

Year	1997	1998	1999	2000	2001
Production	3,491,372	3,491,292	3,501,897	3,430,642	3,274,975
Import	695,714	570,265	552,755	416,711	383,448
Export	392	315	687	29,466	20,548
Domestic supplies	4,186,694	4,061,242	4,053,965	3,817,887	3,637,875

(Production: Ministry of Economy, Trade and Industry, 2002; Import and export: Ministry of Finance, 2003)

4.2 Use information

1,2-dichloroethane is primarily used as a synthetic raw material (for vinyl chloride monomer, ethylenediamine, polyamino resin, and ion-exchange resin). It is also used for film detergent, solvent (organic synthesis, vitamin extracts), pesticide, and fumigant purposes (The Chemical Daily, Co., Ltd., 2003).

4.3 Release Sources Information

4.3.1 Release sources for 1,2-dichloroethane under the Law for PRTR and Promotion of Chemical Management (PRTR Law)

According to the "FY2001 Survey Results on Reported Chemical Release and Transfer, and Non-reported Chemical Release" (Ministry of Economy, Trade and Industry, Ministry of the Environment, 2004a, b) (hereinafter referred to as FY2001 PRTR data) under the Law for PRTR and Promotion of Chemical Management, in the year under review, the amount of 1,2-dichloroethane released or transferred by reporting operators nationwide totaled 915 tons into the air, 4 tons into public water bodies, 1,534 tons as waste, and 19 kg to sewage. There was no release of 1,2-dichloroethane into the soil. The amount of 1,2-dichloroethane released by non-reporting operators was 10 tons in target industries, while not estimated for other industries, households, and movable bodies.

a. Release and transfer in target industries

Table 4-2 shows the amount of 1,2-dichloroethane released and transferred to environmental media (air, water, soil), by type of target industry. Figures were obtained from the FY2001 PRTR data.

When estimating the amount of 1,2-dichloroethane released by non-reporting operators, the Ministry of Economy, Trade and Industry and the Ministry of the Environment did not classify the data by type of environmental medium. Therefore, we estimated the amount of 1,2-dichloroethane released into each environmental medium, assuming that the percent distribution for 1,2-dichloroethane released by non-reporting operators in each industry, by type of environmental media, was the same as that by reporting operators. (National Institute of Technology and Evaluation, 2004).

Table 4-2 Release, etc. of 1,2-dichloroethane to environmental media, by type of target industry(ton/year)

Type of industry	Reporting operators					Non-reporting operators			Total release by reporting and non-reporting operators	
	Release			Transfer		Release (estimates) [1)]				
	Air	Water	Soil	Sewage	Wastes	Air	Water	Soil	Total release [3)]	Percentage (%)
Chemical	806	3	0	<0.5	1,530	10	<0.5	0	819	88

industry										
Warehouse industry	82	0	0	0	1	-	-	-	82	9
Metal products industry	12	0	0	0	0	<0.5	0	0	12	1
Oil/coal products industry	8	0	0	0	0	-	-	-	8	1
Other manufacturing industry	6	0	0	0	3	<0.5	0	0	6	1
Others [2)]	1	2	0	0	<0.5	<0.5	0	0	3	0
Total [3)]	915	4	0	<0.5	1,534	10	<0.5	0	930	100

(National Institute of Technology and Evaluation, 2004)

1. We estimated the amount of 1,2-dichloroethane released into each environmental medium, assuming that the percent distribution for 1,2-dichloroethane released by non-reporting operators in each industry, by type of environmental media, was the same as that by reporting operators.
2. "Others" indicates the total release of 1,2-dichloroethane in the target industries other than the above five industries.
3. Figures are rounded down in this table. Therefore, actual total amounts in each category may be different from the figures above.

-: Not estimated.

The release and transfer of less than 0.5 ton was mentioned as "<0.5" without exception.

According to the amount of 1,2-dichloroethane produced in 2001 and the basic unit of release in the production process (Japan Chemical Industry Association, 2002), the amount of 1,2-dichloroethane released during production was estimated to be 85 tons into the air (National Institute of Technology and Evaluation, 2004). Therefore, the amount of released 1,2-dichloroethane, cited from the FY2001 PRTR data, is considered to be greater in use than during production.

b. Release in non-target industries, or from households and movable bodies

The FY 2001 PRTR data did not estimate the amount of 1,2-dichloroethane released in non-target industries, or from households and movable bodies (Ministry of Economy, Trade and Industry, Ministry of the Environment, 2003b).

4.3.2 Other release sources

1,2-dichloroethane used for pesticide or fumigant purposes can be released into the air at the site of use. However, as there are no data available for the total amount of 1,2-dichloroethane used for pesticide purposes nationwide, the FY2001 PRTR data does not cover these release sources (Ministry of Economy, Trade and Industry, Ministry of the Environment, 2003b).

4.4 Estimated release routes

As outlined in the use information above, 1,2-dichloroethane is primarily used as a synthetic raw material for vinyl chloride monomer, etc. According to that information and FY2001 PRTR data, 1,2-dichloroethane is considered to be primarily released during the use of 1,2-dichloroethane itself or products that contain 1,2-dichloroethane.

In the emission scenario, the amount of 1,2-dichloroethane released nationwide for a year is presumed to be 925 tons into the air and 4 tons into the water. The amount of 1,2-dichloroethane released into the water includes 1,2-dichloroethane released by sewage plants and waste disposal facilities.

5. Environment fate

5.1 Stability in the atmosphere

a. Reaction with OH radical

In the troposphere, reaction rate constant between 1,2-dichloroethane and the OH radical is 2.48×10^{-13} cm^3/molecule/second (measured at 25℃). (SRC:AopWin, 2001). Supposing the concentration of the OH radical is 5×10^5 to 1×10^6 molecules/cm^3, the half-life of 1,2-dichloroethane is estimated to be one to two months.

b. Reaction with ozone

As far as we know, there is no report available on the reaction of 1,2-dichloroethane with ozone.

c. Reaction with nitrate radicals

As far as we know, there is no report available on the reaction of 1,2-dichloroethane with nitrate radicals.

5.2 Underwater stability

5.2.1 Nonbiodegradability

1,2-dichloroethane is stable with regard to hydrolysis, and its half-life at pH7 and 25℃ is estimated to be 72 years (Barbash and Reinhard, 1989). This means that 1,2-dichloroethane cannot virtually be hydrolyzed in a general water environment.

5.2.2 Biodegradability

According to the results of a two-week test on biodegradability of 1,2-dichloroethane under aerobic conditions conducted in accordance with the Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances, BOD-measured degradability of 1,2-dichloroethane at a concentration of 100 mg/L was found to be zero (BOD: biochemical oxygen demand) when activated sludge was 30 mg/L. Apparently, it seems difficult to biodegrade 1,2-dichloroethane. When TOC-measured (TOC: total organic carbon), the degradation rate registered 2%, while the rate became 1% when GC-measured (GC: gas chromatography). (Ministry of International Trade and Industry 1978)

Due to its characteristics of high stream pressure (8.1 kPa at 20℃. See Chapter 3.), it is possible for 1,2-dichloroethane to volatilize during a biodegradability test prior to adequate contact with microorganisms and acclimatization. Actually, during a test on 1,2-dichloroethane at concentrations of 5 and 10 mg/L in a flask placed at a fixed position, 20 to 63% of the entire amount disappeared within the first seven days, 5 to 27% of which was reported to have volatilized (Tabak et al., 1981).

Another test using microorganisms taken from activated sludge in a sewage plant successfully clarified the process of biodegradation of 1,2-dichloroethane. At first, ethylene chlorohydrin was generated through the process of dechlorination. Then, chloroacetic acid was generated from chloroacetaldehyde. Another dechlorination led to complete degradation, following the generation of glycolic acid. (Janssen et al., 1985)

On the contrary, there is a report that 1,2-dichloroethane was not degraded during a 35-day test conducted under anaerobic conditions. (Jafvert and Wolfe, 1987)

The above test results lead to the conclusion that 1,2-dichloroethane is biodegradable under aerobic conditions, when assisted by some biodegradability-facilitating conditions such as acclimatization.

5.2.3 Elimination through sewage treatment

Sewage treatment can eliminate 69 to 95% of the entire volume of 1,2-dichloroethane in waste water. (GDCh BUA, 1994)

5.3 Behavior in the natural water environment

1,2-dichloroethane has a high Henry constant of 120 $Pa.m^3/mol$ (at 23℃. See Chapter 3)

as well as a high steam pressure (8.1 kPa at 20℃. See Chapter 3). Therefore this substance, when discharged to the environment, is considered to mostly migrate to the atmosphere. When 1,2-dichloroethane is stirred underwater, its half-life ranges from 5 to 29 minutes, depending on depth and surface area. (Dilling et al., 1975)

5.4 Bio-concentration

No tests have been conducted yet on the tendency of concentrations of 1,2-dichloroethane in accordance with the Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances. However, this substance is considered to be completely non-accumulative or only slightly accumulative, judging from test results on tetrachloroethylene conducted under the Law (Ministry of Economy, Trade and Industry, 1978). (This test on the tendency of concentrations of tetrachloroethylene conducted for the period of 6 weeks at the underwater concentration of 0.1 mg/L and 0.01 mg/L respectively showed that the concentration factor was 25.8 to 77.1 for 0.1 mg/L and 28.4 to 75.7 for 0.01 mg/L.)

1,2-dichloroethane tends not to be bio-accumulative. A test on the tendency of bio-concentrations of 1,2-dichloroethane using bluegill fish for 14 days shows that the bio-concentration coefficient is 2.0 and that its half-life is less than 2 days. (Barrows et al., 1980)

6. Impact on living creatures in the environment

6.1 Impact on aquatic living creatures

6.1.1 Toxic impact on microorganisms

Table 6-1 shows results of toxicity tests of 1,2-dichloroethene for microorganisms.

Toxicity of this substance has been reported on several species of bacteria. Among the reports on toxicity levels, the lowest value reported was a 48-hour EC_{50} value of 25mg/L (to inhibit generation of anaerobic gas) for Methanogen (Blum and Speece, 1991). Reports on protozoa include a 20-hour EC_5 value of 1,050mg/L (to inhibit reproduction) for Uronema parduczi (Bringmann and Kuhn, 1980a).

Table 6-1: Results of toxicity tests of 1,2-dichloroethene for microorganisms

Species	Temperature (℃)	Endpoint		Concentration (mg/L)	Reference
Bacteria Microcystis	27	8-day threshold of	Inhibit growth	105 (n)	Bringmann & Kuhn, 1976

aeruginosa		toxicity 1)			
Pseudomonas putida	25	16 -hour threshold of toxicity 1)	Inhibit reproduction	135 (n)	Bringmann & Kuhn, 1977
Nitrosomonas	25	24-hour EC_{50}	Inhibit consumption of ammonia	29 (n)	Blum & Speece, 1991
Methanogen	35	48-hour EC_{50}	Inhibit generation of anaerobic gas	25 (n)	
Aerobic heterotroph	25, 35	15-hour EC_{50}	Inhibit consumption of oxygen	470 (n)	
Photobacterium phosphoreum	15	5-minute EC_{50}	Inhibit emission of light	700 (n)	
	ND	15-minute EC_{50}		770 (n)	Freitag et al., 1994
Protozoa Entosiphon sulcatum	25	72-hour threshold of toxicity 2)	Inhibit reproduction	1,127 (n)	Bringmann & Kuhn, 1978
Uronema parduczi	25	20-hour threshold of toxicity 2)	Inhibit reproduction	1,050 (n)	Bringmann & Kuhn, 1980a
Chilomonas paramaecium	20	48-hour threshold of toxicity 2)	Inhibit reproduction	943 (n)	Bringmann & Kuhn, 1980b

ND: No data

(n): Nominal value

1) Concentration at which 3% of the volume in a test zone is affected(EC_3)

2) Concentration at which 5% of the volume in a test zone is affected(EC_5)

6.1.2 Toxic impact on algae

Table 6-2 shows results of toxicity tests of 1,2-dichloroethene for algae.

Test organisms include Selenastrum and Scenedesmus species in fresh water, and the

results show how 1,2-dichloroethene tends to inhibit their growth. Each test was conducted in a closed system by taking into consideration volatility of 1,2-dichloroethene. It is shown that 72- to 96-hour EC_{50} values (to inhibit growth) range from 129 to 294 mg/L. Reported values of NOEC (no-observed-effect-concentration) for Selenastrum, as an index of chronic toxicity in accordance with the OECD test guideline, include 65.6 mg/L (for biomass) and 111 mg/L (for growth rate). (Environment Agency, 1996) There are no reliable reports on algae in seawater.

Table 6-2: Results of toxicity tests of 1,2-dichloroethene for algae

Species	Test method	Temperature (℃)	Endpoint		Concentration (mg/L)	Reference
Species in fresh water						
Selenastrum capricornutum1)	OECD 201 GLP stagnant water in a closed system	22.9-23.3	72-hour EC_{50} 24/48-hour EC_{50} 24/72-hour EC_{50} 72-hour NOEC 24/48-hour NOEC 24/72-house NOEC value	Inhibit growth Biomass Growth rate Growth rate Biomass Growth rate Growth rate	129 240 294 65.6 111 111 (m)2)	Ministry of Environment, 1996
Scenedesmus quadriccauda	stagnant water in a closed system	27	8-day threshold of toxicity 3)	Inhibit growth	710 (n)	Bringmann & Kuhn, 1977
Scenedesmus subspicatus	OECD 201 stagnant water in a closed system	25±1	72-hour EC_{50} value	Inhibit growth	189 (m)	Freitag et al., 1994
	stagnant water in a closed	21-25	<96-hour EC_{50} value	Inhibit growth	166 (m)	Behechti et al., 1995

	system					

(m): Measured value

(n): Nominal value

Closed system: The test vessel or tank is covered but has headspace.

1) Current scientific name is Pseudokirchneriella subcapitata

2) Value measured at the beginning of exposure to 1,2-dichloroethene

3) Concentration at which 3% of the volume in a test zone is affected (EC_3)

6.1.3 Toxic impact on invertebrate animals

Table 6-3 shows results of toxicity tests of 1,2-dichloroethene for invertebrate animals.

The reports on acute toxicity of 1,2-dichloroethene for Daphnia magna (water flea) in fresh water, as shown below, can all be considered reliable, judging from the test method of using stagnant or semi-stagnant water in a closed system by taking into consideration the substance's tendency of volatility, or the method of determining the level of toxicity through measuring the concentration of test substances. Toxicity values (in terms of 48-hour LC_{50}/EC_{50}) range from 99.4 to 270 mg/L.

Results showing chronic toxicity for reproductive functions under the OECD test guidelines include a 21-day NOEC of 1.02 mg/L (Environment Agency, 1996) and 28-day NOEC of 11 mg/L (Richter et al., 1983).

Marine species tested include Crustacea such as Elminuis modestus (a kind of barnacle) and Artemia salina (brine shrimp). Acute toxicity values identified for the latter, in terms of its impact on inhibiting swimming capability, include 36.4 mg/L (Foster and Tullis, 1985).

Table 6-3: Results of toxicity tests of 1,2-dichloroethene for invertebrate animals

Species	Growth stage	Test method	Temperature (℃)	Hardness (mg CaCO3/L)	pH	Endpoint	Concentration (mg/L)	Reference
Species in fresh water								
Daphnia magna (Crustacea, water flea)	Within the first 24 hours after birth	stagnant water in a closed system	22±1	72	6.7-8.1	24-hour LC_{50} 48-hour LC_{50}	250 220 (n)	LeBlanc, 1980
		ASTM[1)] stagnant water in a closed system	20±1	43.5-47.5	7.0-7.7	48-hour LC_{50} 48-hour EC_{50} Inhibit swimming capability	270 160 (m)	Richter et al., 1983
		semi-stagnant water airtight condition	20±1	43.5-47.5	6.6-7.9	28-day NOEC 28-day LOEC reproductive function	11 21 (m)	
		OECD 202	ND	ND	ND	24-hour EC_{50} Inhibit swimming capability	10 (m)	Freitag et al., 1994
		OECD	19.7-	35.5	7.7-	24-hour EC_{50}	185	Ministry of

		202 GLP	20.0		7.8	48-hour EC_{50} Inhibit swimming capability	99.4 (m)	Environment, 1996
		OECD 202 GLP	19.6-20.3	35.5	7.1-7.9	21-day NOEC 21-day LOEC reproductive function	1.02 2.56 (a, n)	
Species in seawater								
Elminuis modestus (a kind of barnacle)	Larvae	stagnant water in a closed system	ND	ND	ND	48-hour LC_{50}	186 (n)	Pearson & McConnell, 1975
Artemia salina (Crustacea, brine shrimp)	30 hours after incubation	stagnant water in a closed system	19	salt content 3.2%	ND	24-hour EC_{50} Inhibit swimming capability	93.6	Foster & Tullis, 1985
		stagnant water in a closed system	19	salt content 25% 50%	ND	24-hour EC_{50} Inhibit swimming capability	36.7 79.7	Foster & Tullis, 1985

ND: no data

(a, n): Nominal value is shown in the table, since measured concentration of the test substance is within ±20% of nominal value.

(m): Measured value

(n): Nominal value

Closed system: The test vessel or tank is covered but has headspace.

Airtight condition: The test vessel is filled to the brim with no headspace left

1) Test guidelines of American Society for Testing and Materials

6.1.4 Toxic impact on fish

Table 6-4 shows results of toxicity tests of 1,2-dichloroethene for fish.

We got reliable data on acute toxicity of 1,2-dichloroethene for fathead minnows (Pimephales promelas), Japanese killifish (Oryzias latipes), guppies (Poecilia reticulate), bluegills (Lepomis macrochirus), rainbow trout (Oncorhynchus mykiss) and largemouth bass (Micropterus salmoides). Tests on those fish were conducted either in a way to create an environment of running water or stagnant water/semi-stagnant water in a closed system by taking into consideration the substance's tendency to volatilize, or in a way to measure the concentration of test substances to determine the level of toxicity. Reported LC_{50} values range from 66.0 to 136 mg/L. The lowest value of 66.0 mg/L, which is a 96-hour LC_{50} value, was detected from largemouth bass through the method of measuring the average concentration of the substance in the test water. (Industrial Bio-Test Laboratories, Inc., 1971)

Reported chronic toxicity values include 59 mg/L of LOEC and 29 mg/L of NOEC for fathead minnows, as measured in terms of impact on their incubation rate, survival rate and growth

during the early living stage of 32 days covering the time of fertilization and the fry period (Benoit et al., 1982), a LC_{50} value of 34 mg/L for rainbow trout, as measured during the 27-day period starting from fertilization until the fourth day after incubation (Black et al., 1982), and a LC_{50} value of < 56 mg/L for silver salmon, as measured during the 21-day period starting from fertilization (Reid et al., 1982).

Marine species tested include marbled flounders (Limanda limanda). For this fish, an acute toxicity value of 115 mg/L has been reported as the 96-hour LC_{50} value (Pearson and McConnell, 1975).

Table 6-4: Results of toxicity tests of 1,2-dichloroethene for fish

Species	Growth stage	Test method	Temperature (℃)	Hardness (mg CaCO3/L)	pH	Endpoint	Concentration (mg/L)	Reference
Species in fresh water								
Pimephales promelas (Fathead minnow)	Eggs of two to eight hours old	Running water	25±1	45	7.4	32-day NOEC 32-day LOEC Incubation, survival and growth	29 59 (m)	Benoit et al., 1982
	25 to 30 days old	Running water	25±1	45.5	7.5	96-hour LC_{50}	118 (m)	Veith et al., 1983
	30 to 35 days old	U.S. EPA Running water	25±2	45.0-45.5	6.7-7.6	96-hour LC_{50}	116 (m)	Walbridge et al., 1983
	31 days old	Running water	25	44.8	7.4	96-hour LC_{50}	136 (m)	Geiger et al.,1985
Oryzias latipes (Japanese killifish)	1.81 cm 0.0907 g	OECD 203 GLP Semi-stagnant water under airtight condition	23.3-23.9	35.5	7.1-7.8	96-hour LC_{50}	>126 (m)	
Lepomis macrochirus (Bluegill)	35-75 mm	Stagnant water	18	ND	7	96-hour LC_{50}	94.0 (m)	Industrial Bio-Test Laboratories, Inc., 1971
Poecilia reticulata (Guppy)	Two to three months old	Semi-stagnant water in a closed system supportive agent	22±1	25	ND	7-day LC_{50}	106 (n)	Konemann, 1981
Oncorhynchus mykiss (Rainbow trout)	Eggs within 30 minutes after fertilization	Running water in a closed system	13.1±0.1	93.9±0.4	7.8±0.01	23-day LC_{50} (on the day of incubation) 27-day LC50 (on the 4th day after incubation)	34 34 (m)	Black et al., 1982
Micropterus salmoides (Largemouth bass)	35-75 mm	Stagnant water	13	ND	7	96-hour LC_{50}	66.0 (m)	Industrial Bio-Test Laboratories, Inc., 1971
Oncorhynchus kisutch (Silver salmon)	Eggs having eyes	Semi-stagnant water	3.0±0.5	ND	5.3-5.8	21-day LC50	<56 (m)	Reid et al., 1982
Species in seawater								
Limanda	15-20 cm	Running	ND	ND	ND	96-hour LC_{50}	115	Pearson &

limanda (Marbled flounder of the flounder family)		water					(n)	McConnell, 1975

ND: no data

(a, n): Nominal value is shown in the table, since measured concentration of the test substance is within ±20% of nominal value.

(m): Measured value

(n): Nominal value

Closed system: The test vessel or tank is covered but has headspace.

Airtight condition: The test vessel is filled to the brim with no headspace left

1) Organic solvent

6.1.5 Toxic impact on other aquatic living creatures

Table 6-5 shows results of toxicity tests of 1,2-dichloroethene for amphibians.

The tests were conducted on embryos of salamanders (Ambystoma gracile) and frogs (Rana pipiens) taken within 30 minutes after fertilization, to detect their incubation rate and survival rate when exposed to 1,2-dichloroethene for the period of 9 and 9.5 days respectively. The test results show that the LC_{50} value is 2.54 mg/L when exposed for 9.5 days and 4.40 mg/L when exposed for 9 days (on the fourth day after incubation). (Black et al., 1982)

Table 6-5: Results of toxicity tests of 1,2-dichloroethene for amphibian animals

Species	Growth stage	Test method	Temperature (℃)	Hardness (mg CaCO3/L)	pH	Endpoint	Concentration (mg/L)	Reference
Species in fresh water								
Pimephales promelas (Fathead minnow)	Eggs within 30 minutes after fertilization	Running water in a closed system	20.2±0.5	98.2±1.1	8.4±0.03	5.5-day LC50 (on the day of incubation)	6.53	Black et al., 1982
						9.5-day LC50 (on the fourth day after incubation)	2.54 (m)	
	Eggs within 30 minutes after fertilization	Running water in a closed system	20.2±0.5	98.2±1.1	8.4±0.03	5.5-day LC50 (on the day of incubation)	4.52	
						9.5-day LC50 (on the fourth day after incubation)	4.40 (m)	

(m): Measured value

Closed system: The test vessel or tank is covered but has a headspace.

6.2 Impact on terrestrial living creatures

6.2.1 Toxic impact on microorganisms

As far as we know, there are no test reports available on the toxic impact of

1,2-dichloroethene on microorganisms (bacteria or germs in soil).

6.2.2 Toxic impact on plants

We've found several test reports on toxic impact of 1,2-dichloroethene on plants.

They include a 24-hour LC_{50} value of 3×10^3 mg/kg for barley (Ehrenberg et al., 1974) and a 2-hour EC_{50} value of 17.1 mg/L (concentration at which 50% are affected) in terms of impact on germination for tobacco pollen.

6.2.3 Toxic impact on animals

It has been reported that a test on the toxic impact of 1,2-dichloroethene on striped earthworms was conducted by exposing this organism to a 1,2-dichloroethene-stained filter paper, and the resulting 48-hour LC_{50} value was 60 μ g/c ㎡.

6.3 Impact on living creatures in the environment (summary)

There is a relatively large number of test reports available on the impact of 1,2-dichloroethene on living creatures in the environment, and those results show the substance's toxicity in terms of lethal impact, swimming capability-inhibiting impact, growth-inhibiting impact, reproductive function-inhibiting impact, etc.

Since 1,2-dichloroethene is highly volatile, toxicity tests should be conducted either in a way to create an environment of running water or stagnant water/semi-stagnant water in a closed system by taking into consideration the substance's tendency to volatilize, or in a way to measure the concentration of test substances to determine the level of toxicity.

As for impact on microorganisms, we obtained reports on bacteria and protozoa. For the former, the lowest value reported was a 48-hour EC_{50} value of 25mg/L to inhibit generation of anaerobic gas for Methanogen. For the latter, a 20-hour threshold of toxicity of 1,050mg/L to inhibit reproductive function (EC_5) has been reported for Uronema parduczi.

As for the impact on algae, we obtained reports on 72- to 96-hour EC_{50} values to inhibit growth of Selenastrum and Scenedesmus respectively. The reported values range from 129 to 294 mg/L, which means that 1,2-dichloroethene can be considered as having no acute toxicity to those algae (under the GHS categorization). Reported values of NOEC (no-observed-effect-concentration) for Selenastrum, as an index of chronic toxicity in accordance with the OECD test guideline, include 65.6 mg/L (for biomass) and 111 mg/L (for growth rate).

Reported results of acute toxicity test of 1,2-dichloroethene for invertebrate animals range from 36.4 to 270 mg/L. From the results, it has been found that the substance exhibits acute toxicity to brine shrimp of Crustacea (to the degree of level III under the GHS categorization). Reported NOEC values, as an index of chronic toxicity for reproductive function, range from 1.02 to

11 mg/L for Daphnia magna (water flea).

As for acute toxicity for fish, reported values range from 66.0 to 136 mg/L, of which the lowest value is a 96-hour LC_{50} value of 66.0 mg/L for largemouth bass. This value falls under level III acute toxicity under the GHS categorization. Reported chronic toxicity values, in terms of NOEC and LC_{50} as an index of lethal impact or growth-inhibiting impact, range from 29 to 56 mg/L for fathead minnows, rainbow trout and silver salmon.

We also obtained reports on amphibians. Reported LC_{50} values for embryos of northwestern salamanders and leopard frogs taken within 30 minutes after fertilization range from 2.54 to 4.40 mg/L.

When comparing marine living creatures with those in fresh water, it can be assumed that crustaceans living in seawater are slightly more susceptible to 1,2-dichloroethene than their counterparts in fresh water, or that susceptibility is almost the same. As for the comparison between seawater and fresh water, we were unable to obtain sufficient data on fish and no data was available on algae

Reported data on terrestrial living creatures include a 24-hour LC_{50} value of 3×10^3 mg/kg for barley and a 2-hour EC_{50} value of 17.1 mg/L to inhibit germination for tobacco in the category of plants, as well as a 48-hour LC_{50} value of 60 μ g/c ㎡ for striped earthworms as measured by exposing this organism to a 1,2-dichloroethene-stained filter paper.

The above-mentioned reports show that acute toxicity of 1,2-dichloroethene to aquatic living creatures has been detected for some crustaceans and fish, registering level-III values under GHS categorization.

Among reported toxicity values, the lowest one for aquatic living creatures is a 21-day NOEC of 1.02 mg/L to inhibit reproductive function of a crustacean, Daphnia magna.

7. Human health effects

7.1 In vivo fate

Table 7-1 shows the test results for the in vivo fate of 1,2-dichloroethane.

7.1.1 Absorption

1,2-dichloroethane is quickly absorbed by humans and test animals by all routes of administration; oral, inhalation, or skin.

Rats given 150 mg/kg orally reached their maximum blood concentration of 30-44 μg/mL in 15 minutes (Reitz, et al., 1982). In a test of rats given 25-150 mg/kg orally, blood concentration in rats given more than 50 mg/kg was not linearly correlated with the administered dose, indicating saturation in gastrointestinal absorption (Spreafico et al., 1980).

Two reports were submitted in relation to human inhalation exposure to 1,2-dichloroethane: a person inhaling 1,2-dichloroethane for 30 minutes died after 20 hours (U.S. DHHS, 1999); 1,2-dichloroethane accumulated in the breast milk (2.8 mg/100 mL) of a woman occupationally inhaling and dermally absorbing the substance (15.6 ppm) (U.S. DHHS, 1999). Rats inhaling 1,2-dichloroethane reached their maximum blood concentration in 1-2, or 2-3 hours (Reitz et al., 1980, 1982; Spreafico et al., 1980). The peak blood concentration in rats given 150 ppm of 1,2-dichloroethane for six hours was 8-10 μg/mL (Reitz et al., 1980, 1982).

In a closed epicutaneous test, the rate of dermal absorption of 1,2-dichloroethane by mice was 479.3 nmol/min/cm^2. From this figure, the amount of dermal absorption by humans whose hands were immersed in 1,2-dichloroethane was calculated to be 36.6 mg/min.

7.1.2 Distribution

The analysis on the distribution of 1,2-dichloroethane to each tissue shows that absorbed 1,2-dichloroethane accumulates in fat tissues through both oral and inhalation exposure.

In the test of rats given 1,2-dichloroethane orally, the concentration of the substance in liver peaked the fastest among all organs (in 10 minutes after exposure). The concentration of 1,2-dichloroethane peaked in fat tissues in 45-60 minutes, and the peak concentration was about five times as high in fat as in blood (Spreafico et al., 1980). Concentrations of 1,2-dichloroethane in each organ were 20-30 times as high in rats inhaling 250 ppm as those inhaling 50 ppm. The accumulation of 1,2-dichloroethane was 8-9 times as large in fat tissues as in blood (Spreafico et al., 1980).

In the test of pregnant rats exposed to 153-1,999 ppm for five hours, the concentration of 1,2-dichloroethane in maternal blood and in fetuses of rats increased linearly with increasing exposure levels, indicating transplacental distribution of 1,2-dichloroethane. The concentration of 1,2-dichloroethane was 0.316 times as high in fetuses as in maternal blood (Withey and Karpinski, 1985).

Withey and Colins (1980) reported that the distribution of 1,2-dichloroethane after intravenous injection coincided well with 2- or 3- compartment models. D'Souza (1987) also reported that the actual measurement of blood concentration in rats and mice coincided well with the value calculated from the PB-PK model developed by the 3- compartment model.

*1. PB-PK model: Abbreviation of the Physiologically Based Pharmacokinetic Model that enables incorporation of physiological and anatomical data on humans and animals.

7.1.3 Metabolism and excretion

Fig. 7-1 shows the pathways of metabolism of 1,2-dichloroethane (U.S. DHHS, 1999).

In the test of rats given 150 mg/kg of radiolabeled 1,2-dichloroethane orally, thiodiacetic acid and sulfate conjugates appeared in the urine. 85.7% of the radioactivity was excreted in the urine, and 7.7% as carbon dioxide in the exhaled air. (Reitz et al., 1980, 1982). In relation to oral administration, another report shows that S-carboxymethyl cysteine, thiodiacetic acid, and chloroacetic acid were detected in both mice dosed 37.5 or 150 mg/kg and rats dosed 25 or 100 mg/kg. In mice, 18.21% of the radioactivity was excreted as carbon dioxide in the exhaled air, and in rats, 8.20%. (Mitoma et al., 1985). In addition, there is a report saying that glycolic acid sulfide and thioether were detected. In this test, the urinary excretion of radioactivity was 62.1% for lower doses but 7.4% for higher doses, which suggests saturated metabolism or gastrointestinal absorption (Payan et al., 1993).

Metabolites formed through inhalation exposure are similar to those through oral administration. In the test of animals exposed to 150 ppm for six hours, thiodiacetic acid and sulfate conjugates appeared in the urine. The percentages of each metabolite to the total in inhalation exposure are the same as those in oral administration. 84% of the radioactivity was excreted in the urine, and 7% as carbon dioxide in the exhaled air. (Reitz et al., 1980; 1982). In another test of rats exposed to 50 ppm, glycolic acid sulfide, sulfate conjugates, and chloroacetic acid were detected (Cheever et al., 1990).

As for intraperitoneal injection, in the test of mice given a single shot of 50-170 mg/kg radiolabeled 1,2-dichloroethane, the remaining radioactivity was excreted as chloroacetic acid, S-carboxymethyl cysteine/sulfate conjugates, thiodiacetic acid, 2- chloroethanol, and S,S' ethylene-bis-cysteine in the urine, and as carbon dioxide in exhaled air. 51-73% of the radioactivity was excreted in the urine, and 4-12% as carbon dioxide in the exhaled air (Yllner, 1971).

A study shows that the glutathione conjugate of 1,2-dichloroethane binding to DNA may cause mutagenic and carcinogenic damage, and another study indicates that 1,2-dichloroethane is bound to DNA in rats given radiolabeled 1,2-dichloroethane by oral administration and inhalation exposure (Cheever et al., 1990; Reitz, 1980, 1982). The measurement of SH concentration in liver after oral administration and inhalation exposure shows the consumption of glutathione by 1,2-dichloroethane (Reitz et al., 1982).

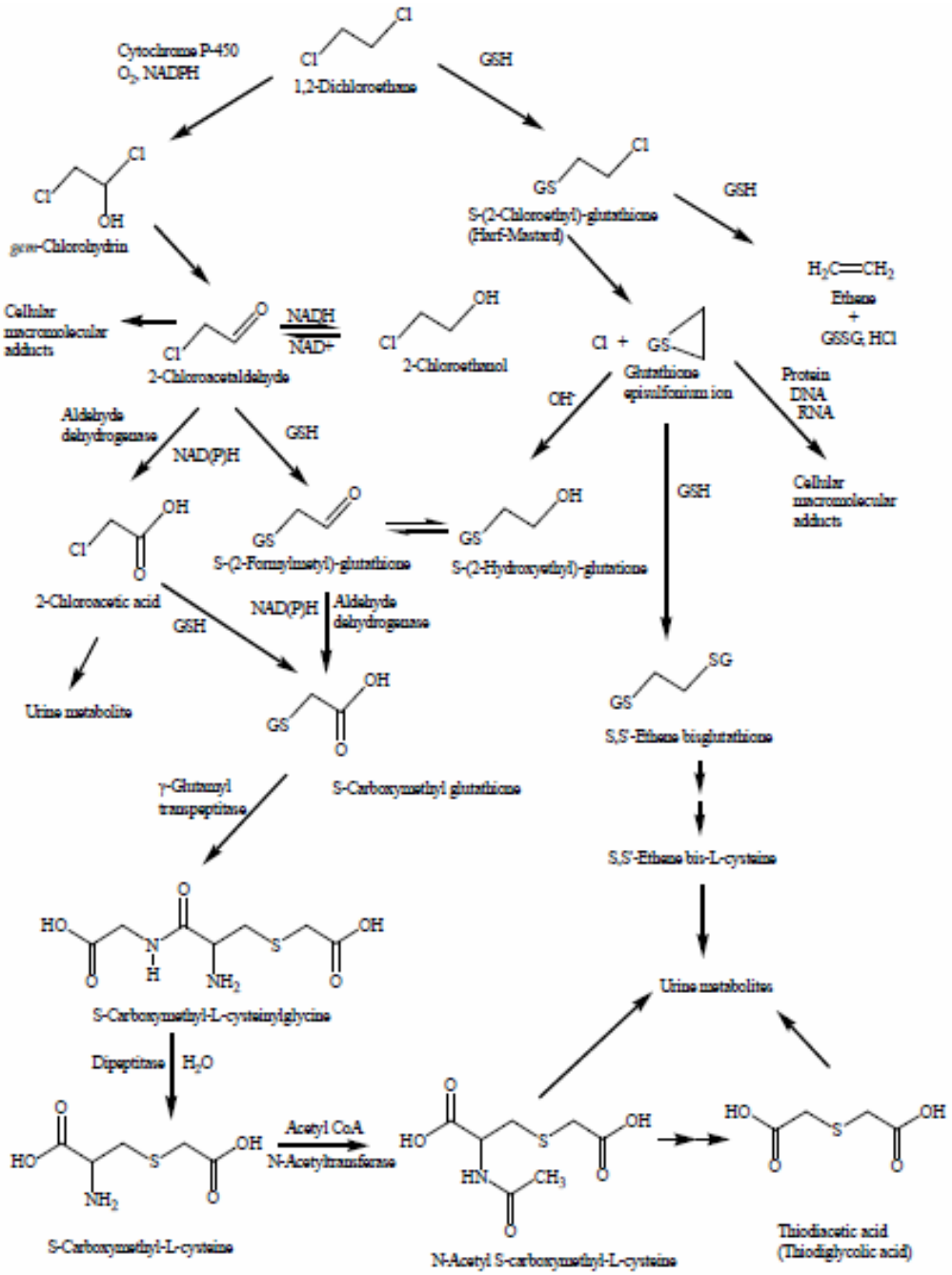


Fig. 7-1 Metabolism of 1,2-dichloroethane (Cited from U.S. DHHS, 1999).

Table 7-1 Test results for the in vivo fate of 1,2-dichloroethane

Animal species	Administration method	Quantity	Results	Reference
Human (nurse, age unknown)	Inhalation Skin	15.6 ppm	1,2-dichloroethane (2.8mg/100mL) was detected from the breast milk of a breast-feeding mother.	US DHHS, 1999
Rat (SD, male, 14 months of age)	Single intravenous injection	1, 5, or 25 mg/kg	The disappearance of 1,2-dichloroethane in the blood was fast and biphasic. The 1, 5, or 25 mg/kg of 1,2-dichloroethane injected into the blood was detectable for 30 minutes, 60 minutes, and 2 hours, respectively. After this period, the remaining 1,2-dichloroethane was undetectable. The speed of disappearance declined linearly with increasing dosage, suggesting the existence of a saturation process in excretion. Blood $T^{1/2}$ (min) 1 mg/kg 7.30 5 9.49 25 14.07 AUC (μg min/mL) 1 mg/kg 9 5 54 25 595 Concentration at the beginning (μg/mL) 1 mg/kg 1.50 5 8.0 25 38.12	Spreafico et al., 1980

Rat (SD, male, 14 months of age)	Oral Single dose Repeated doses (5 days/week x 2 weeks)	Single dose: 25, 50, or 150 mg/kg Repeated doses: 50 mg/kg/day)	The concentration of 1,2-dichloroethane in liver reached a peak level in 10 minutes, the fastest among all organs. The disappearance is biphasic. 1,2-dichloroethane kinetics in the lungs were the same as in blood. However, the concentration of 1,2-dichloroethane in the lungs was lower than in blood. The concentration of the substance in fat tissues reached a peak in 45-60 minutes, later than in other organs. On the contrary its concentration level was higher. When 50 or 150 mg/kg was given to rats, the concentration level was about five times as high in fat as in blood. The disappearance of 1,2-dichloroethane from fat is monophasic. The accumulation of the substance in fat was saturated. The blood concentration in rats given more than 50mg/kg was not correlated with increasing dosage, indicating saturation in gastrointestinal absorption. The concentration of 1,2-dichloroethane in rats given 50 mg/kg did not differ between a single dose and repeated doses for 10 days, as well as between males and females.	Spreafico et al., 1980

	Blood	Fat	Lung	Liver
$T^{1/2}$ (min)				
25 mg/kg	24.62	23.22	24.10	18.47
50	44.07	30.11	38.26	42.31
150	56.70	57.63	44.57	66.47
AUC (µg min/mL)				
25 mg/kg	446	5119	136	679
50	1700	12543	538	1897
150	7297	29468	648	5384
Maximum concentration (µg/mL or g)				
25 mg/kg	13.29	110.67	2.92	30.02
50	31.94	148.92	7.20	55.00
150	66.78	259.88	8.31	92.10

Rat (SD, male, 14 months of age)	Single inhalation for 5 hours	50 or 250 ppm	The concentration of 1,2-dichloroethane peaked in 2-3 hours. Concentrations in each tissue were 20-30 times as high in rats exposed to 250 ppm as in those exposed to 50 ppm. The accumulation of 1,2-dichloroethane was 8-9 times as high in fat as in blood. The disappearance was fast in the lungs but slow in fat. The rate of disappearance depends on dosage. No saturation was observed.	Spreafico et al., 1980

	Blood	Fat	Lung	Liver
$T^{1/2}$ (min)				
50 ppm	12.69	22.63	11.26	10.72
250	22.13	28.12	15.53	17.51
AUC (μg min/mL)				
50 ppm	26	391	6	17
250	1023	13558	279	694
Concentration at the beginning (μg/mL or g)				
50 ppm	1.42	10.24	0.39	1.02
250	30.92	265.47	13.88	22.06

Rat (Osborne-Mendel, male, age unknown)	Single inhalation for 6 hours	150 ppm	Changes in the concentration of 1,2-dichloroethane in blood The blood concentration peaked 1-2 hours after the commencement of exposure, and reached a plateau 2 hours later at 8 μg/mL. After exposure, the concentration level fell sharply. The disappearance was biphasic. Half-life period: First phase (6 minutes) Second phase (35 minutes) AUC: 3,018 (μg min/mL)	Reitz et al., 1980

Rat (Osborne-Mendel, male)	Single oral gavage Single inhalation Radiolabeled [1,2-^{14}C] was administered.	Oral: 150 mg/kg Inhalation: 150 ppm	In the 48-hour observation of rats given 150 mg/kg or 150 ppm (both values are the maximum in the previous carcinogenicity tests), the total amount of radioactivity, the amount of unchanged 1,2-dichloroethane excreted in the exhaled air, and the amount of metabolites were larger in rats given doses orally than in those exposed through inhalation. On the other hand, there were no differences between the two routes in terms of the distribution of radioactivity, routes of excretion, and type of metabolites. The distribution of radioactivity was examined for organs that developed tumors in an oral carcinogenicity test and those that did not, and no differences of distribution were found among these organs. In the past, Maltoni et al. conducted a carcinogenicity test by inhalation exposure, and the NCI also conducted a test by oral administration. Tumors did not develop in the former, but developed in the latter (See Table 7-8). This time the test was conducted to clarify the difference of the results between the previous two studies. However, the test results show that there were no differences in the toxicokinetics of 1,2-dichloroethane between oral and inhalation exposure, and the difference of test results in the previous two studies was not clarified. In addition, there were no remarkable differences in the macromolecular binding of radioactivity [a)] between oral and inhalation exposure. Distribution of radioactivity 48 hours later	Reitz et al., 1980

	Oral (μ mol/kg)	%	Inhalation (μ mol/kg)	%
Collected radiolabeled EDC	1539	-	512	-
Unchanged EDC in exhaled air	447	-	9.4	-
Metabolites	(1092)	(100)	(503)	(100)
Urine	926	85.7	432	84.4
CO2	83.1	7.7	36.1	7.0
Carcass [b)]	46.9	4.3	22.7	4.4
Feces	23.6	2.1	8.90	1.7
Cage	12.5	1.1	3.34	0.7

Distribution to organs 48 hours later (nmol/g tissue)

	Oral	Inhalation
Liver	154	75
Kidney	120	77
Lung	51	35

Rat (Osborne-Mendel, male, age unknown)	Single oral gavage Single inhalation Radiolabeled [1,2-^{14}C] was administered.	Oral: 150 mg/kg Inhalation: 150 ppm	Macromolecular binding (nmol/g tissue) Oral / Inhalation Liver 175 / 268 Kidney 183 / 263 Lung 65 / 130 Spleen 106 / 147 Anterior stomach 160 / 71 Stomach 90 / 156	Reitz et al., 1980
Rat (Osborne-Mendel,	Comparison between a single	Oral: 150 mg/kg	* Changes in blood concentration Inhalation: The disappearance of 1,2-dichloroethane from blood was biphasic.	Reitz et al., 1982

Rat (Osborne-Mendel, male, age unknown)	Comparison between a single oral gavage and a single 6-hour inhalation	Oral: 150 mg/kg Inhalation: 150 ppm	* Macromolecular binding There was no particular difference between oral and inhalation (Reitz, R.H., et al., 1980). * DNA alkylation and mutagenicity in relation to bacteria If salmonella typhimurium TA1535 is incubated with 1,2-dichloroethane, alkylation will be linearly correlated with increasing reversion colonies. Cytosol concentration (%) 2.2 7.8 27 71 DNA alkylation (dpm/mg DNA) 8.65 27 107 137 Reversion colonies (revertants/108 cells) 4.6 23.5 80.2 111 * DNA alkylation in rats DNA alkylation was 3-5 times as high in oral administration as in inhalation exposure. DNA alkylation in spleen is one-third of that in other organs. No abnormal circumstances were observed in an autopsy, as well as biochemical and histopathological tests. DNA alkylation in rats [(μ mol/mol) DNA of bound EDC] Experiment -1: Liver 21.3 8.2; Spleen 5.8 1.8; Kidney 17.4 5.2; Stomach 14.9 2.8 Experiment -2: Liver 13.9 3.3; Spleen 2.5 1.8; Kidney 14.5 2.0; Stomach 6.7 1.9	Reitz et al., 1982

Rat (Osborne-Mendel, male, age unknown)	Comparison between a single oral gavage and a single 6-hour inhalation	Oral: 150 mg/kg Inhalation: 150 ppm	Glutathione depletion Samples of the liver were taken from the body 4 hours after oral administration and 6 hours after inhalation exposure, and the non-protein SH concentration in the liver was measured and converted to glutathione. Concentrations in both routes of entry were considerably lower than those in the control group. Glutathione depletion	Reitz et al., 1982

	Control group (No treatment)	Oral	Inhalation
SH concentration mg/g (Converted to glutathione)	1.35	0.35	0.31

Mouse (ICR, male, age unknown)	Skin contact Closed epicutaneous test 15 minutes 2.92 cm^2	0.5 mL	Out of 2,078 µg, the total amount absorbed by mice, 76.0 µg was excreted in exhaled air during exposure. The skin absorption rate was 479.3 nmoles/min/ $cm^{2.}$ The skin absorption rates of 1,2-dichloroethane and 7 other types of chlorinated solvents were almost linearly proportional to aqueous solubility. On the basis of these results, the amount of 1,2-dichloroethane absorbed by humans whose hands are immersed in the substance for one minute is calculated to be 36.6 mg, which is equivalent to the amount obtained from 1-minute inhalation of 3,615 ppm. Test results in mice Remaining DCE in body (µg) 2,002 Expiratory excretion (µg) 76.0 Total skin absorption (µg) 2,078 Skin absorption rate (nmol/min/ $cm^{2)}$ 479.3 Forecasted results in humans* Remaining DCE in body after 1-minute exposure (mg) 36.6 1-minute inhalation exposure level that is equivalent to the value above (ppm) 3,615 Calculation formula Surface area of both hands 800 cm^2 Respiratory volume 5 L/min Retention rate of inhaled 1,2-dichloroethane 50 % Remaining DCE in body after 1-minute exposure = Surface area x Remaining DCE in body per 1 cm^2 of applied area / 15 minutes = 800 cm^2 x 2002µg x 1/2.92 cm^2 x 1/15 min x 10^{-3} = 36.6 mg/min 1-minute inhalation exposure level that is equivalent to the value above = Remaining DCE after 1-minute skin contact / (Expiratory volume x Retention rate) x ppm conversion = 36.6 mg.min / (5L/min x 0.5 x 98.97/24.45 x 1/1000) = 3,615 ppm	Tsuruta, 1975

Rat (SD, pregnant female, age unknown)	5-hour inhalation 17th day of pregnancy	153, 305, 552, 1,039, 1,509, or 1,999 ppm	Immediately after exposure, the concentration of 1,2-dichloroethane in maternal blood and in fetuses (whole body) of rats and the weight of fetuses were measured. The concentration of 1,2-dichloroethane in both maternal blood and in fetuses increased linearly with increasing exposure level. The concentration of the substance was 0.316 times as high in fetuses as in maternal blood. The concentration in fetuses depends on their location in the uterus. The concentration of 1,2-dichloroethane was higher in the ovaries than in the uterine cervix. Fetal weight was low in both ends of the uterus, but high in the center thereof. Fetal weight was not correlated with the concentration of 1,2-dichloroethane in fetuses.	Withey & Karpinski, 1985
Rat (Wistar, male, age unknown)	Single oral gavage	100mg/kg (Solvent: water or corn oil)	The blood concentration of 1,2-dichloroethane was measured by collecting the blood 300 minutes after gavage. AUC was smaller for corn oil than for water, and the maximum concentration level was also lower for corn oil than for water. However, corn oil takes longer to reach the maximum concentration level. Comparison of AUC between water and corn oil (300 minutes after dose) (μg min/mL) Comparison of the excretion rate, maximum blood concentration, and peak time between water and corn oil	Withey et al., 1983

Comparison of AUC between water and corn oil (300 minutes after dose) (μg min/mL)

	Corn oil	Water	Ratio
AUC (μg min/mL)	1242	4825	3.88

Comparison of the excretion rate, maximum blood concentration, and peak time between water and corn oil

	Corn oil	Water
β min^{-1}	0.0156	0.0201
Maximum concentration (μg/mL)	15.9	84.6
Time (minute)	10.6	3.2

Rat (Wistar, male, age unknown)	Single intravenous injection	3, 6, 9, 12, or 15 mg/kg	In order to measure the blood concentration of 1,2-dichloroethane, blood samples were collected from 2 minutes after injection to the time when 1,2-dichloroethane became undetectable. The distribution of 1,2-dichloroethane fits a 2-compartment model for 3 and 6 mg/kg, and a 3-compartment model for 9, 12, and 15 mg/kg. 2-compartment model $\text{Ln } C_t = \text{Ln } (Ae^{-\alpha t} + Be^{-\beta t})$ 3-compartment model $\text{Ln } C_t = \text{Ln } (Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t})$	Withey & Colins, 1980

(mg/kg)	3.0	6.0	9.0	12.0	15.0
Vd (mL)	42.40	44.06	78.64	59.71	65.43
A (µg/mL)	22.60	50.67	39.87	61.82	71.23
α (min^{-1})	0.22	0.15	0.16	0.21	0.26
B (µg/mL)	3.72	3.31	11.14	15.23	24.79
β (min^{-1})	0.048	0.029	0.019	0.039	0.048
C (µg/mL)	-	-	1.412	1.425	2.518
γ (min^{-1})	-	-	0.0112	0.0106	0.0123

Rat (Wistar, male, age unknown)	Single intravenous injection	15 mg/kg	Samples were collected from heart, liver, lung, spleen, kidney, brain, and perinephric fat tissues during 5-300 minutes after injection. Additional samples were collected only from perinephric fat tissues during 24-30 hours after injection (This is because 1,2-dichloroethane became undetectable in the other organs). The absorption and excretion of 1,2-dichloroethane in organs were similar to those in blood. However, perinephric fat tissues took longer than the blood to absorb and excrete the substance.	Withey & Colins, 1980

Organs	α (min^{-1})	β (min^{-1})	A (μg/mL)	B (μg/mL)
Blood	0.4132	0.0242	58.0	24.2
Heart	0.0323	-	6.72	-
Lung	0.0226	-	4.20	-
Liver	0.0399	-	9.38	-
Spleen	0.0514	-	6.00	-
Kidney	0.0253	-	7.70	-
Brain	0.0378	-	9.20	-
Fat tissue	-	0.0088	36.9	-

Guinea pig (male and female, age unknown)	Skin contact for 12 hours Closed epicutaneous test (3.1 cm^2)	1.0mL	The blood concentration of 1,2-dichloroethane declined remarkably after increasing for 30 minutes. However, it took an upturn again after an hour and continued to increase until the end of exposure. The graph of changes in the excretion rate is not curved, and it is presumed that an upper compartment of a 2 compartment model fits. Blood concentration	Jakobson et al., 1982

Number of applied areas	Number of guinea pigs	30 minutes after excretion	6 hours after excretion
1	4	1.4	3.8
2	4	4.9	7.1

PB-PK model

Development of a PB-PK model

D'Souza et al., 1987

A PB-PK model was developed for the metabolism of 1,2-dichloroethane under the following requirements:

1. Metabolism is conducted in the lungs and liver.
2. There are three compartments: Richly Perfused Tissues, Slowly Perfused Tissues, and Fat.
3. Metabolism must occur by P-450-mediated oxidation (Saturation will occur) and glutathione conjugation (High doses will cause GSH depletion).

As a result, the actual measurement of blood concentration in rats and mice coincided well with the PB-PK model-based GHS concentrations in the liver and lungs.

Values used for calculation

Distribution coefficient ratio	SD	F344	B6C3F[1]	Human
Blood: air	27.6	30.4	29.7	21.1
Richly perfused: blood	1.1	1.2	1.0	-
Slowly perfused: blood	0.8	0.8	0.8	-
Fat: blood	12.2	11.4	12.1	-

Rate constants, etc.

DCE Vmax = 3.25 mg/h/kg, Km = 0.25 mg/L, Kf = 9.0/h kg

GSH Kgs = 0.0014/h kg, Hfee = 4,500/h kg, Kgsm = 0.14/h kg

Extrapolation of data from rodents to humans

When the production level of glutathione conjugates against the administered dosage is plotted based on the PB-PK model, the production level in liver appears the same among mice, rats, and humans. However, the production level in the lungs was two and half times as high in mice as in humans. Therefore it is presumed that the lung cancer rate is 1/2.5 times as high for humans as for mice. Therefore, the coefficient "12.7" generally used in accordance with the ratio of body surface was not appropriate for this case.

PB-PK model [c)]			Production level of glutathione conjugates In relation to the previous carcinogenicity tests on the inhalation or oral administration of 1,2-dichloroethane, calculations were made for the production level of glutathione conjugates in both the liver and lungs. Previous reports show that glutathione conjugates binding to DNA cause genetic toxicity. The production levels of glutathione conjugates in the liver and lungs were lower for 150 ppm inhalation exposure than for 75 mg/kg oral administration. It is presumed that since the production level of glutathione conjugates was lower for inhalation exposure than for oral administration, no carcinogenicity was found in the inhalation exposure test. Production level of glutathione conjugates (mg/L; calculated value) Type of dose / Liver / Lungs Oral gavage 150 mg/kg: 630 / 131 75 mg/kg: 372 / 71 Inhalation exposure 150 ppm (7h): 230 / 64	D'Souza et al., 1987
Rat (Osborne-Mendel, male, 4-6 weeks of age)	Oral gavage Non-radiolabeled 1,2-dichloroethane (5 days/week for 4 weeks) + radiolabeled 1,2-dichloroethane (single dose)	25 or 100 mg/kg	* Radioactivity collection rate (%) Exhaled air / CO_2 in exhaled air / Urine + Feces + Liver + Kidney / Carcass 7.65 / 28.21 / 81.88 / 2.37 81.03% of radioactivity was collected in the forms of CO_2 in exhaled air, extracts from urine/faces/liver/kidney, and the carcass, indicating that a large quantity of radioactivity was metabolized. * Liver protein binding (nmol eq/mg protein) 25 mg/kg / 100 mg/kg 0.18 / 1.07 The liver protein binding of 1,2-dichloroethane was smaller than that of other similar types of chlorinated hydrocarbon compounds. * S-carboxymethyl cysteine, thiodiacetic acid, and chloroacetic acid were detected as metabolites.	Mitoma et al., 1985

Mouse ($B6C3F_1$, male, 4-6 weeks of age)	Oral gavage Non-radiolabeled 1,2-dichloroethane (5 days/week for 4 weeks) + radiolabeled 1,2-dichloroethane (single dose)	37.5 or 150 mg/kg	* Radioactivity collection rate (%) Exhaled air: 7.65; CO_2 in exhaled air: 18.21; Urine + Feces + Liver + Kidneys: 81.88; Carcass: 2.37 81.03% of radioactivity was collected in the forms of CO_2 in exhaled air, extracts from urine/faces/liver/kidney, and the carcass, indicating that a large quantity of radioactivity was metabolized. * Liver protein binding (nmol eq/mg protein) 3.75: 0.14; 150 mg/kg: 0.52 The liver protein binding of 1,2-dichloroethane was smaller than that of other similar types of chlorinated hydrocarbon compounds. * S-carboxymethyl cysteine, thiodiacetic acid, and chloroacetic acid were detected as metabolites.	Mitoma et al., 1985
Rat (SD, male, age unknown)	Single oral gavage	0, 0.12, 0.25, 0.50, 1.01, 2.02, 4.04, or 8.08 mmol/kg	In this test, ^{14}C-labeled 1,2-dichloroethane was given to rats, and their urine samples were collected 24 hours after the doses in order to detect thiodiglycolic acid (TDGA) and thioethers. The percentage of excreted radioactivity to the administered dose decreased linearly with the increase in the administered dose. However, TDGA was stable at 21.8% for rats given up to 1.01mmol/kg. The excretion of TDGA increased in proportion to the administered dose. It is presumed that saturation in metabolism and gastrointestinal absorption mainly caused the declining excretion rate. Urinary excretion of radioactivity (with the administered dose being 100%) 0.12, 0.25 mmol/kg: 62.1 % 8.08 mmol/kg: 7.4 % Urinary excretion of TDGA (with the administered dose being 100%) 0.12-1.01 mmol/kg: 21.8 %	Payan et al., 1993

Rats (SD, male/female, 5.5-6 weeks of age)	Inhalation + (Disulfiram in the diet) or (Ethanol in the drink) 7 hours/day 5 days/week Radiolabeled 1,2-dichloroethane was given to rats after tests for 2 years were completed.	50 ppm + (Disulfiram 0.5%) or (Ethanol 5%)	(DCE: 1,2-dichloroethane; DS: Disulfiram; ET: Ethanol) Blood concentration The blood concentration of 1,2-dichloroethane was high in the [DCE+DS] and [DCE] groups. Toxicokinetics When radiolabeled 1,2-dichloroethane was given to rats through a single oral administration, the amount of the administered dose had an impact on the excretion. In the control group, 47-55% of radioactivity was excreted in the urine, and 28-30% was unchanged and excreted in exhaled air. In the [DCE+DS] group, however, 35-36% of radioactivity was excreted in the urine, and 41-55% was unchanged and excreted in exhaled air.	Cheever et al., 1990

Group	Gender	0.25 hours after exposure	2.25 hours after exposure
DCE	Male	0.28	0.22
DCE+DS	Male	1.46	1.20
DCE+ET	Male	0.36	0.38
DCE	Female	0.26	0.28
DCE+DS	Female	1.54	1.08
DCE+ET	Female	0.30	0.35

Male (with the administered dose being 100%)

Group	Urine	Volatile organics	CS 2	Feces	Total
Control	46.6	30.5	0.5	1.8	79.4
DS	35.2	40.5	<0.1	1.0	76.7
ET	45.6	29.8	0.1	2.6	78..2
DCE	42.5	27.3	0.1	0.9	70.8
DCE+ DS	27.6	57.6	<0.1	0.9	86.0
DCE + ET	51.1	17.7	0.2	1.9	71.0

Female

Group	Urine	Volatile organics	CS 2	Feces	Total
Control	55.0	28.0	0.7	1.1	84.7
DS	36.434	55.3	<0.1	0.2	91.9
ET	41.6	29.8	0.2	2.4	73.9
DCE	33.9	40.3	0.1	0.9	75.3
DCE+ DS	24.9	57.7	<0.1	0.2	82.9

Rats (SD, male/female, 5.5-6 weeks of age)	Inhalation + (Disulfiram in the diet) or (Ethanol in the drink) 7 hours/day 5 days/week Radiolabeled 1,2-dichloroethane was given to rats after tests for 2 years were completed.	50 ppm + (Disulfiram 0.5%) or (Ethanol 5%)	(DCE: 1,2-dichloroethane; DS: Disulfiram; ET: Ethanol) Urinary metabolites In the test, ^{14}C-labeled 1,2-dichloroethane was given to rats of each group one week before the completion of the test. For all of the [DCE+DS], [DCE + ET], and [DCE] groups, thiodiglycolic acid, thiodiglycolic acid sulfoxide, and chloroacetic acid were detected as metabolites. Urinary metabolites i. Fraction I ii. Thiodiglycolic acid sulfoxide iii. Fraction III iv. Thiodiglycolic acid v. Chloroacetic acid Male	Cheever et al., 1990

Group	i	ii	iii	iv	v
Control	1.7	26.7	5.0	65.3	0.7
DS	2.3	32.7	6.3	57.0	1.7
ET	2.3	28.7	4.7	63.0	0.3
DCE	2.3	28.7	7.0	60.0	1.7
DCE+ DS	1.7	28.0	5.0	60.7	4.0
DCE + ET	3.7	31.3	7.3	54.3	2.7

Female

Group	i	ii	iii	iv	v
Control	2.0	23.7	4.7	68.3	1.0
DS	1.5	24.0	5.0	65.5	3.5
ET	2.0	22.3	6.0	67.3	1.3
DCE	3.0	20.0	5.3	69.3	1.7
DCE+ DS	1.7	18.0	4.3	71.0	4.3
DCE + ET	1.3	28.7	7.0	60.7	1.3

Covalent binding to DNA in liver

In the test, 150mg/kg of ^{14}C-labeled 1,2-dichloroethane were given to the rats of each group via oral gavage 10-14 days after the completion of the test. In the control group, covalent binding to DNA in liver was somewhat higher than other groups, but there were no remarkable differences among each group.

(μ mole/mol DNA)

Group	Male	Female	Male and Female
Control	43.5	36.4	40.0
DS	41.6	29.0	35.3
ET	37.5	26.9	33.2
DCE	18.9	35.0	28.6
DCE+ DS	35.6	22.5	29.0
DCE + ET	53.3	23.1	38.2

Mouse (gender, type, and age unknown)	Single intraperitoneal injection	50, 100, 140, or 170 mg/kg	In this test, radiolabeled 1,2-dichloroethane was given to mice through an intraperitoneal injection in order to examine the excretion of radioactivity. 51-73% of radioactivity was excreted in the urine, and 4-12% as carbon dioxide in exhaled air. Metabolites identified in this test were chloroacetic acid, S-carboxymethyl cysteine, thiodiacetic acid, 2- chloroethanol, and S,S' ethylene-bis-cysteine. The results of this test were found to be remarkably similar to those obtained from mice dosed with chloroacetic acid. Therefore, it is presumed that the metabolism of 1,2-dichloroethane occurs mainly via chloroacetic acid.	Yllner, 1971
Rat (SD, age unknown, liver)	Incubated with hepatic cytosol at 37 ℃ for 30 minutes.	3mL of 1,2-dichloroethane , including the following: phosphate buffer (50μ mol); GSH (30μ mol); 1,2-dichloroethan (225μ mol); cytosol (6 mg protein)	1,2-dichloroethane metabolism to ethylene in hepatic cytosol is independent of NADPH, but remarkably dependent on the presence of reduced GSH. The metabolism of 1,2-dichloroethane in renal cytosol is about 50% of that in hepatic cytosol, and metabolism in the cytosol of lungs, brain, and muscle cells was less than 10%. Substances reacting with the SH group and GHS S- transferases impeded the metabolism of 1,2-dichloroethane.	Abders & Livesey, 1980

a) The macromolecular binding of radioactivity refers to the covalent binding of radiolabeled chemicals or their metabolites with biological macromolecules, such as DNA, RNA, and protein.

b) The carcass refers to the entire body minus all organs.

c) The PB-PK model is an abbreviation of the Physiologically Based Pharmacokinetic Model that enables incorporation of physiological and anatomical data on humans and animals.

7.2 Epidemiological studies and case reports

Table 7-2 shows epidemiological studies and case reports regarding humans exposed to 1,2-dichloroethane.

1,2-dichloroethane causes irritation to human mucosa. The ingestion of large amounts of 1,2-dichloroethane will cause serious acute toxicity, sometimes resulting in death. Exposure to high concentrations of 1,2-dichloroethane will produce the same results. Clinical symptoms will appear within two hours after ingestion. The major symptoms are reported to be headache, dizziness, hyposthenia, nausea, vomit consisting of blood and bile, dilated pupils, epigastralgia, and a feeling of constriction of the chest. Cyanosis is also reported in some cases. In the autopsies of dead samples, lung edema and bleeding and congestion of main organs were reported (Garrison and Leadingham, 1954; Hueper and Smith, 1935; Lochhead & Close, 1951; Martin et al., 1969; Nouchi et al., 1984; Oak ridge National Laboratory, 1979; Prezdziak & Bakula, 1975; Sayers et al., 1930; Schiinborn et al., 1970; Yodaiken and Babcock, 1973.)

From the above data, it is presumed that 1,2-dichloroethane affects the central nervous system and circulatory system via oral or inhalation routes. The lethal oral dose of 1,2-dichloroethane is presumably 15-60mL.

Some reports say that chronic exposure to 1,2-dichloroethane will cause nervous disorder, hepatic or renal dysfunction, irritation to mucosa, stomachache, nausea, anorexia, and other health problems (Bove et al., 1995; NIOSH, 1976; Zhao et al., 1989).

In addition, epidemiological studies were conducted for workers exposed to 1,2-dichloroethane, including those employed at oil plants. However, any of these studies did not prove any relationship between 1,2-dichloroethane and the cancer rate directly (Chen et al., 2000; Hogstedt et al., 1979; Khubutiya, 1964).

Table 7-2 Epidemiological studies and case reports regarding humans exposed to 1,2-dichloroethane

Target group (gender/number of persons)	Type of exposure	Amount of exposure	Results	Reference
30 year-old male who suffers from schizophrenia	Oral	40mL (ethylene dichloride plexiglass cement)	Soon after ingestion: He suffered from a mild redness of the conjunctiva, and his breath became pungent. After taking a gastric lavage, he vomited a large quantity of gastric juices with an irritating odor and undigested food. Subsequently, he went into shock with his breathing becoming shallow, and his skin temperature becoming lower. He was kept warm in an oxygen tent and given an intravenous drip of coramine and caffeine. 3 hours later: He recovered consciousness, but became hyperactive and repeatedly vomited. 4 hours later: He passed a large quantity of stool with a foul odor. His pulse became fast and blood pressure became low. He received a 500 cc blood transfusion and a 1,500 cc glucose injection to his vein. Subsequently he showed high susceptibility and went into a semicoma. He also vomited many times to the extent that he had serious bleeding from the intestines. 22 hours later: He died.	Garrrison & Leadingham, 1954
63 year-old male	Accidentally ingested 1,2-dichloroethane instead of gin	2 ounces (about 60 mL)	Soon after accidental ingestion: Stupor, vomiting, diarrhea, cyanosis, decreased body temperature 22 hours later: Died due to circulatory disorder.	Hueper & Smith, 1935
57 year-old male	Oral Presumably, ingestion for the purpose of suicide	40 mL	He died due to gastroenteritis, hepatic necrosis, bleeding tendency due to the deficiency of coagulation factors, and circulatory disorder.	Martin et al., 1969

14 year-old boy	Accidental ingestion	15 mL	2 hours after accidental ingestion: He was staggering with a serious headache. 6 days later: He died due mainly to hypoglycemia and hypercalcemia. In his autopsy, serious hepatic necrosis, tubulonecrosis, and adrenal localized degeneration and necrosis were found.	Yodaiken & Babcock, 1973
25 year-old male	Ingestion for the purpose of suicide	50 mL	He suffered from partial cirrhosis of the liver. However, he recovered and left hospital 87 days after ingestion.	Prezdziak & Bakula, 1975
50 year-old male	Accidental ingestion	30 mL	He died 10 hours after ingestion.	Lochhead & Close, 1951
50 year-old male	ND	Ingested 714 mg/kg/day (hours or days unknown) of 1,2-dichloroethane.	Congestion and bleeding of the kidneys	Schiinborn et al., 1970
51 year-old sailor	Inhaled the gas containing 1,2-dichloroethane when discharging the substance remaining in a tanker.	Inhaled the concentrated gas for 30 minutes.	Soon after exposure: He crouched and showed drowsiness. Shortly after being rescued from the tank, he recovered consciousness but became susceptible to irritation. 1 day after: After complaining of drowsiness and breathing difficulties, he became delirious with tremor and coma. 5 days after: He died due to multiple organ failure.	Nouchi et al., 1984
Human	Inhalation	ND	Irritation to nose and eyes appeared 6 minutes after inhalation of 2,000 ppm, 3-10 minutes after 4,000-4,500 ppm, 1-2 minutes after 10,000-35,000 ppm, and 1 minute after 60,000-70,000 ppm. People whose eyes were exposed to 1,2-dichloroethane suffered from pain, irritation, and dacryorrhea. However, people do not suffer from serious disorders except where they do not remove the substance immediately by washing their eyes.	Sayers et al., 1930
Human	Inhalation	4,800mg/m^3, 2 minutes	No symptom Chronic exposure to 1,2-dichloroethane causes various health problems, such as nervous disorder, hepatic or renal dysfunction, irritation to mucosa, stomachache, nausea, and anorexia.	Sayers et al., 1930

Human	Skin	ND	Skin contact with 1,2-dichloroethane often causes serious intoxication. Continuous exposure or long-term exposure causes defatted, dry, and cracked skin.	Oak ridge National Laboratory, 1979
83 persons employed by the aircraft industry in Russia that were chronically exposed to 1,2-dichloroethane	Exposed to 1,2-dichloroethane during 70-75% of their working hours.	Inhalation exposure The exposure level was within the range of 5-40 ppm.	The rates of digestive disorder, neurosis, myeloradiculitis, and other diseases were higher for workers exposed to 1,2-dichloroethane than those unexposed. Out of 83 workers exposed to 1,2-dichloroethane, 19 persons suffered from hepatic or biliary disorder, 13 from neurosis, 11 from autonomic dystonia, 10 from goiter or hyperthyrea, and 5 from inertia.	NIOSH, 1976
118 Polish farmers	Used 1,2-dichloroethane as a fumigation.	15-60 ppm (Exposure level during work was presumably 16 mg/m^3. From tests performed under the same conditions as in work, it is presumed that exposure level is generally 60 mg/m^3, and the level during pouring the substance is 240 mg/m^3.)	90 out of 118 farmers suffered from the following: conjunctival congestion (69%), hyposthenia (46%), pharyngeal redness (42%), bronchial diseases (35%), metallic taste in mouth (34%), headache (33%), dermatographia (31%), nausea (26%), cough (25%), pain in right hypochondrium (25%), conjunctival burning sensation (20%), rapid pulse (18%), and breathing difficulty after exercise (18%).	NIOSH, 1976
80,938 new born babies and 594 stillborn babies in Northern New Jersey. (excluding multiple-fetuses and those born with chromosomal abnormalities)	Drinking water (running water)	19 ppb	The odds ratio for exposure to DCE causing central nervous system damage and major circulatory disorders is 1.5 or more.	Bove et al., 1995

54 females employed at synthetic fabric plants in China and 44 spouses of males employed at such plants	Female workers were exposed to 1,2-dichloroethane during pregnancy, and spouses of male workers were exposed from at least a year before their pregnancies.	Inhalation exposure 0.4-384 ppm	The rate of early delivery increased. However, it should be considered that most cases involved exposure to other chemicals in addition to 1,2-dichloroethane. Environmental or behavioral factors should be also taken into account.	Zhao et al., 1989
Workers exposed to 1,2-dichloroethane (number of persons unknown)	ND	ND	Hyperchromic erythrocytes were found in one-third of workers exposed to 1,2-dichloroethane, but megaloblasts were not found. Medium to high sedimentation rates due to increased globulin in blood were found in about half of workers exposed. They also suffered from leucopenia due to the decrease in the absolute numbers and ratios of neutrophilic leukocytes and lymphocytes, as well as medium to advanced monocytosis. Turc's cells were also observed in the peripheral blood of one of the five samples. It is presumed that the retinal endothelium stimulated by 1,2-dichloroethane causes the development of monocytosis and Turc's cells.	Khubutiya, 1964
89 workers involved in the production of ethylene oxide	ND	ND	It is impossible to conclude that particular chemicals relate to the high death rate and cancer rate. However, ethylene oxide and 1,2-dichloroethane are the most likely causes.	Hogstedt et al., 1979

People employed at polyvinyl chloride plants in China (number of persons unknown)	ND	Exposed to the mixture of vinyl chloride monomer (VCM) and 1,2-dichloroethane (EDC). Concentration levels are as follows: Low level of VCM and EDC (VCM: 0.25-0.39 ppm; EDC: 0.20-0.29 ppm); Low level of VCM and medium level of EDC (VCM: 0.16-0.27 ppm; EDC: 0.69-1.31 ppm); Medium level of VCM and EDC (VCM: median of 1.63 ppm; EDC: median of 0.77 ppm)	The frequency of sister chromatid exchange increased due to exposure to 1,2-dichloroethane. This tendency was remarkable among non-smokers.	Cheng et al., 2000

7.3 Toxicity to laboratory animals

7.3.1 Acute toxicity

The results of an acute toxicity experiment of 1,2-dichloroethane on laboratory animals are shown in Table 7-3 (Barsoum and Saad, 1934; Heppel et al., 1945; Munson et al., 1982; Spencer et al., 1951; Stauffer Chemical Co., 1973; Union Carbide Corp., 1987). The LD_{50} of rats in an acute toxicity experiment of 1,2-dichloroethane by oral administration was 794 mg/kg.

Major symptoms observed in the acute toxicity experiment by oral administration for rats are a decrease in the locomotor activity and ataxy (Stauffer Chemical Co., 1973). Major symptoms observed for inhalation exposure of rats are depression of the central nervous system, cyanopathy, hypothermia, coma, and apnea. From the autopsy findings of surviving animals, weight increase of liver and kidney, elongation of prothrombin time, decrease of phosphatase, increase of lipid in liver, congestion, bleeding necrosis, lipid alteration, congestion in kidney, bleeding and alteration of the cortical layer were observed (Spencer et al., 1951)

Table 7-3 The results of acute toxicity experiment of 1,2-dicloroethane

	Mouse	Rat	Rabbit	Guinea pig
Oral administration LD_{50}	413-911 mg/kg	794 mg/kg	890 mg/kg	—
Inhalation LC_{50}	≦3,000 ppm	12,000 ppm (0.53 h) 3,000 ppm (2.75 h) 1,000 ppm (7.20 h)	≦3,000 ppm (7h)	≦3,000 ppm (7h)
Transdermal LD_{50}	—	—	4890 mg/kg	—
Intratracheal LD_{50}	—	120 mg/kg	—	—

7.3.2 Stimulus and corrosion

The results of stimulus and corrosion experiments on 1,2-dichloroethane are shown in Table 7-4.

In the report of experiments on rabbits for the stimulus of 1,2-dichloroethane, it was evaluated that the skin stimulus is medium level in 24 hours closed application, and that there was no stimulus or slight stimulus in 4 hours application (Duprat et al., 1976; Stauffer Chemical Co., 1973). As for eye stimulus, it was evaluated that there was no stimulus or slight stimulus (Duprat et al., 1976; Stauffer Chemical Co., 1973).

There were no reports on corrosion for laboratory animals as far as was surveyed.

Table 7-4 The results of stimulus and corrosion experiments on 1,2-dichloroethane

Animals	Method of experiment Method of administration	Period of administration	Volume of administration	Results	Reference
Rabbit	Skin stimulus, Draize method	Single	0.5 mL	Medium skin stimulus	Duprat et al., 1976
Rabbit	Eye stimulus, Draize method	Single	0.1 mL	Slight eye stimulus	Duprat et al., 1976
Rabbit	Skin stimulus	4 hours application	0.5 mL	No stimulus - Slight stimulus	Stauffer Chemical Co., 1973
Rabbit	Eye stimulus	Single	0.1 mL	No stimulus	Stauffer Chemical Co., 1973

7.3.3 Sensitization

There were no reports on sensitization of 1,2-dichloroethane for laboratory animals as far as was surveyed.

7.3.4 Repeated dose toxicity

The results of repeated dose tests on 1,2-dichloroethane on laboratory animals are shown in Table 7-5.

As the results of oral administration experiments in which 0 ppm, 500 ppm, 1,000 ppm, 4,000 ppm, and 8,000 ppm were administered with drinking water to B6C3F1 mice, it was reported that alteration of kidney tubules was observed with male mice which were administered more than 4,000 ppm and that nine out of ten female mice administered 8,000 ppm died. The authors defined the NOAEL as 2,000 ppm for male mouse and 4,000 ppm for female mouse (U.S.NTP, 1991).

As the results of experiments in which 0 mg/kg/day, 37.5 mg/kg/day, 75 mg/kg/day, and 150 mg/kg/day of 1,2-dichloroethane were administered by gavage administration to male and female SD rats (8 weeks old) for 90 days, it was reported that an increase in relative weight of kidney and liver, a decrease of hemoglobin, and an increase in the number of thrombocytes were observed with the male group that was administered 75 mg/kg/day and an increase in relative weight of the kidney was observed with the female group that was administered the same. It was also reported that there was a decrease of weight and food intake, an increase in relative weight of brain, testis, kidney, liver and adrenal glands of male group that was administered 150 mg/kg/day, and an increase in relative weight of liver and kidney, a decrease in the number of erythrocytes, hemoglobin, hematocrit, ratio of lymphocyte, and an increase in the numbers of leukocytes and thrombocytes and in the ratios of neutrophils and monocytes were observed in the female group that were administered the same. The authors defined the NOAEL as 37.5 mg/kg/day (Daniel et al., 1994).

As the results of experiments in which 0 mg/kg/day, 30 mg/kg/day, 60 mg/kg/day, 120 mg/kg/day, 240 mg/kg/day, and 480 mg/kg/day of 1,2-dichloroethane were administered by gavage to male F344 rats (6 weeks old) for 13 weeks and 0 mg/kg/day, 18 mg/kg/day, 37 mg/kg/day, 75 mg/kg/day, 150 mg/kg/day, and 300

mg/kg/day to female F344 rats (same age) for the same period, it was reported that, with male groups, cerebellar necrosis was observed with the group administered 240 mg/kg/day, and death (all samples), forestomach mucosal hyperplasia, inflammation, and thymus necrosis were observed with the groups administered 240 mg/kg/day or more. As for female groups, death (9 out of 10 samples), cerebellar necrosis, forestomach mucosal hyperplasia, inflammation, and thymus necrosis were observed with the groups administered 300 mg/kg/day. The authors defined the NOAEL as 120 mg/kg/day for male rats and 150 mg/kg/day for female rats (Morgan et al, 1990; U.S. NTP, 1991).

In addition, results were reported by the experiments in which 0 ppm, 500 ppm, 1,000 ppm, 2,000 ppm, 4,000 ppm, and 8,000 ppm were administered with drinking water for 13 weeks to F344 rats, SD rats, and Osborne-Mendel rats (6 weeks old) respectively. With F344 rats, reversible alteration of kidney tubules epithelium was observed with the group administered 1,000 ppm or more. With Osborne-Mendel rats and SD rats, an increase in the relative weight of the liver or kidneys was observed from the smallest dosage, but no influence was observed by administration of 1,2-dichloroethane in the tests for hematology, blood chemistry parameters, and pathologic histology (Morgan et al., 1990; U.S. NTP, 1991). This assessment report therefore does not judge the changes as having an important influence on deciding NOAEL. Incidentally, in the above 2 experiments (Morgan et al., 1990; U.S. NTP, 1991), the difference of toxicity due to the difference of administered methods of drinking water and gavage administration was examined by setting the doses administered to the F344 rats as almost the same, and the result of experiments reported that the changes appeared stronger in the case of gavage administration.

With inhalation exposure, results were reported of experiments by which 0 ppm, 5 ppm, 10 ppm, 50 ppm, and 150 ppm were administered to male and female SD rats starting from 3 months old for 3, 6, or 18 months and to those starting from 12 months old for 12 months, and of the hematological and blood biochemical tests. No influence was observed in any of the groups exposed from 3 months old for 3, 6, or 18 months. On the other hand, with those exposed from 12 months old for 12 months, increase of ALT and uric acid and a decrease of cholesterol were observed with the group of both male and female rats administered 50 ppm or more, an increase in γ-GTP was observed with the female group administered the same amount, and an increase of glucose was observed with male and female groups administered 150 ppm (Spreafico et al., 1980). Considering that histopathological examination was not conducted with this experiment, and taking into consideration that the change in the serum parameter that shows hepatotoxicity was observed, although such influence was observed only in the exposure to the older animals (12 months old), this primary assessment report judges the NOAEL of this experiment as 10 ppm (41.1 mg/m^3).

These results shows that the target organs are the liver and kidneys, however it is necessary to note that most of the repeated dose toxicity tests for 1,2-dichloroethane using mice and rats were conducted using limited end points of a small number of groups. As a result of the above, the minimum NOAEL for oral intake is 37.5 mg/kg/day of 90 days gavage administration using SD rats (Daniel et al., 1994), and that for inhalation exposure is 10 ppm (41.1 mg/m^3) of 12 months exposure using SD rats (Spreafico et al., 1980).

Table 7-5 The results of the repeated dose toxicity test of 1,2-dichloroethane

Animals	Method of administration	Period of administration	Volume of administration	Results	Reference
$B6C3F_1$ Mouse, 6 weeks old, male and female	Drinking water	13 weeks	0, 500, 1,000, 2,000, 4,000, or 8,000 ppm (Equivalent to Male: 0, 249, 448, 781, 2,710, or 4,207 mg/kg/day and Female: 0, 244, 647, 1,182, 2,478, or 4,926 mg/kg/day)	4,000 ppm Male: Slight alteration of kidney tubule	U.S. NTP, 1991
				8,000 ppm Male: Alteration of kidney tubule Female: 9 dead out of 10	
				NOAEL: Male: 2,000 ppm (equivalent to 781 mg/kg/day) Female: 4,000 ppm (equivalent to 2,478 mg/kg/day)	
SD mouse male and female, 8 weeks old, 10 mice/group	Gavage administration	10 days	0, 30, 100, or 300 mg/kg/day	100 mg/kg/day	Daniel et al., 1994
				Male: Increase in relative weight of liver, increase of serum cholesterol, inflammation of forestomach mucous and lamina propria	
				Female:	

				Inflammation of forestomach mucous and lamina propria	
				300 mg/kg/day	
				Male: Dead (8 samples)	
				Female: Dead (all samples)	
SD mouse male and female, 8 weeks old, 10 mice/group	Gavage administration	90 days	0, 37.5, 75, or 150 mg/kg/day	75 mg/kg/day	Daniel et al., 1994
				Male: Increase in relative weights of kidney and liver, decrease of hemoglobin, increase of the number of thrombocytes	
				Female: Increase in relative weights of kidney	
				150 mg/kg/day	
				Male: Decrease of weight and food intake, increase in relative weights of brain, testis, kidney, liver, and adrenal glands	
				Female: Increase in relative weights of kidney and liver, decrease in the number of erythrocyte, hemoglobin, hematocrit, ratio of lymphocyte, increase in the number of leukocyte and thrombocyte	

				and in the ratio of neutrophils and monocytes	
				NOAEL: 37.5 mg/kg/day	
F344 rat male and female, 6 weeks old, 10 rats/group	Gavage administration	13 weeks	Male: 0, 30, 60, 120, 240, or 480 mg/kg/day Female: 0, 18, 37, 75, 150, or 300 mg/kg/day	Male:	Morgan et al., 1990 ; U.S. NTP, 1991
				240 mg/kg/day Dead (all samples), cerebellar necrosis, forestomach mucosal hyperplasia, inflammation, thymus necrosis	
				480 mg/kg/day Dead (all samples), forestomach mucosal hyperplasia, inflammation, thymus necrosis	
				Female:	
				300 mg/kg/day Dead (9 samples), cerebellar necrosis, forestomach mucosal hyperplasia, inflammation, thymus necrosis	
				NOAEL:	
				Male: 120 mg/kg/day	
				Female: 150 mg/kg/day	
F344 rat male and female, 6 weeks old, 10 rats/group	Drinking water	13 week	0, 500, 1,000, 2,000, 4,000, or 8,000 ppm (Equivalent to Male: 0, 49, 86, 147, 259, or 515 mg/kg/day and Female:	1,000 ppm or more Male and female: reversible alteration of kidney tubules epithelium	Morgan et al., 1990; U.S. NTP, 1991

			0, 58, 102, 182, 302, or 601 mg/kg/day)		
SD rat male and female, 6 weeks old, 10 rats/group			(Equivalent to Male: 0, 60, 99, 165, 276, or 518 mg/kg/day and Female: 0, 76, 106, 172, 311, or 531 mg/kg/day)	500 - 8,000 ppm Increase in relative weight of kidney or liver	
Osborne-Mendel rat male and female, 6 weeks old, 10 rats/group			(Equivalent to Male: 0, 54, 88, 146, 266, or 492 mg/kg/day and Female: 0, 82, 126, 213, 428, or 727 mg/kg/day)	500 - 8,000 ppm Increase in relative weight of kidney or liver	
SD rat male and female, 8-10 rats	Inhalation	From 3 months old, for 3 months, 6 months, or 18 months	0, 5, 10, 50, or 150 ppm (Equivalent to 0, 20.6, 41.1, 205.5, or 616.5 mg/kg/day)	No influence observed in any of the groups.	Spreafico et al., 1980
		Administered from 12 months of age for 12 months		Group administered 50 ppm or more	
				Male and female:	
				Increase of ALT, decrease of cholesterol, increase of uric acid Female: increase of γ-GST	
		7 hours/day 5 days/week		150 ppm:	
				Male and female: increase of glucose	
				NOAEL: 10 ppm (41.1 mg/m^3)	
				Judgment of this assessment report	

7.3.5 Reproductive and developmental toxicity

The results of reproductive and developmental toxicity experiments for 1,2-dichloroethane are shown in Table 7-6.

As the results of experiments on ICR mice in which 0 mg/kg/day, 5 mg/kg/day, 15 mg/kg/day, and 50 mg/kg/day of 1,2-dichloroethane were administered with drinking water to F_0 for 25 weeks (5 weeks + twice during mating period, pregnancy, lactation period, 2 weeks discontinuation of administration) and to F_1 for 24 weeks (10 weeks + mating, pregnancy, lactation period, 2 weeks discontinuation of administration), it was reported that no influence was observed in either parent or progeny for any of the groups (Lane et al., 1982).

As the results of teratogenicity tests by oral administration and inhalation exposure to female SD rats, reproductive toxicity such as an increase of embryo absorption was observed in the parent groups of 6 - 20 days pregnancy administered 2.0 mmol/kg/day or more by oral administration and in the parent groups of 6 - 15 days or 6 - 20 days pregnancy administered 300 ppm or more by inhalation exposure, but no influence was observed with the progeny (Payan et al., 1995; Rao et al., 1980; Schlahcter et al., 1979).

As the result of experiments on male and female SD rats in which 0 ppm, 25 ppm, 75 ppm, 150 ppm (103 mg/m^3, 308 mg/m^3, 617 mg/m^3) of 1,2-dichloroethane were administered by inhalation exposure before mating, twice during pregnancy, and during lactation period, no influence was observed with either parent or the progeny in any of the groups (Murray et al., 1980; Rao, et al., 1980).

As the result of experiments on female NZW rabbits by which 0 ppm, 100 ppm, 300 ppm (0 mg/m^3, 411 mg/m^3, 1,233 mg/m^3) of 1,2-dichloroethane were administered by inhalation exposure for 13 days from 6 days pregnancy to 18 days pregnancy, some of the parents administered 100 ppm or more died, but no influence was observed with any of the groups of the progeny (Rao, et al., 1980; Schlahcter et al., 1979).

As the result of the above reproductive and developmental toxicity tests, the NOAEL of mouse parent and progeny is assumed to be 50 mg/kg/day or more by oral administration for 2 generations of mice and the NOAEL of rat parent and progeny is assumed to be 150 ppm or more by inhalation exposure for 1 generation. In addition, as the result of teratogenicity tests to pregnant rats, the NOAEL of the parent is 100 ppm by inhalation exposure and 160 mg/kg/day by oral administration, but no influence was observed with progeny up to 300 ppm by inhalation exposure and 240 mg/kg/day by oral administration.

Table 7-6 The results of reproductive and developmental toxicity experiments on 1,2-dichloroethane

Animals	Method of administration	Period of administration	Volume of administration	Results	Reference
ICR Mouse male and female, 9 weeks old (F_0) Male: 10 mice/group, Female: 30 mice/group	Drinking water	F_0: 25 weeks (5 weeks + twice during mating period, pregnancy, lactation period, 2 weeks discontinuation of administration)	Equivalent to 0, 5, 15, or 50 mg/kg/day	No influence was observed in both parent and progeny with all groups	Lane et al., 1982
		F_1: 24 weeks (10 weeks + mating period, pregnancy, lactation period, 2 weeks discontinuation of administration)		NOAEL: 50 mg/kg/day or more	
SD rat female, 25-26 mice/group, no report about age	Oral administration	6-20 days pregnancy, laparotomy on 21st day	0, 1.2, 1.6, 2.0, or 2.4 mmol/kg/day (0, 120, 160, 200, or 240 mg/kg/day)	Parents 2.0 mmol/kg/day: Inhibition of weight increase, dead fetus, increase in embryo absorption 2.0 mmol/kg/day: Premature delivery, increase of dead birth, increase in embryo absorption	Payan et al., 1995
				Progeny No influence was observed in any of the groups	
SD rat female, 25-26 mice/group,	Inhalation exposure	6-15 days pregnancy, laparotomy on 21st day	0, 150, 20, 250, or 300 ppm/6 hours/day	Parents 300 ppm: Inhibition of weight increase, death	Payan et al., 1995

no report about age				Progeny No influence was observed in any of the groups	
SD rat female, 16-30 mice/group, no report about age	Inhalation exposure	6-15 days pregnancy, laparotomy on 21st day	0, 10, or 300 ppm/7 hours/day (Equivalent to 0, 411, or 1,233 mg/m^3)	Parents 100 ppm: Relatively heavy weight 300 ppm: Lethargy, ataxia, decrease of weight, decrease of food intake, death, all embryos died Progeny No influence was observed in any of the groups	Rao et al., 1980
SD rat female, 30 rats (groups administered 0 and 100 ppm), 16 rats (group administered 300 ppm), no report about age	Inhalation exposure	6-15 days pregnancy, laparotomy on 21st day	0, 10, or 300 ppm/7 hours/day (Equivalent to 0, 411, or 1,233 mg/m^3)	Parents 100 ppm: Promotion of weight increase, increase of water intake 300 ppm: 10 out of 16 died, decrease of absolute weight of liver, absorption in all embryos Progeny No influence was observed in any of the groups	Schlahcter et al., 1979
NZW rabbit female, 19-21 rabbits/group, no report about age	Inhalation exposure	6-18 days pregnancy, laparotomy on 29th day	0, 100, or 300 ppm/7 hours/day	Parents 100 ppm or more: Death	Schlahcter et al., 1979 ; Rao et al., 1980

SD rat	Inhalation exposure	Male: 60 days + twice during mating period + 0-20 days pregnancy of female + 5-20 days after delivery of female + 7 days (recovery period)	0, 25, 75, or 150 ppm/6 hours/day 5 days/week (7 days/week during mating period) (Equivalent to 0, 103, 308, or 617 mg/m^3)	No influence was observed in any of the groups of parent and progeny	Murray et al., 1980; Rao et al., 1980
		Female: 60 days + twice during mating period + 0-20 days pregnancy + 5-20 days after delivery + 7 days (recovery period)		NOAEL: 150 ppm or more	

7.3.6 Genetic Toxicity

Table 7-7 shows the result of 1,2-dichloroethane genetic toxicity tests.

1,2-dichloroethane demonstrates genetic toxicity in in vitro and in vivo tests for a range of endpoints.

For in vitro testing, reverse mutation test of salmonella typhimurium using bacteria was positive regardless of whether or not S9 was added (Barber et al., 1981; Brem et al., 1974; Rannug et al., 1978). Rannug et al (1978) found that addition of reduced glutathione to S9 strengthens mutation activity, and glutathione-S-transferase is related to this activity, and also 1,2-dichloroethane's glutathione conjugate has strong mutation activity. In tests with coli bacillus, DNA recovery testing without S9 addition was positive (Brem et al., 1974). Also, prophage induction testing had a weak positive reaction when S9 was added (DeMarini and Brooks, 1992). However, in in vivo testing using coli bacillus K12/343/113 given intraperitoneally to a mouse by way of a host, mutation was not induced (King et al., 1979). In the test using A. nidulans, genetic mutation and body cell recombination were negative, but nondisjunction of chromosome (heteroploidy) was reported(Crebelli and Carere, 1988) . As for DNA binding, DNA adducts were found in the experiment using regular DNA and those incubated in a test tube. The amount of these adducts increased by adding liver microsome or cytoplasmic soluble fraction (Arfellini et al., 1984).

In the test using cultured cells, several genetic mutation tests with human cells and Chinese hamster ovary (CHO) cells were reported and they were positive. In the test using two kinds of human cells, there was a dose-related, higher mutation induction in AHH-1 cell which had strong glutathione S-transferase activity (Crespi et al., 1985; Ferreri et al., 1983; Tan and Hsie, 1981). In the transformation test, BALB/c-3T3 cell was exposed to vapor in a sealed place and the result was negative (Arthur D. Little, Inc., 1983). However, transformation was promoted in a test using hamster fetus cell injected with SA7 virus using the same vapor method (Hatch et al., 1983). Cell transformation was observed in the experiment with mouse C3H/10T1/2 cell (Schultz et al., 1992). In human lymph cell testing, there was no clear relationship to dosage, but in vitro micronucleus testing and comet assays were both positive when S9 was not added (Tafazoli et al., 1998). In irregular DNA synthesis testing, the result was positive when S9 was added (Perocco and Prodi, 1981).

For in vivo tests, there was no significant increase of micronucleus in bone marrow and peripheral blood when 1,2-dichloroethane was given intraperitoneally to a mouse or given orally to a transgenic mouse for 41 weeks (Armstrong and Galloway, 1993; King et al., 1979; Sasaki et al., 1994).
Sister chromatid exchange testing and comet assays with mouse were both positive (Giri and Que Hee, 1988; Sasaki et al., 1998). In comet assays, stomach, liver, kidney, bladder, lung, brain, and bone marrow were studied, and DNA damage was found in all of those organs. Also, one strand of DNA was broken in the liver when DNA damage testing was conducted on the mouse (orally and intraperitoneally). However, the result was negative for inhalation exposure testing (Storer and Conolly, 1983, 1985; Storer et al., 1984). As for DNA binding, several tests with mice and rats were reported, and all were positive. While a high level of binding was found in the liver and kidney, not much binding occurred in the lungs. Also, more binding occurred in rats than mice (Arfellini et

al., 1984; Baertsch et al., 1991; Banerjee, 1988). Eye color reverse mutation test and sex-linked, recessive, fatal test, wing hair spot test, and chromosome loss and nondisjunction test with drosophila were reported, and they were all positive (Kramers et al., 1991; Nylander et al., 1978; Romert et al., 1990; Valencia et al., 1984; Vogel and Nivard, 1993).

Table 7-7 The result of genotoxicity test of 1,2-dichloroethane

	Test name	Test material	Test condition	Dose	Result -S9	Result +S9	Reference
in vitro	Reversion test	Salmonella typhimurium TA1535 TA100 TA1535 TA1537 TA1538	Plate method, Sealed-gas exposure	(μmol/plate) 31.8-231.8 31.8-231.8 31.8-231.8 Unknown Unknown	 - + + - -	 - + + - -	Barber et al., 1981
		Salmonella typhimurium TA1530 TA1535 TA1538	Spot test	(μmol) 10 10 10	 + + +	 NT NT NT	Brem et al.,1974
		Salmonella typhimurium TA1535	Plate method	(mol/plate) 20-60	 +	 +	Rannug et al., 1978
	DNA repair test	Escherichia coli poliA^{+}/A^{-}	Spot test	10μL	+	NT	Brem et al., 1974
	Prophage induction test	Escherichia coli TH-008	Overnight treatment as stated in text. No record of treatment times.	(μM) －S9: 19,736-631,568 ＋S9: 19,736-1,263,136	-	w+	DeMarini & Brooks, 1992
	Chromosome nondisjunction test	Aspergillus nidulans P1	3-hour treatment in liquid medium.	0-2 %	+	NT	Crebelli & Carere, 1988
	Gene mutation test	Aspergillus nidulans 35	Treatment in buffer solution.	0-2 %	+	-	
	Somatic recombination test	Aspergillus nidulans P1	3-hour treatment in liquid medium.	0-2 %	-	-	
	DNA binding test	Commercial DNA	Incubation	2.5μ Ci ^{14}C-DCE/1.5mg DNA	+	+	Arfellini et al., 1984

			(37℃, 90 minutes)			
	Gene mutation test	CHO-K1-BH4 (HGPRT)	5-hour treatment	-S9: 5-50 mM +S9:1-3 mM	+ +	Tan & Hsie, 1981
		Human lymphoblast AHH-1(HGPRT) TK6(TK+/-)	 28-hour treatment 20-hour treatment	(μg/mL) 100-1,000 200-1,000	 + NT + NT	Crespi et al., 1985
		Human EUE cell	24-hour treatment	10^{-3}-5×10^{-2} M	+ NT	Ferreri et al., 1983
	Cell transformation test	BALB/c-3T3 cl. 1-13	24-hour vapor exposure in closed system. 72-hour treatment in open system.	4-250 μg/mL 5-50 μg/mL	- NT - NT	Arthur D. Little Inc., 1983
		SA7 virus-inoculated hamster fetal cell	20-hour vapor exposure in closed system.	0.2-0.8 mL/flask	+ NT	Hatch et al., 1983
		C3H/10T1/2	48-hour treatment	200-600 μg/mL	+ NT	Schultz et al., 1992
	Micronuclei test	Human lymphocyte	-S9: 72 hours +S9: 3 hours	2-20 mM	+ -	Tafazoli et al., 1998
	Comet assay	Human lymphocyte	3-hour treatment	2-6 mM	+ -	
	Unscheduled DNA synthesis test	Human lymphocyte	4-hour treatment	2.5-10μL/mL	- +	Perocco & Prodi, 1981
in vivo	Micronuclei test	ICR mouse	Intraperitoneal injection, peripheral blood	0-360 mg/kg	-	Sasaki et al., 1994
		NMRI mouse	24-hour intraperitoneal injection twice	4 mmol/kg	-	King et al., 1979

	Eμ-PIM-1transgenic mouse	Oral administration (7 days/week) 14, 41 weeks peripheral blood	Male: 100, 200 mg/kg Female: 150, 300 mg/kg	-	Armstrong & Galloway, 1993
Host-mediated assay	Escherichia coli K12(343/113)/N MRI mouse	Single intraperitoneal injection	2 mmol/kg (Maximum tolerated dose)	-	King et al., 1979
Sister chromosome exchanges (SCEs)	Swiss mouse	Single intraperitoneal injection Bone narrow	0-16 mg/kg	+	Giri & Que Hee, 1988
Comet assay	CD-1 mouse	Single intraperitoneal injection Stomach, liver, kidney, bladder, lung, brain and bone narrow	200 mg/kg	+	Sasaki et al., 1998
DNA damage test (single-strand break)	$B6C3F_1$ mouse	Single intraperitoneal injection, liver	1-3 mmol/kg	+	Storer & Colony, 1983
	$B6C3F_1$ mouse	Single oral administration, intraperitoneal injection and inhalation exposure Liver	Oral 100-400 mg/kg Intraperitoneal 100-300 mg/kg Inhalation 150-500 ppm	+ + -	Storer et al., 1984
	$B6C3F_1$ mouse	Single intraperitoneal injection, liver	200 mg/kg	+	Storer & Colony, 1985
DNA binding test	Arochlor 1254-pretreated rat/mouse	Single intraperitoneal injection, liver	1.38 mg/animal	+ +	Banerjee, 1988
	BALB/c mouse Wistar rat	Single intraperitoneal injection Stomach, liver, kidney, lung,	8.7μmol/kg	+ +	Arfellini et al., 1984
	F344 rat	Inhalation exposure Liver, lung	80 ppm x 4 hours 4,400 ppm x few minutes	+	Baertsch et al., 1991

	Eye-color reversion test	Drosophila melanogaster	Feeding	0.1-0.5% (Larval stage)	+	Nylander et al., 1978
		Drosophila melanogaster	Inhalation exposure	200-400 ppm x 17 hours (Larval stage)	+	Vogel & Nivard, 1993
	Sex-linked recessive lethal test	Drosophila melanogaster	Inhalation exposure	800 mg/m^3 x 6 hours 8 mg/m^3 x 96 hours 7 mg/m^3 x 1 week 7 mg/m^3 x 2 weeks	+	Kramers et al., 1991
	Wing hair spot test	Drosophila melanogaster	Inhalation exposure	40-250 mg/m^3 (From embryonic stage to pupal stage)	+	
	Wing hair spot test	Drosophila melanogaster	Feeding	50-1,000 ppm (Time unknown)	+	Romert et al., 1990
	Chromosome loss test/ Somatic recombination test	Drosophila melanogaster	Inhalation exposure	Unknown	+	Valencia et al., 1984

-: negative, +: positive, w+: weak positive, NT: not tested

7.3.7 Carcinogenicity

The results of the carcinogenicity test for 1,2-dichloroethane are shown in Chart 7-8.

For gavage administration to B6C3F male and female mice, male mice were administered 0, 97, 195 mg/kg/per day and female mice were administered 0, 149, 299 mg/kg/per day for 78 weeks. The incidence rate for bronchiolus/alveolar adenoma increased for male mice which were administered 97, 195 mg/kg/per day, and the incidence rate for bronchiolus/alveolar adenoma, cancer of the mammary gland, endometrium polyp/sarcoma increased for female mice which were administered 149 mg/kg/per day and for female mice which were administered 299 mg/kg/per day, in addition to the changes for the 149 mg group, incidence rate for gastric epidermoid cancer increased. (NCI, 1978; Ward, 1980)

For inhalation administration, there weren't any significant effects from an experiment of 78 weeks exposure of 0, 5, 10, 50, 150, 250 ppm to female Swiss mice (Maltoni et al., 1980). On the other hand, in an experiment of 104 weeks exposure of 0, 10, 30, 90 ppm to male and female mice, the incidence rate for hepatic sarcoma increased for male mice which were administered 10, 30, 90 ppm and the incidence rate for hepatocyte adenoma, bronchiolus/alveolar adenoma/cancer, bronchus/alveolar adenocarcinoma, mammal gland adenocarcinoma, and endometrium polyp increased for female mice which were administered 90 ppm. (Nagano et al., 1998)

For percutaneous administration, in an experiment administering 0, 42, 126 mg/per mouse three times a week from the age of six to eight weeks until 576 days of age to male and female ICR mice, the incidence rate for lung tumor/papilloma increased for female mice that were administered 126 mg. (Van Duuren et al., 1979)

For gavage administration to rats, in an experiment administering 0, 47, 95 mg/kg/per day of 1,2-dichloroethane for 78 weeks to male and female Osborne-Mendel rats, the incidence rate for hypodermal gland adenoma, gastric epidermoid cancer, vascular sarcoma increased for male rats that were administered over 47mg/kg/per day and the incidence rate for adenocarcinoma and mammary gland tumor increased for female rats that were also administered over 47mg/kg/per day (NCI, 1978; Ward, 1980).

In administering mixed bait to male and female rats (genealogy unknown), there weren't any effects from experiments administering 0, 250, 500 ppm for a period of two years (Alumot et al., 1976).

For inhalation exposure, in experiments of exposure of 0, 5, 10, 50, 150, 250 ppm for 78 weeks to SD rats, the incidence rate for fibroma of mammary gland and fibroma adenoma increased for female rats that were administered 5, 10, 50, 150, 250 ppm (Maltoni et al., 1980). Also in experiments of exposure of 0, 10, 40, 160 ppm for 104 weeks to F344 rats, there weren't any effects on either male and female rats that were administered 10 ppm, but incidence rates for hypodermic fibroma for male rats that were administered 40ppm, incidence rates for hypodermic fibroma, fibroma adenoma of mammary gland, mesothelioma for male rats that were administered 160 ppm, and incidence rates for hypodermic fibroma, fibroma adenoma of mammary gland, epidermal gland adenoma and adenocarcinoma for female rats that were administered 160 ppm increased (Nagano et al., 1998). However, there weren't any effects on either male or female rats that were administered 0, 50 ppm for a period of two years (Cheever et al., 1990).

Effects of 1,2-dichloroethane in oncogenecity tests were as follows. For oral administration, tumors were found hypodermically, in the stomach, mammary gland, lungs, the uterus, and the vascular tract. For inhalation exposure, tumors were found hypodermically, in the mammary gland, the uterus, and the liver and for

percutaneous administration, tumors were found in the lungs.

Further, the results of carcinogenicity assessment by international agencies are shown in Chart 7-9. IARC is classified under Group 2B (substance which is possibly carcinogenic to humans).

Table 7-8 Result of carcinogenicity of 1,2-dichloroethane

Animal	Administration method	Administration period	Dose	Result	Reference
$B6C3F_1$ mouse (Male, Female) Control group: 20 mice/group Treated group: 50 mice/group	Gavage administration	78 weeks + 13 weeks (Observation period)	Male: 0, 97, or 195 mg/kg (Equal to 0, 100, or 200 mg/kg) Female: 0, 149, or 299 mg/kg (Equal to 0, 200, or 400 mg/kg)	Male: Increase in bronchiolar/alveolar adenoma (0, 97, or 195 mg/kg group: 0/19, 1/47, or 15/38) Female: Increase in bronchiolar/alveolar adenoma (0, 144, or 299 mg/kg group: 1/20, 7/50, or 15/48) Increase in adenocarcinoma in glandula mammaria (0, 144, or 299 mg/kg group: 0/20, 9/50, or 7/48) Increase in endometrial polyp/ sarcoma (0, 144, or 299 mg/kg group: 0/20, 5/49, or 5/47) Increase in squamous carcinoma in stomach (0 or 299 mg/kg group: 1/20 or 5/48)	NCI, 1978; Ward, 1980
Swiss mouse (Male, Female) 11 weeks old 90 mice/group	Inhalation	78 weeks (7 hours/day, 5 days/week)	0, 5, 10, 50, 150, or 250 ppm	No effects in each group	Maltoni et al., 1980
BDF_1 mouse (Male, female) 6 weeks old 50 mice/group	Inhalation	104 weeks (6 hours/day, 5 days/week)	0, 10, 30, or 90 ppm	Male: Increase in angiosarcoma in liver (0, 10, 30, or 90 ppm group: 0/50, 4/49, 6/50, or 5/50) Female: Increase in hepatocellular adenoma (0, 10, 30, or 90 ppm group: 1/49, 1/50, 1/50, or 6/50)	Nagano et al., 1998

				Increase in bronchiolar/alveolar adenoma or bronchiolar/alveolar cancer (0, 10, 30, or 90 ppm group: 5/49, 1/50, 4/50, or 11/50) Increase in adenocarcinoma in glandula mammaria (0, 10, 30, or 90 ppm group: 1/49, 2/50, 1/50, or 6/50) Increase in endometrial polyp (0, 10, 30, or 90 ppm group: 2/49, 0/50, 1/50, or 6/50)	
Ha mouse ICR mouse (Male, female) 6-8 weeks old 30 mice/group	Transdermal administration	Min: 6-8 weeks Max: 576 days (3 times/week)	0, 42, or 126 mg/mouse	Male: No effects in each group Female: Increase in lung papilloma (0, 42, or 126 mg/kg group: 11/30, 17/30, or 26/30)	Van Duuren et al., 1979
Osborne-Mendel mouse (Male, female) 20 mice/control 50 mice/treated	Gavage administration	78 weeks + 32 weeks (Observation period)	0, 47, or 95 mg/kg (Equal to 0, 0-75, or 0-150 mg/kg)	Male: Increase in subcutaneous fibroma (0, 47, or 95 mg/kg group: 0/20, 5/50, or 6/50) Increase in squamous carcinoma in stomach (0, 47, or 95 mg/kg group: 0/20, 3/50, or 9/50) Increase in angiosarcoma (0, 47, or 95 mg/kg group: 0/20, 9/50, or 7/50) Female: Increase in adenocarcinoma in glandula mammaria (0, 47, or 95 mg/kg group: 0/20, 1/50, or 18/50) Increase in mammary gland tumor (0, 47, or 95 mg/kg group: 0/20, 14/50, or 8/50)	NCI, 1978; Ward, 1980
Rat	Oral	2 years	0, 250, or 500 ppm	No effects in any male/female group.	Alumot et al.,

(Line unknown) 5 weeks old (Male, female) 18 rats/group	administration (Feeding)				1976
SD rat (Male, female) 12 weeks old 90 rats/group	Inhalation	78 weeks (7 hours/day, 5 days/week)	0, 5, 10, 50, or 150-250 ppm	Male: No effects in any group. Female: Increase in breast fibroma/ fibroadenoma (5, 10, 50, or 150-250 ppm group: 65/90, 43/90, 58/90, or 52/90)	Maltoni et al., 1980
F344 rat (Male, female) 6 weeks old 50 rats/group	Inhalation	104 weeks (6 hours/day, 5 days/week)	0, 10, 40, or 160 ppm	Male: Increase in subcutaneous fibroma (0, 10, 40, or 160 ppm group: 6/50, 9/50, 12/50, or 15/50) Increase in breast fibroadenoma (0, 10, 40, or 160 ppm group: 0/50, 0/50, 1/50, or 5/50) Increase in mesothelioma (0, 10, 40, or 160 ppm group: 1/50, 1/50, 1/50, or 5/50) Female: Increase in subcutaneous fibroma (0, 10, 40, or 160 ppm group: 0/50, 0/50, 1/50, or 5/50) Increase in breast fibroadenoma	Nagano et al., 1998

				(0, 10, 40, or 160 ppm group: 4/50, 1/50, 6/50, or 13/50) Increase in adenoma in glandula mammaria (0, 10, 40, or 160 ppm group: 3/50, 5/50, 5/50, or 11/50) Increase in adenocarcinoma in glandula mammaria (0, 10, 40, or 160 ppm group: 1/50, 0/50, 1/50, or 5/50)	
SD rat (Male, female) 6 weeks old 50 rats/group	Inhalation	2 years	0 or 50 ppm	No effects in any male/female group	Cheever et al., 1990

Table 7-9 Carcinogenicity evaluation of 1,2-dichloroethane in international organizations, etc.

Organization/source	Classification	Classification criteria
IARC (2001)	Group 2B	Possibly carcinogenic to humans.
ACGIH (2002)	A4	Not classifiable as a human carcinogen
Japan Society for Occupational Health	Group 2-B	Possibly carcinogenic to humans. Substance with comparably insufficient evidence.
U.S. EPA (2002)	Group B2	Probable human carcinogen. Agents for which there is "sufficient: evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies.
U.S. NTP (2002)	R	Reasonably anticipated to be a human carcinogen.

7.4 Effects on Human Health (Summary)

In the tests of humans and animals, 1,2-dichloroethane is quickly absorbed orally, by inhalation, and through skin.

1,2-dichloroethane irritates mucosa, and shows strong and acute toxicity when a large amount is taken orally or by exposure to high density gas, which can be fatal.

Experiments with rabbits reported irritability, irritability to skin was reported as none to medium, and irritability to the eyes was reported as none to light. As for sensitivity, there are no reports for either humans or animals.

In the test for acute toxicity, 1,2-dichloroethane was given orally to animals. LD_{50} was 794 mg/kg for rats.

As for repeated administration toxicity of 1,2-dichloroethane to rats, the target organs were liver, kidney, stomach, cerebellum, and the blood system. NOAEL was 37.5 mg/kg/day for compulsive oral administration for 90 days, and 10 ppm (41.1 mg/m3) for 12-month inhalation exposure test.

As for reproduction toxicity, there is teratogenic action in 1,2-dichloroethane. In the test of teratogenic action by inhalation to pregnant rats, NOAEL of parents was 100 ppm (approximately 411mg/m3/day), while 300 ppm (approximately 1,233 mg/m3/day) for babies. Also, NOAEL of 2-generation mice oral administration test is estimated to be 50 mg/kg/day or more for parents and babies, and NOAEL of one generation rat inhalation exposure test is estimated to be 150 ppm (approximately 617 mg/m3) or more for parents and babies.

Mutagenic property of 1,2-dichloroethane was positive in most in vitro tests such as the reverse mutation test by salmonella typhimurium, genetic mutation test of cultured cells of humans and Chinese hamster ovary, transformation test by mouse C3H/10T1/2 cells, small cells test, comet assay etc. For in vivo tests, there was no significant increase in mouse micronuclei assay. However, the mouse sister chromatid exchange test, comet assay, and DNA damage tests were positive. Also, the mouse/rat DNA binding test and several other tests with drosophila were positive.

1,2-dichloroethane has a tendency to cause cancer in mice and rats, and cancer can be found in the skin, stomach, lacteal glands, lungs, uterus, blood vessels when it is orally administered, in skin, lacteal glands, uterus, liver when it is inhaled, and in lungs when it is administered through skin.

These mutagenic properties and causes of cancer are considered to be due to binding of

1,2-dichloroethane's glutathione conjugate and DNA. IARC is categorized as Group 2B (materials which may have a potential to cause cancer to humans).

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Revised record

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	Approval of deliberation of 14th Safety Assessment and Management Subcommittee (Chemical Substance Council/Examination Meeting, METI)
September 2004	Ver.1.1
	Correction by the change of the “Guideline for the Documentation of Initial Risk Assessment Report”
	Addition of new information