HAZARD ASSESSMENT REPORT

ACETALDEHYDE

CAS No. 75-07-0

Chemicals Evaluation and Research Institute (CERI), Japan

This report was prepared by CERI in collaboration with National Institute of Technology and Evaluation (NITE) under the sponsorship of New Energy and Industrial Technology Development Organization (NEDO).

Preface to the English Version of the Hazard Assessment Reports

For six years from April 2001 to March 2007, Chemicals Evaluation and Research Institute (CERI/Japan) was engaged in a project named “Chemical Risk Assessment and Development of Risk Assessment Methods” under "Comprehensive Chemical Substance Assessment and Management Program" funded by New Energy and Industrial Technology Development Organization (NEDO/Japan). Under this project, about 150 chemical substances were selected among those designated as Class-I Chemicals in the Law for Pollutant Release and Transfer Register and Promotion of Chemical Management (hereafter PRTR Law)[1)]. The selection criteria of these chemicals were their priorities for risk assessment based on their production levels and environmental/human health concerns.

CERI developed the hazard assessment reports of these selected chemical substances based on the review and evaluation of the environmental and human health hazard data obtained from the existing evaluation documents released by the regulatory agencies and international organizations as well as those from the published scientific literatures. The data review and compilation of the reports were conducted according to the guidelines[2)] and the guidance manual[2)] developed for this project. The proposed hazard assessment reports by CERI were reviewed by the experts in the relevant scientific fields from both inside and outside this project for accuracy, relevance and completeness. The final reports were published in Japanese after going through the deliberation by the “Council on Chemical Substances” under the Ministry of Economy, Trade and Industry (METI/Japan), which is responsible for regulation of chemical substances in Japan.

This project was the first attempt in Japan to develop comprehensive hazard assessments of chemical substances for application in risk assessment. In order to share the outcomes of the project globally, CERI independently selected the following seven chemical substances and developed the English version of the hazard assessment reports:

(1) Acetaldehyde
(2) Chlorobenzene
(3) Hydrazine
(4) *N*, *N*-Dimethylformamide
(5) Poly(oxyethylene)nonylphenylether
(6) 3,3’-Dichloro-4,4’-diaminodiphenylmethane
(7) Dimethyl-2,2-dichlorovinyl phosphate (Dichlorvos)

We hope that the hazard assessment reports from our project contribute to the risk assessment and management of chemical substances globally, and appreciate your feedback. .

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1) Details of the PRTR Law, the list of designated chemical substances, and release data in Japan are available on Internet at: http://www.prtr.nite.go.jp/index-e.html.

2) Guidelines and the guidance manual in Japanese are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html. Also, the initial risk assessment reports in Japanese developed in this project which include calculations of margin of exposure based on the result of hazard assessment and exposure assessment, are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html.

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Summary

Acetaldehyde is a colorless liquid or colorless gas at around room temperature having a boiling point of 21℃ and a high vapor pressure of 99 kPa at 20℃. It is freely soluble in water and organic solvents. Acetaldehyde is mainly used as raw material for synthesis of ethyl acetate. Domestic production volume of acetaldehyde in 2001 was approximately 370,000 tons in Japan.

Considering from the uses of acetaldehyde and the annual emission data for fiscal year 2001 in Japan (the 2001 PRTR data), the main release route into the air is through emissions from internal-combustion engines of mobile sources, and that into the water is through emissions in the manufacturing process of acetaldehyde. As the scenario of acetaldehyde releases in Japan, it is estimated that 9,674 tons is released annually into the air, and 69 tons into water.

Acetaldehyde released into the aquatic environment is eliminated mainly by biodegradation, but elimination by volatilization cannot be ignored under the conditions where volatilization rate of acetaldehyde from the aquatic environment is high. Low bioaccumulation potential is suggested in aquatic organisms.

Many studies have been conducted to assess the toxic effects of acetaldehyde on organisms in the environmental using indices including mortality, immobilization and growth inhibition. In the acute toxicity studies, the 120-hr EC_{50} values (growth inhibition) for marine diatom ranged from 237 to 249 mg/L. The acute toxicity of acetaldehyde to invertebrates has been reported for freshwater water flea and seawater mysid shrimp, and the 48-hr EC_{50} (immobilization) for water flea was 48.3 mg/L and the 96-hr LC_{50} for mysid shrimp was 27.4 mg/L. The acute toxicity of acetaldehyde to fish has been reported in freshwater fish, fathead minnow, bluegill, guppy, rainbow trout and one of minnow species. The reliable lowest 96-hr LC_{50} is 30.8 mg/L for fathead minnow.

The lowest reported value in acute toxicity tests on aquatic organisms was a 96-hr LC_{50} of 27.4 mg/L for mysid shrimp. No reports on long-term toxicity of acetaldehyde were obtained in this investigation.

Acetaldehyde is an exogenous chemical substance to which humans are exposed as well as an endogenous substance that is internally generated within humans and animals. Acetaldehyde is generated from ethanol in the liver and finally degraded to carbon dioxide and water through acetic acid. Acetaldehyde is absorbed through the lung and gastrointestinal tract. Absorbed acetaldehyde is distributed in the blood, liver, kidney, spleen, heart and muscle.

Acetaldehyde induces moderate irritation in human eyes and respiratory tract including the throat and nose. In experimental animals, acetaldehyde showed moderate irritation in the eyes and skin of rabbits. No reports were obtained on sensitization of acetaldehyde in this investigation.

The acute toxicity studies of acetaldehyde showed that oral LD_{50} values were 1,230 mg/kg in mice and 660 to 1,930 mg/kg for rats. The LC_{50} values following inhalation exposure to rats ranged 13,100 ppm (4 hours) to 20,200 ppm (0.5 hour). The symptoms caused by acetaldehyde were increases in heart rate and blood pressure, pulmonary edema and effects on the central nervous system.

Regarding repeated dose toxicity of acetaldehyde, oral administration to rats for 4 weeks caused slight hyperkeratosis of the forestomach at a dose of 675 mg/kg/day. The NOAEL is 125 mg/kg/day. Inhalation exposure caused damage of epithelium of the respiratory tract in rats and hamsters. The NOAEL values are 150 ppm (270 mg/m^3) for rats exposed for 4 weeks and 390 ppm (700 mg $/m^3$) for hamsters exposed for 13 weeks based on the effects of upper respiratory tract.

Regarding reproductive and developmental toxicity, intravenous and intraperitoneal injections of acetaldehyde caused malformation in fetuses. Oral administration of acetaldehyde at dose of 200 mg/kg/day on gestation days 6 to 18 to rats showed in skeletal defects in fetuses. However, this report is an abstract only, which detailed data are not described.

In genotoxicity studies of acetaldehyde, there are many positive results in *in vitro* studies including gene mutation, chromosomal aberration, sister chromatid exchanges. Also in *in vivo* studies, the frequency of sister chromatid exchange was increased in intraperitoneal studies using hamsters and mice, and positive results were observed in a micronucleus assay. From the overall evaluation of these data, acetaldehyde is considered to be genotoxic.

There are no reliable epidemiological data for carcinogenicity of acetaldehyde to humans. In rats, 27-month inhalation exposure of acetaldehyde at doses of 750 ppm (1,350 mg/m^3) and above caused dose-dependent increases in nasal adenocarcinoma and squamous cell carcinoma. Also, in hamsters, 52-week inhalation exposure of acetaldehyde at doses of 2,500 ppm (4,500 mg/m^3) and above exhibited significant increases in laryngeal and nasal tumors. Therefore, acetaldehyde is considered to be carcinogenic in experimental animals. Some data suggest the promoter activity of acetaldehyde to respiratory tumorigenesis, but the data are limited to make a definitive conclusion. Acetaldehyde is categorized as Group 2B (the agent is possibly carcinogenic to humans) by the IARC.

Contents

1. Identity of the substance

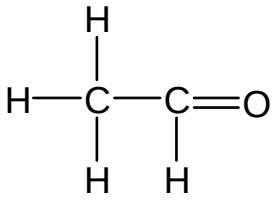
1.1 Chemical name : Acetaldehyde

1.2 Class reference number in Chemical Substance Control Law[1)] : 2-485

1.3 PRTR[2)] number (Law for PRTR and Promotion of Chemical Management) : 1-11

1.4 CAS registry number : 75-07-0

1.5 Structural formula



1.6 Molecular formula : C_2H_4O

1.7 Molecular weight : 44.05

2. General Information

2.1 Synonyms

Ethanal, Aldehyde acetate, Ethyl aldehyde

2.2 Purity

>99.5 % (Commercial products) (CERI/Japan, 2002)

2.3 Impurities

Crotonaldehyde (<0.1 %), Aldol, Propionaldehyde, Acetone, Paraldehyde,

Acids (<0.02 %) (Commercial products) (CERI/Japan, 2002)

2.4 Additives/Stabilizers

No additives and stabilizers (Commercial products) (CERI/Japan, 2002)

2.5 Current regulations in Japan[3)]

Law for PRTR and Promotion of Chemical Management:	Class-I designated chemical substance
Fire Service Law:	Dangerous goods class IV special flammable substance

[1)] The Low Concerning the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc., Japan. Provisional translation is available on Internet at: http://www.safe.nite.go.jp/english/kasinn/kaiseikasinhou.html

[2)] Pollutant Release and Transfer Register

[3)] As this document covers basic information on Japanese regulations (unofficial translations), you should confirm the details using it.

Industrial Safety and Health Law:	Dangerous substance inflammable substance, Hazardous substance to be notified in terms of whose name, Mutagenic chemical substance
Air Pollution Control Law:	Harmful air pollution substance (The priority substance)
Ship Safety Law:	Flammable liquid
Civil Aeronautics Law:	Flammable liquid
Port Regulation Law:	Flammable liquid
The Offensive Odor Control Law:	Specified offensive odor substance. Concentration in air ranges between 0.05 ppm and 0.5 ppm.
High Pressure Gas Safety Law:	Flammable gas, Liquefied gas

Additional information

Food Sanitation Law:	Disapproval substance	
The guideline values of concentration levels of chemical substances in the indoor air of houses:	0.03 ppm	(Ministry of Health, Labour and Welfare)

3. Physico-chemical properties

Appearance:	Colorless liquid or colorless gas	(U.S. NLM:HSDB, 2002)
Melting point:	-123.5°C	(Merck, 2001)
Boiling point:	21°C	(Merck, 2001)
Flash point:	-39°C (closed-cup)	(NFPA, 2002)
Ignition point :	185°C	(IPCS, 1999)
	175°C	(NFPA, 2002)
Explosion limit :	4-57 vol% (in air)	(IPCS, 1999)
	4-60 vol% (in air)	(NFPA, 2002)
Specific gravity:	0.788 (16°C/4°C)	(Merck, 2001)
Vapor density:	1.52 (Air = 1)	
Vapor pressure:	99 kPa (20°C)	(IPCS, 1999)
Partition coefficient:	log Kow (*n*-octanol/water) = -0.34 (measured), -0.17 (estimated)	(SRC:KowWin, 2002)
Dissociation constant :	pKa = 13.6 (25°C)	(SRC:PhysProp, 2002)
Mass spectrum:	Main mass fragments	
	m/z 29 (standard peak= 1.0), 44 (0.81), 43 (0.33)	(NIST, 1998)
Soil adsorption coefficient:	Koc = 1 (estimated) (SRC:PcKocWin, 2002)	
Solubility:	water: miscible	
	alcohol: miscible	(Merck, 2001)
Henry's constant:	6.76 Pa·m^3/mol (6.67×10^{-5} atm·m^3/mol) (25°C, measured)	(SRC:PhysProp, 2002)
Conversion factor:	(Gas phase, 20°C) 1 ppm = 1.83 mg/m^3, 1 mg/m^3 = 0.546 ppm	

Others: The substance can form explosive peroxides in contact with air. The substance may polymerize under the influence of acid and alkaline substances such as sodium hydroxides in the presence of metals such as iron with fire or explosion hazard.
(IPCS, 1999)

4. Sources of release to the environment

4.1 Production, import, export and domestic supply

The production, import, export and domestic supply of acetaldehyde for 5 years from 1997 to 2001 in Japan are shown in Table 4-1.

Table 4-1 Production, import, export and domestic supply of acetaldehyde (tons)

Year	1997	1998	1999	2000	2001
Production	435,835	414,099	414,679	401,055	371,701
Import	0	0	0	1	0
Export	8	7	10	5	1
Domestic supply	435,827	414,092	414,669	401,051	371,700

(Production: MITI/Japan, 1998-2000; METI/Japan, 2001-2002; Export and import: MOF/Japan, 2003)

4.2 Uses

The estimated use pattern of acetaldehyde is shown in Table 4-2 (NITE/Japan, 2003).

Acetaldehyde is mainly used as raw material for synthesis of ethyl acetate. It is also used as raw material for synthesis of pentaerythritol, glyoxal, pyridine, lactonitrile and acetic acid. Other uses include fungicide, insect deterrent, reagents (photo developer, medical), fuel additive and adhesive.

Table 4-2 Estimated use patterns

Use	Ratio (%)
Raw material for ethyl acetate synthesis	62
Others	38
Total	100

(NITE/Japan, 2003)

4.3 Releases

4.3.1 Releases under PRTR system

According to “Total Release and Transfers for FY 2001 (hereafter the 2001 PRTR Data)” under the PRTR system (METI/Japan and MOE/Japan, 2003a), 120 tons of acetaldehyde was released into the air, 67 tons into public water, and 300 tons was transferred as wastes from the business institutions required to report their releases and transfer. No acetaldehyde was reported to be released into land. In addition, it is estimated that 4 tons of acetaldehyde was released from the business institutions in the industries

that were designated under the PRTR system but exempted from notification, and 9,552 tons from mobile sources. No estimation was made for the amounts of releases from the industries outside the scope of the PRTR system and those from households.

a. Release and transfer from the industries within the scope of PRTR system

The amounts of releases into the environmental media (air, water and land) and transfer by the industries designated under the PRTR system are shown in Table 4-3. METI/Japan and MOE/Japan (2003a) did not provide the amounts of releases to the environmental media for the estimations of releases from the business institutions exempted from notification. The ratio for each environmental medium of the releases estimated for the business institutions exempted for notification is calculated based on the assumption that ratios of releases into the air, water and land were the same as those obtained by notification (NITE/ Japan, 2003).

Table 4-3 Releases and transfer of acetaldehyde to environmental media by industries

(tons/year)

Industries	By Notification					Notification Exempted			Total amount of releases by notification and by estimation	
	Release			Transfer		Release (estimated)[1)]				
	Air	Water	Land	Sewer	Wastes	Air	Water	Land	Total release[2)]	Ratio (%)
Chemical and allied products	102	58	0	0	300	1	0	0	161	84
Plastic products	11	6	0	0	0	0	0	0	17	9
Textile mill products	7	3	0	0	0	0	0	0	10	5
Electrical machinery, equipment and supplies	–	–	–	–	–	1	1	0	2	1
Total[2)]	120	67	0	0	300	3	1	0	191	100

(NITE/Japan, 2003)

1) Based on the assumption that ratios of releases into the air, water and land were the same as those of the releases obtained by notification, the amounts of releases from the business institutions exempted from notification were estimated.

2) The total may not correspond with the sum of rounded values in each column of the table.

－: Not notified or estimated

Based on the production volume and the emission factor at manufacturing sites of acetaldehyde in 2001 (Japan Chemical Industry Association, 2002a), the amounts of releases into the air and water are estimated to be 55 and 60 tons per year, respectively (NITE/Japan, 2004). Therefore, the releases of acetaldehyde into the water are considered to occur mostly during the manufacturing process. However, it is not possible to estimate the releases into the air from these data.

b. Releases from the non-designated industries, households, and mobile sources

Based on the 2001 PRTR Data, amounts of release from mobile sources are estimated, and are presented in Table 4-4. METI/Japan and MOE/Japan (2003a) do not provide the amounts of releases by environmental media for the estimation of release from mobile sources. It was assumed that the all generated acetaldehyde was released into the air (NITE/Japan, 2004).

Acetaldehyde is produced from incomplete combustion of vehicle fuels including gasoline and diesel oil. Therefore, the amounts of release from mobile sources are estimated on automobiles, motorcycles, special motor vehicles and marine vessel with gasoline/diesel engine (METI/Japan and MOE/Japan, 2003b).

Table 4-4 Releases of acetaldehyde from mobile sources into environmental media (tons/year)

	Air	Water	Land
Mobile sources [1)]	9,552	0	0

(NITE/Japan, 2004)

1) All generated acetaldehyde was considered to be released into the air.

4.3.2 Releases from other sources

As the possible sources of acetaldehyde other than those included in the 2001 PRTR data, it has been reported that acetaldehyde is produced from combustion and photo-oxidation of hydrocarbons in the air (IPCS, 1995).

It has been also reported that acetaldehyde is released from cigarette smoke at a rate of 0.87–1.37mg/cigarette (Hoffman et al., 1975). "The amount of release from cigarette smoke" was not estimated in the 2001 PRTR Data, but was defined as the release from sources outside the scope of the PRTR system and estimated to be 535 tons per year in the 2002 PRTR Data (METI/Japan and MOE/Japan, 2004).

Further, it has been indicated that a trace of acetaldehyde is included in alcoholic beverages, fruit juices, essential oils and coffee (IARC, 1999).

The "Progress Report of the Committee on Sick House Syndrome (Indoor Air Pollution) –Summary on the discussions at the 8th and 9th meetings" issued by the Japan Ministry of Health, Labor and Welfare (MHLW/Japan) describes that possible indoor release sources other than cigarette smoke are adhesives and antiseptics of building materials etc.

4.4 Estimated routes of releases

As described in Section 4.2, acetaldehyde is used mainly as raw material for synthesis of ethyl acetate. Judging from the uses of acetaldehyde and the 2001 PRTR Data, the main release route into the air is through emissions from internal-combustion engines of mobile sources and that into the water is through emissions in the manufacturing process. The major release route to the indoor environment is through releases from building materials and furniture and other products using adhesives.

As the scenario of acetaldehyde releases in Japan, it is estimated that 9,674 tons of acetaldehyde is released annually into the air, and 69 tons into water. Releases into the environment after processing of

wastes at waste disposal facilities are not considered for estimation of the amount transferred as wastes and that transferred into sewers.

5. Environmental fate

5.1 Stability in the atmosphere

a. Reaction with OH radical

The reaction rate constant of acetaldehyde with OH radical is 1.6×10^{-11} cm^3/molecule-sec (25°C, measured value) in the tropospheric air (SRC: AopWin, 2002). On the assumption of OH radical concentration of 5×10^5 to 1×10^6 molecule /cm^3, the half-life is calculated as 0.5 to 1 day.

b. Reaction with ozone

The reaction rate constant of acetaldehyde with ozone is 6.0×10^{-21} cm^3/molecule-sec (25°C, measured value) in the tropospheric air (SRC: AopWin, 2002). On the assumption of ozone concentration of 7×10^{11} molecule /cm^3, the half-life is calculated as 5 years.

c. Reaction with nitrate radical

The reaction rate constant of acetaldehyde with nitrate radical is 2.8×10^{-15} cm^3/molecule-sec (25°C, measured value) in the tropospheric air (SRC: AopWin, 2002). On the assumption of nitrate radical level of 2.4×10^8 to 2.4×10^9 molecule /cm^3 (10 - 100 ppt), the half-life is calculated as 2 to 20 days.

d. Direct degradation by sunlight

As acetaldehyde absorbs light at and above 290 nm (U.S.NLM:HSDB, 2002), it can be degraded directly by light in the air.

5.2 Stability in water

5.2.1 Abiotic degradation

As acetaldehyde has no chemical bonds that are subject to hydrolysis, it is not hydrolyzed in the aquatic environment (US. NLM:HSDB, 2002). It is presumed that acetaldehyde can be oxidized in the aquatic environment (Environmental Canada, 2000) to produce acetic acid.

5.2.2 Biodegradation

Acetaldehyde is ranked as a readily biodegradable substance based on the result of the aerobic biodegradation study required under the Chemical Substances Control Law, Japan. The study result indicated that the degradation rate of acetaldehyde was 80% in biological oxygen demand (BOD) determination under the condition of 100 mg/L of test substance concentration, 30 mg/L of activated sludge concentration and 4 weeks of test period. The degradation rates were 93% and 100%, respectively in the dissolved organic carbon (DOC) determination and by measurement with gas chromatography (GC) (MITI/Japan, 1980). Biodegradation studies using activated sludge or

microorganisms showed that acetaldehyde was biodegraded in various conditions (Ludzack and Ettinger, 1960; 1975; Speece, 1983; Thom and Agg, 1975). Also, it was reported that acetaldehyde was biodegraded under anaerobic condition (Chou and Speece, 1978).

5.2.3 Removal in sewage treatment

No reports were obtained on acetaldehyde removal in sewage treatment in this investigation.

5.3 Behavior in the aquatic environment

Removal of acetaldehyde by volatilization from water to air using Henry's constant was examined. The half life in a model river (water depth: 1 m; flow velocity: 1 m/sec; wind velocity: 3 m/sec) was estimated as 6.5 hours, and that in a model lake (water depth: 1 m; flow velocity: 0.05 m/sec; wind velocity: 0.5 m/sec) was estimated as 5.3 days (Lyman et al., 1990).

Degradation and volatilization rates of acetaldehyde in the aquatic environment are affected with the environmental conditions including temperature, wind and flow velocity. The half-life in the surface water with consideration of these factors was 30 to 100 hours (Mackay et al., 1995). Acetaldehyde is water-miscible and has a high vapor pressure (99 kPa at 20°C), and its Henry's constant is 6.76 Pa・m^3/mol (25°C) (see the Chapter 3).

Based on the information summarized here and in Section 5.2, it is assumed that acetaldehyde released into the aquatic environment is eliminated by biodegradation. However, under the conditions where volatilization rate of acetaldehyde from the aquatic environment is high, elimination by volatilization cannot be ignored.

5.4 Bioaccumulation

No reports on the measurement of bioconcentration factor (BCF) of acetaldehyde were obtained in this investigation. The BCF of acetaldehyde is estimated as 3.2 based on the *n*-octanol-water partition coefficient (log Kow: -0.34) (SRC: BcfWin, 2002), which suggests low bioaccumulation in aquatic organisms.

6. Effects on organisms in the environment

6.1 Effects on aquatic organisms

6.1.1 Microorganisms

The toxicity studies of acetaldehyde to microorganisms are summerized in Table 6-1.

The toxicity of acetaldehyde to bacteria and protozoa has been reported. The lowest values of the toxicity are 342 mg/L obtained as the 0.5-hr EC_{50} in bioluminescence inhibition for marine luminescent bacterium (*Photobacterium phosphoreum*) (Curtis et al., 1982), and 44 mg/L as the 9-hr EC_{50} in growth inhibition for ciliata (*Tetrahymena pyriformis*) (Sauvant et al., 1995).

Table 6-1 Toxicity of acetaldehyde to microorganisms

Species	Temperature (°C)	Endpoint		Concentration (mg/L)	Reference
Bacteria *Photobacterium phosphoreum* (marine luminescent bacterium)	15	0.5-hr EC_{50}	luminescence inhibition	342 (n)	Curtis et al., 1982
Protozoa *Entosiphon sulcatum* (flagellata)	25	72-hr toxic threshold [1)]	Growth inhibition	52 (n)	Bringmann, 1978
Uronema parduczi (ciliata)	25	20-hr toxic threshold [1)]	Growth inhibition	57 (n)	Bringmann & Kuhn, 1980
Chilomonas paramaecium (flagellata)	20	48-hr toxic threshold [1)]	Growth inhibition	82 (n)	Bringmann et al, 1980
Tetrahymena pyriformis (ciliata)	28	9-hr EC_{50}	Growth inhibition	44 (n)	Sauvant et al., 1995

ND: No data available

(n): Nominal concentration

1) Concentration giving 5% effect compared to the control (EC_5)

6.1.2 Algae

The toxicity studies of acetaldehyde to algae are summerrized in Table 6-2.

The toxicity of acetaldehyde to freshwater green algae, *Chlamydomonas* and marine diatom, *Nitzschia* has been reported. The lowest values of the toxicity are 23 mg/L obtained as the 2-hr EC_5 in photosynthesis inhibition in freshwater green algae (*Chlamydomonas reinhardti*) (Brack and Frank, 1998), and 237 to 249 mg/L as the 120-hr EC_{50} in growth inhibition in marine diatom (*Nitzschia linearis*) (Patrick et al., 1968). In the former study, an endpoint different from usual growth inhibition studies was used.

No reports on NOEC values of growth inhibition in freshwater and marine algae were obtained in this investigation.

Table 6-2 Toxicity of acetaldehyde to algae

Species	Method/ Condition	Tem-perature (°C)	Endpoint		Concen-tration (mg/L)	Reference
Freshwater species						
Chlamydomonas reinhardti (green alga)	Static, Closed [1)]	20	2-hr EC_5	Photo-synthesis inhibition	23 (n)	Brack & Frank, 1998
Marine species						
Nitzschia linearis (diatom)	Static	22	120-hr EC_{50}	Growth inhibition	237-249 (n)	Patrick et al., 1968

(n): Nominal concentration

1) Closed system: a test container and water bath are closed with a cover such as a lid, and a headspace is kept.

6.1.3 Invertebrates

The toxicity studies of acetaldehyde to invertebrates are summerized in Table 6-3.

The acute toxicity of acetaldehyde to freshwater crustacea (*Daphnia magna*) and marine crustacea (brown shrimp and mysid) has been reported. The lowest values of the acute toxicity are 48.3 mg/L obtained as the 48-hr EC_{50} in immobilization in *Daphnia magna* (Randall and Knopp, 1980), and 27.4 mg/L obtained as the 96-hr LC_{50} in mysid (Carr, 1987). In addition, 4.7 to 7.0 mg/L of EC_{50} in *Daphnia magna* was reported (Office of Pesticide Program, 2000). However, the details of this study are unknown.

No reports on long-term toxicity in freshwater and marine species were obtained in this investigation.

Table 6-3 Toxicity of acetaldehyde to invertebrates

Species	Growth Stage	Method/ Condition	Temperature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concentration (mg/L)	Reference
Freshwater species								
Daphnia magna (crustacea, water flea)	<24 hours	Static	22	89.5-180	7.0-8.2	48-hr EC_{50} Immobilization	48.3 (n)	Randall & Knopp, 1980
		Static	ND	ND	ND	48-hr EC_{50} Immobilization	4.7-7.0 (n)	Office of Pesticide Program, 2000
Marine species								
Crangon crangon (crustacea, brown shrimp)	Adult	Semi-static	15	ND	ND	48-hr LC_{50}	> 100 (n)	Portmann & Wilson, 1971
Americamysis bahia (crustacea, mysid)	<48 hours	ASTM[1] Static, Closed [2]	20.5	NaCl concentration: 32‰	7.98	96-hr LC_{50}	27.4 (n)	Carr, 1987

ND: No data available

(n): Nominal concentration

1) Test guideline by the American Society for Testing and Materials

2) Closed system: a test container and water bath are covered with a lid, etc., and a headspace is kept.

6.1.4 Fish

The toxicity studies of acetaldehyde to fish are summerized in Table 6-4.

The acute toxicity (96-hr LC_{50}) of acetaldehyde has been reported for freshwater fish including fathead minnow, bluegill, guppy, rainbow trout and one of golden orphe. Of LC_{50} data obtained from reliable studies considering acetaldehyde volatility, the lowest value is 30.8 mg/L (96-hr) in the fathead minnow, *Pimephales promelas*, which was the mean measured concentration of test solutions (Brooke et al., 1984). In addition, 96-hr LC_{50} values were reported to be 2.1 mg/L in bluegill and 2.2 mg/L in rainbow trout (Office of Pesticide Program, 2000). However, the details of these studies are unknown.

In marine fish, 24-hr LC_{50} in pinfish (*Lagodon rhomboides*) was 70 mg/L (Daugherty and Garrett, 1951).

No reports on long-term toxicity in freshwater and marine species were obtained in this investigation.

Table 6-4 Toxicity of acetaldehyde to fish

Species	Growth Stage	Method/ Condition	Temp. (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concentration (mg/L)	Reference
Freshwater species								
Pimephales promelas (fathead minnow)	17.5 mm 0.554 g 30 days	Flow-through	23.9	53.0	7.6	96-hr LC_{50}	30.8 (m)	Brooke et al., 1984
	17.5 mm 0.078 g 27 to 33 days	Flow-through	21.6	46.6	7.1	96-hr LC_{50}	37.2 (m)	Geiger et al., 1990
Poecilia reticulata (guppy)	2 to 3 months	Semi-static, Closed [1)]	21-23	ND	ND	14-day LC_{50}	35 (m)	Deneer et al., 1988
Lepomis macrochirus (bluegill)	5.3-7.2 cm 3.5-3.9 g	Static	18	ND	ND	96-hr LC_{50}	53 (n)	Patrick et al., 1968
	ND	Static	ND	ND	ND	96-hr LC_{50}	2.1 (m)	Office of Pesticide Program, 2000
Oncorhynchus mykiss (rainbow trout)	ND	Static	ND	ND	ND	96-hr LC_{50}	2.2 (m)	Office of Pesticide Program, 2000
Leuciscus idus (golden orphe, cyprinidae)	ND	Static	ND	ND	ND	48-hr LC_{50}	124-140 (n)	Juhnke & Luedemann 1978
Marine species								
Lagodon rhomboides (pinfish, sparidae)	57-113 mm	Static	13.7-20.4	ND	ND	24-hr LC_{50}	70 (n)	Daugherty & Garrett, 1951

ND: No data available

(m): Measured concentration, (n): Nominal concentration

(1) Closed system: a test container and water bath are closed with a cover such as a lid, and a headspace is kept.

6.1.5 Other aquatic organisms

No reports on toxicity of acetaldehyde in other aquatic organisms (e.g., amphibians) were obtained in this investigation.

6.2 Effects on terrestrial organisms

6.2.1 Microorganisms

Acetaldehyde is used as fumigant to control bacteria and molds associated with fruit rot (Aharoni and Barkai-Golan, 1973; Aharoni and Stadelbacher, 1973; Yuen et al., 1995). The concentrations that caused growth inhibition and death in 11 species of fungi ranged between 540 and 357,000 mg/m^3. The most sensitive responses identified were 95% and 91% of growth inhibition in *Penicillium italicum* and *P. digitatum*, respectively, after a 5-day exposure to acetaldehyde vapor at a concentration of 540 mg/m^3 (Yuen et al., 1995).

6.2.2 Plants

Color change and necrosis of outer leaves were observed in lettuce (*Lactuca sativa*) following a 4-hour exposure to acetaldehyde (54,000-108,000 mg/m^3), but no effect was found at a concentration of 36,000 mg/m^3 (Aharoni et al., 1979; Stewart et al., 1980). Seeds of onion, carrot, Palmer Amaranth and tomato were treated with acetaldehyde for 3 days to investigate the effects on germination. Germination inhibition was observed in 50% and more of seeds of all species at the highest concentration in the study, 1,520 mg/L (Baradow and Connic, 1988).

6.2.3 Animals

In two slug species, *Arion hortensis* and *Agriolimax reticulatus*, 96-hr LC_{50} were 8.91 and 7.96 mg/L, respectively (Henderson, 1970). In the investigation of the effects of acetaldehyde on two aphid species, *Myzus persicae* and *Acythosiphon kondai* showed 100% mortality at all life stages when exposed to acetaldehyde at the concentrations of 3,600 and 4,500 mg/m^3, respectively (Aharoni et al., 1979).

In mallard duck and bobwhite quail, 8-day LC_{50} values were 5,000 and 808 ppm, respectively (Office of Pesticide Program, 2000).

6.3 Summary of effects on organisms in the environment

Many studies have been conducted to assess the hazardous effects of acetaldehyde on organisms in the environment using indices including mortality, immobilization and growth inhibition. No reports on long-term toxicity in aquatic species were obtained in this investigation. Acetaldehyde is readily biodegradable in water and highly volatile. However, the reported values in most of the toxicity studies except those with fish, were based on the nominal concentrations.

In microorganisms, the toxicity of acetaldehyde to bacteria and protozoa was reported, and the lowest values of the toxicity are 342 mg/L obtained as the 30-min EC_{50} in bioluminescent inhibition for marine luminescent bacterium (*Photobacterium phosphoreum*), and 44 mg/L as the 9-hr EC_{50} in growth inhibition for ciliata (*Tetrahymena pyriformis*) (Sauvant et al., 1995).

In the algae growth inhibition studies, the 120-hr EC_{50} (growth inhibition) in marine diatom (*Nitzschia linearis*) ranged from 237 to 249 mg/L.

The acute toxicity of acetaldehyde to invertebrates was reported in freshwater species such as water flea (*Daphnia magna*) and marine species such as brown shrimp (*Crangon*) and mysid (*Americamysis bahia*), and 48.3 mg/L was obtained as the 48-hr EC_{50} (immobilization) in *Daphnia magna* and 27.4 mg/L as the 96-hr LC_{50} in *mysid*.

The acute toxicity of acetaldehyde to fish was reported in freshwater fish such as fathead minnow, bluegill, guppy, rainbow trout and one of golden orphe. The reliable lowest 96-hr LC_{50}, which was estimated considering acetaldehyde volatility, is 30.8 mg/L in fathead minnow, which is the mean measured concentration of the test solutions. The acute toxicity to marine fish was reported in pinfish alone and the 24-hr LC_{50} value was 70 mg/L.

In terrestrial organisms, toxicity of acetaldehyde to bacteria, plant, invertebrates and birds were reported. Of these organisms, acetaldehyde had the strongest effect on bacteria, and the most sensitive

responses identified were observed in *Penicillium italicum* and *P. digitatum*, which showed 95% and 91% of growth inhibition, respectively, after a 5-day exposure to acetaldehyde vapor at the concentration of 540 mg/m^3.

Based on the data summarized above, the lowest value of toxicity in aquatic organisms is the 96-hr LC_{50} of 27.4 mg/L for mysid shrimp (crustacea).

Although formal classification criteria is not used in this investigation, it can be considered that the acute toxicity values of acetaldehyde to aquatic organisms is corresponding to the GHS acute toxicity hazard category III (harmful).

7. Effects on human health

7.1 Kinetics and metabolism

Acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenase (ALDH) and finally degraded to carbon dioxide and water. Acetaldehyde is also a metabolic intermediate of ethanol, i.e., ethanol in blood is transferred into liver and metabolized to acetaldehyde .

a. Absorption

Acetaldehyde is absorbed through the lung and gastrointestinal tract. Although there are no adequate quantitative studies on dermal absorption of acetaldehyde, it is shown from studies on toxicity of acetaldehyde described later that absorption through the skin is possible (IPCS, 1995).

b. Distribution

In the nasal inhalation study of acetaldehyde in eight volunteers at the concentrations ranging from 100 to 800 mg/m^3, 45% to 70% of the exposed amount of acetaldehyde was retained in the respiratory tracts (Egle, 1970).

In a inhalation study (1-hr) in SD rats, acetaldehyde was distributed in the blood, liver, kidney, spleen, heart, myocardium and skeletal muscle. The concentration in the liver was relatively low due to the rapid metabolism of acetaldehyde (Hobara et al., 1985; Watanabe et al., 1986).

The possibility that acetaldehyde can enter the fetal circulatory system through the placenta is suggested. Pregnant ICR mice were given intraperitoneally a dose of 200 mg/kg on gestation day 10, and acetaldehyde was detected in the fetuses 2 hours after the administration. After intraperitoneal administration of ethanol at 79 mg/kg, acetaldehyde at a low level of concentration or near the limit of detection was detected in the fetuses 12 hours after the administration (Blakley and Scott, 1984b).

After an oral administration of ethanol at a dose of 4,500 mg/kg in male and female Wistar rats, it was confirmed that produced acetaldehyde was distributed in the blood and brain interstitial fluid (Westcott et al., 1980).

Most of acetaldehyde in the blood of volunteers after alcohol ingestion was distributed in erythrocytes. The concentration of acetaldehyde in the erythrocyte was approximately 10-fold higher

than that in the plasma, indicating high transition of acetaldehyde to hemocytes (Baraona et al., 1987).

c. Metabolism

Acetaldehyde is metabolized to acetic acid by nicotinamide adenine dinucleotide (NAD)-dependent aldehyde dehydrogenase (ALDH), which exists in the liver and nasal mucosa, and finally degraded to carbon dioxide and water. (Brien and Loomis, 1983)

Regarding ALDH, there are two types of ALDH in mitochondrial and cytosolic forms. Kinetic characteristics of enzymatic reaction of liver mitochondrial ALDH are similar among human, rat and Syrian hamster, while, the Km value of human cytosolic ALDH1 was approximately 180 μM but those of rat and Syrian hamster were 15 and 12 μM, respectively (Klyosov et al., 1996). In human liver, mitochondrial ALDH alone oxidizes acetaldehyde at physiological concentrations, but in rodent liver, both mitochondrial and cytosolic ALDHs have a role in acetaldehyde metabolism (IARC, 1999). Approximately 40% of Oriental population is inactive in mitochondrial ALDH2, which is associated with alcohol intolerance (Yoshida et al., 1984).

In humans, inhaled acetaldehyde is retained in the respiratory tract at a high rate, and, therefore, acetaldehyde metabolism is mainly associated with thiol compounds (cysteine and glutathione) and subsequently hemimercaptal and thiazolidine intermediates are produced. Thioether and disulfide are excreted in the urine, however, most of them are metabolized to acetic acid by ALDH2, and finally degraded to carbon dioxide and water (Brien and Loomis, 1983; Cederbaum and Rubin, 1976; Hemminki, 1982; Nicholls et al., 1992; Sprince et al., 1974).

It is shown that acetaldehyde (purity: 99%) that is incubated with ribonucleosides and deoxyribonucleosides forms adducts with cytosine or purine nucleoside, and one of acetaldehyde guanosine adducts is *N*2-ethylguanosine (Hemminki and Suni, 1984).

d. Excretion

In an intravenous administration of acetaldehyde solution (0.5% to 5%) in rabbits, metabolites were excreted at a rate of 7 to 10 mg/min (Hald and Larsen, 1949).

In an intraperitoneal administration of acetaldehyde at a single dose of 6.2 mmol (273 mg) in rats, sulfur-containing metabolites in urine was significantly increased (approximately 100%) (Hemminki, 1982).

In an oral administration of acetaldehyde at a dose of 600 mg/kg in dogs, no excretion of unmetabolized acetaldehyde was comfirmed in urine (Booze and Oehme, 1986).

7.2 Epidemiological studies and case reports

Epidemiological studies and case reports of acetaldehyde are summarized in Table 7-1.

Acetaldehyde vapor is reported to cause coughing and burning pain in the nose, throat and eyes. Exposure to acetaldehyde solution causes burning, lacrimation and blurred vision. Prolonged dermal exposure to acetaldehyde probably causes erythema and burning, and repeated exposure causes dermatitis induced by dermal irritation or sensitization (Proctor and Hughes, 1978).

After 15-minute exposure to acetaldehyde vapor at a concentration of 50 ppm (90 mg/m^3) in 12 human volunteers, mild irritation to eyes was observed (Silverman et al., 1946).

Transient conjunctivitis was observed in humans exposed to acetaldehyde at a concentration of 200 ppm (360 mg/m^3) for 15 minutes (Proctor and Hughes, 1978).

All of 14 males (18-45 years old) exposed to acetaldehyde at a concentration of 134 ppm (241 mg/m^3) for 30 minutes showed mild irritation in the respiratory tract (Sim and Pattle, 1957).

Intravenous infusion of human subjects with 5% acetaldehyde at a rate of 20.6 to 82.4 mg/min for up to 36 minutes resulted in increases in heart rate, ventilation rate and respiratory dead space, and a decrease in alveolar carbon dioxide level. These symptoms are qualitatively and quantitatively similar to the symptoms observed in the subjects who ingested ethanol after administration of disulfiram, ALDH-inhibitor (Asmussen et al., 1948).

The perception threshold of acetaldehyde vapor was reported to be less than 0.2 μg/m^3 (Ruth, 1986).

An accidental exposure to acetaldehyde resulted in headache, coma, irritation of eyes, skin, respiratory tract and throat, bronchitis, pulmonary edema, paralysis and death (U.S. NRC, 1981).

In all of 12 volunteers of Oriental ancestry who underwent patch test with 75% acetaldehyde solution, dermal irritation (erythema) was observed (Wilkin and Fortner, 1985).

To analyze the relationship between ALDH2 genotype and esophageal cancer, two case-control studies were conducted. The first is a case-control study in 40 male chronic alcoholics who were diagnosed with esophageal cancer between 1991 and 1995 (case) with 55 chronic alcoholics who were hospitalized in 1991 and selected randomly (control) in Hospital A. In chronic alcoholics with esophageal cancer, the number of patients with ALDH2 *1/*1 and ALDH2 *1/*2 genotypes were 19 and 21, respectively, and in the control alcoholics, 48 and 7, respectively. The odds ratio of ALDH2 *1/*2 to ALDH2 *1/*1 was 7.6 (95% confidence interval (CI): 2.8-20.7) which was statistically significant. The second is a case-control study in non-alcoholics of 29 male patients with drinking habit diagnosed with esophageal cancer in Hospital B (case) and 28 male staff of Hospital A with drinking habit (control). In patients with esophageal cancer and drinking habit, the number of males with ALDH2 *1/*1 and ALDH2 *1/*2 genotypes were 8 and 21, respectively, and in the control group, 23 and 5, respectively. The odds ratio was 12.1 (95%CI: 3.4-42.8) which was statistically significant. These results suggested that ALDH2 *2 allele is a high risk factor for esophageal cancer and that a high blood acetaldehyde concentration has an important role in development of esophageal cancer (Yokoyama et al., 1996a).

To examine the relationship of ALDH2 polymorphism with drinking and smoking, 1,000 Japanese alcoholics underwent endoscopy with iodine staining of the upper esophagus. Of the alcoholics, 53 were histologically diagnosed with cancer: 36 esophageal squamous cell carcinoma, 16 gastric adenocarcinoma, 1 gastric signet ring cell carcinoma, 9 nasophageal and laryngeal squamous cell carcinoma and 1 duodenal adenocarcinoma. Eight of the patients with esophageal cancer had multi cancers. There were no differences in age, drinking volume and period between the patients with and without cancer, however, strong alcohol (whiskey or distilled spirit) and heavy smoking (50 or more packs/year) enhanced risks. The ratios (number) of patients holding ALDH2 *1/*2 genotype were

52.8% (19/36) in patients with esophageal cancer, 55.6% (5/9) with nasopharyngeal and laryngeal cancer and 87.5% (7/8) with multi cancers, which were significantly higher than 12.2% (80/655) in patients without cancer. These results suggest that smoking, high-proof liquor and genotype are three risk factors (Yokoyama et al., 1996b).

To study the relationship between ALDH2 polymorphism and cancers, the ALDH2 polymorphism of lymphocyte DNA was investigated in 487 Japanese alcoholics without cancer and 237 with cancer (nasopharyngeal and laryngeal cancer: 34, esophageal cancer: 87, gastric cancer: 58, colon cancer: 46, hepatocellular carcinoma: 18, lung cancer: 7, other cancer: 9, multi cancers: 19). The ratios (number) of the patients without cancer holding ALDH2*2 allele to those without cancer was 9%, while that of the patients with nasopharyngeal and laryngeal cancer or esophageal cancer was 52.9%, followed by 22.4% and 21.7% of those with gastric and colon cancer, indicating a significantly high ratio in patients with cancer, and the highest was 78.6% of the patients with esophageal cancer associated with nasopharyngeal and laryngeal or gastric cancer. After adjustment of age, drinking and smoking habit, the odds ratio of patients holding ALDH2*2 allele was 11.14 (95%CI: 5.09-24.36) in nasopharyngeal and laryngeal cancer, 12.50 (7.23-21.61) in esophageal cancer, 3.49 (1.64-7.44) in gastric cancer, 3.35 (1.51-7.45) in colon cancer, 8.20 (1.27-53.15) in lung cancer and 54.20 (11.51-255.23) in esophageal cancer associated with nasopharyngeal and laryngeal or gastric cancer, which were statistically significant but the odds ratios in other cancers including hepatocellular carcinoma (0.71) were not statistically significant. These results suggest that acetaldehyde has a role in carcinogenesis in the organs other than the upper gastrointestinal tract (Yokoyama et al., 1998).

To examine the relationships of hepatocellular carcinoma with ALDH2 polymorphism and drinking habit, a hospital-based case-control study was conducted from 1993 to 1994 in 20 hospitals in the south district of Hyogo Prefecture, Japan. In this study, 102 Japanese patients with hepatocellular carcinoma (male: 85, female: 17) were compared with 125 controls (male: 101, female: 24) who were selected considering disease, gender, age and residential area. The amount of drinking is calculated as follows: one-drink is defined as a drink converted to 15 ml of pure ethanol, and the accumulated amount of alcohol in the last 30 years is defined as drinks/day × year. After adjustment of age and smoking habit, the odds ratio of highly accumulated drinkers (40 drinks/day × year) was 2.7 (95%CI: 1.3-5.5), while that of patients with ALDH2 polymorphism was 1.1 (95%CI: 0.6-2.1), showing no relationship with ALDH2 polymorphism. The results of this study supported no involvement of ALDH2 polymorphism in hepatocellular carcinoma but suggested that heavy drinking is directly associated with induction of hepatocellular carcinoma (Takeshita et al., 2000).

Table 7-1 Epidemiological studies and case reports of acetaldehyde

Population gender/number	Exposure condition	Dose	Results	Reference
Volunteers: 12	Exposure to vapor	50 ppm (90 mg/m^3)	Mild irritation to eyes	Silverman et al.,1946
ND	15 minutes	200 ppm (360 mg/m^3)	Transient conjunctivitis	Proctor & Hughes,1978

Population gender/number	Exposure condition	Dose	Results	Reference
Male: 14 persons (18-45yrs)	30 minutes	134 ppm (241 mg/m^3)	Mild irritation in the respiratory tract	Sim & Pattle,1957
ND	Intravenous up to 36 minutes	5%solution: 20.6-82.4 mg/min	Increased heart rate, increased ventilation rates and respiratory dead space, and a decreased alveolar carbon dioxide level	Asmussen et al.,1948
ND	ND	ND	Perception threshold of acetaldehyde vapor: less than 0.2 $\mu g/m^3$	Ruth, 1986
ND	Accidental exposure	ND	Headache, coma, irritation of eyes, skin, respiratory system and throat, bronchitis, pulmonary edema, paralysis and death	U.S. NRC, 1981
Asian volunteers: 12	Patch test	75% solution	Dermal irritation (erythma)	Willkin & Foetner, 1985
Male chronic alcoholics with esophageal cancer: 40 Control: 55	Case-control study 1		Analysis between ALDH genotype and esophageal cancer Genotype ALDH2*1/*1 ALDH2*1/*2 Odds ratio (*2/ *1) Control 48/55 7/55 Esophageal cancer 19/40 21/40 7.6 (95%CI [1]: 2.8-20.7) Odds ratio: significant	Yokoyama et al., 1996a
Male non-alcoholics with esophageal cancer: 29 Control: 28	Case-control study 2		Analysis between ALDH genotype and esophageal cancer Genotype ALDH2*1/*1 ALDH2*1/*2 Odds ratio (*2/ *1) Control 23/28 5/28 Esophageal cancer 8/29 21/29 12.1 (95%CI: 3.4-42.8) Odds ratio: significant Conclusion: The results of Studies 1 and 2 suggest that ALDH2*1/*2 allele is a high risk factor for esophageal cancer and that a high blood acetaldehyde concentration has an important role in development of esophageal cancer.	

Population gender/number	Exposure condition	Dose	Results	Reference
Alcoholics:1,000 Patients with cancer (definitive diagnosis): 53 Patients without cancer: 655	Case-control study		Analysis between ALDH2 polymorphism and esophageal cancer Patient with cancer with ALDH2*1/*2 (N) (N) Esophageal squamous cell carcinoma 36 19 with esophageal cancer 8 7 Gastric adenocarcinoma 16 ― Gastric signet ring cell carcinoma 1 ― Nasopharyngeal and laryngeal squamous cell carcinoma 9 5 Duodenal adenocarcinoma 1 ― Patient without cancer 655 80 ALDH2*1/*2 genotype holding ratio is significant in esophageal cancer, nasopharyngeal and laryngeal cancer, and multi cancers. Conclusion: ALDH2*1/*2 allele is a high risk factor for esophageal cancer and nasopharyngeal and laryngeal cancer. The results suggest that smoking and high-proof drinks are also risk factors.	Yokoyama et al., 1996b
Alcoholics: Patients with cancer: 237 Patients without cancer: 487	Case-control study		Analysis between ALDH2 polymorphism and esophageal cancer Patient with cancer with ALDH2*1/*2 Odds R. (N) (%) (95%CI) Nasopharyngeal and laryngeal cancer 34 52.9 11.14 (5.09-24.36) Esophageal cancer 87 52.9 12.50 (7.23-21.61) Gastric cancer 58 22.4 3.49 (1.64-7.44) Colon cancer 46 21.7 3.35 (1.51-7.45) Hepatocellular carcinoma 18 ― 0.71 Pulmonary cell carcinoma 7 ― 8.20 (1.27-53.15) Multi cancers 19 78.6 54.20 (11.51-255.23 Other cancer 9 ― ― Patient without cancer ― 9 The number ratios of patients holding ALDH2*1/*2 genotype is significant in patients with esophageal cancer, nasopharyngeal and laryngeal cancer, and multi cancers. Conclusion: ALDH2*1/*2 allele is a high risk factor for esophageal cancer and nasopharyngeal and laryngeal cancer. The results suggest that smoking and high-proof drinks are also risk factors.	Yokoyama et al., 1998

Population gender/number	Exposure condition	Dose	Results	Reference
Patient with hepatocellular carcinoma: 102 Male: 85 Female: 17 Control: 125 Male: 101 Female: 24	Case-control study		Analysis of hepatocellular carcinoma with ALDH2 polymorphism and drinking habit Patient with hepatocellular carcinoma: odds ratio (95%CI) High amount of cumulative drinking (adjusted for age/smoking) 2.7 (1.3-5.5) ALDH2 polymorphism 1.1 (0.6-2.1) ALDH2 polymorphism 0.8 (0.5-1.5) Conclusion: Development of hepatocellular carcinoma has association not with ALDH2 polymorphism but with high amount of cumulative drinking.	Takeshita et al., 2000

ND: No data available
(1) CI: confidence interval

7.3 Studies in experimental animals and *in vitro* studies

7.3.1 Acute toxicity

Acute toxicity studies of acetaldehyde to experimental animals are summarized in Table 7-2 (Appelman et al., 1982; Booze and Oehme, 1986; Feron and De Jong, 1971; Kruysse et al., 1975; O'Shea and Kaufman, 1979; Skog, 1950; Smyth et al., 1951; Sprince et al., 1974; Truitt and Walsh, 1971; U.S. NRC, 1981).

In the oral administration studies of acetaldehyde in rats, the LD_{50} values ranged from 660 to 1,930 mg/kg (Smyth et al., 1951; Sprince et al., 1974), and the 4-hour inhalation study showed the LC_{50} of 13,100 ppm (24,000 mg/m^3) (Appelman et al., 1982).

The major general symptoms were central nervous system depression, decrease in respiration rate, increases in heart rate and blood pressure, pulmonary edema and proteinurina (Environment Canada, Health Canada, 2000).

Table 7-2 Acute toxicity of acetaldehyde

	Mouse	Rat	Hamster	Rabbit	Dog
Oral LD_{50} (mg/kg)	1,230	660 1,930	ND	ND	＞600
Inhalation LC_{50} (ppm)	ND	13,100 (24,000 mg/m^3) (4 hours) 20,200 (3,7000 mg/m^3) (0.5 hours)	17,000 (31,000 mg/m^3)	ND	ND
Dermal LD_{50} (mg/kg)	560	640	ND	ND	ND
Intravenous LD_{50} (mg/kg)	165	ND	ND	ND	ND
Intraperitoneal LD_{50} (mg/kg)	500	ND	ND	ND	ND
Subcutaneous LD_{50} (mg/kg)	ND	ND	96.1	ND	ND

ND: No data available

7.3.2 Irritation and corrosion

No reliable data were obtained on skin and eye irritation study in experimental animals in this investigation. Although the details were not available, it was reported that application of 0.5 mg acetaldehyde on rabbit skin induced moderate irritation and application of 0.04 mg of acetaldehyde on rabbit eyes caused severe irritation (Union Carbide, 1963).

In a oral repeated dose toxicity study, symptoms resulted from irritation were observed at the administered sites (see 7.3.4), and it was also reported that irritation was found in the upper respiratory tract of mice and rats in the inhalation exposure studies (Babiuk et al., 1985; Cassee et al., 1996; Steinhagen and Barrow, 1984). These results suggest that acetaldehyde causes irritation to the gastric, nasal and respiratory mucosa.

7.3.3 Sensitization

No reports on sensitization in experimental animals were obtained in this investigation.

7.3.4 Repeated dose toxicity

Repeated dose toxicity studies of acetaldehyde to experimental animals are summarized in Table 7-3.

a. Oral administration

Male and female Wistar rats were given drinking water containing acetaldehyde at doses of 0, 25, 125 and 675 mg/kg/day for 4 weeks. Slight to moderate focal hyperkeratosis was observed in the forestomach of male and female rats of the 675 mg/kg/day group. The NOAEL for this study was reported as 125 mg/kg/day (Til et al., 1988).

Oral administration (via drinking water) to rats with 0 and 0.05% acetaldehyde solutions (equivalent to 0 and 40 mg/kg/day) for 6 months, an increase in collagen synthesis was found in the liver of the 0.05% group (Bankowski et al., 1993), although its toxicological significance is unknown (IPCS, 1995).

b. Inhalation exposure

In a 5 days inhalation study in ICR mice with acetaldehyde at doses of 0 and 324 mg/m^3 (0 and 180 ppm) with the dosing regimen of 3 hours/day, the bactericidal activity of alveolar macrophages in the pulmonary was reduced by 11.2% at 324 mg/m^3 group. However, there was no difference in mortality by streptococcal infection (Aranyi et al., 1986).

Male SD rats were exposed to acetaldehyde at 750 mg/m^3 for 4 days and then the concentration was increased progressively up to 2,100 mg/m^3 over a period of 22 days. No death was observed. It is considered that increasing acetaldehyde induced metabolic adaptation in rats (Lamboeuf et al., 1987; Latge et al., 1987).

Male and female Wistar rats were exposed to acetaldehyde at concentrations of 0, 400, 1,000, 2,200 and 5,000 ppm (0, 720, 1,800, 3,950 and 9,000 mg/m^3) for 4 weeks (6 hours/day, 5 days/week). In the males at 1,000 ppm and above and the females at 5,000 ppm, body weight gain was suppressed. The

relative liver weight was decreased in the males and females at 5,000 ppm and the relative lung weight was increased in the males at 5,000 ppm. The mortality was elevated in the males and females at 2,200 ppm and above. The histopathological examination revealed the degeneration of the nasal mucosa at 400 ppm and above, and the hyperplasia and metaplasia as well as degeneration of the nasal mucosa at 2,200 ppm and above. The LOAEL of this study was reported as 400 ppm (720 mg/m^3) (Appelman et al., 1982).

In another inhalation study, male Wistar rats were exposed to acetaldehyde for 4 weeks (6 hours/day, 5 days/week). Exposure conditions were further divided into the following: (1) 6-hour continuous inhalation exposure at concentrations of 0, 150 and 500 ppm (0, 270 and 900 mg/m^3); (2) 3-hour continuous inhalation exposure plus 1.5-hour interval plus 3-hour continuous inhalation exposure at the same doses as (1); (3) 3-hour continuous inhalation exposure plus 1.5-hour interval plus 3-hour continuous inhalation exposure at concentrations of 0, 110 and 500 ppm, and 5-minute inhalation exposure at high doses (6-fold doses of the established doses) for 4 times during each exposure, i.e., 8 times in total. In the 500-ppm group of Condition (1), degeneration of the olfactory epithelium was observed. Also in the 500-ppm group of Condition (2), degeneration of the olfactory epithelium was found. In the 500-ppm group of Condition (3) with eight exposures of the high dose, body weight gain was suppressed. NOAEL was reported as 150 ppm (270 mg/m^3) based on the results of Condition (1) (Appelman et al., 1986).

Male Wistar rats were exposed to acetaldehyde at concentrations of 0 and 243 ppm (0 and 437 mg/m^3) for 5 weeks (8 hours/day, 5 days/week). The animals in the 243 ppm group showed increases in residual volume and functional residual capacity in pulmonary function test, and, histopathologically, hyperplasia of the olfactory epithelium and polymorphonuclear and mononuclear infiltration of the submucosa in the nasal cavities (Saldiva et al., 1985).

To investigate the relationship between ethanol tolerance and biochemical changes of the membrane, rats were exposed to acetaldehyde at relatively high doses (750 to 13,230 mg/m^3) for short time. Changes of phospholipid component of the brain synaptosomal membrane (an increase of *L*-α-phosphatidylserine) and increased activities of monoamine oxidase and Na^+ and K^+-ATPases were observed. These results suggest that protein binding and reactions with monoamines and membrane phospholipids of acetaldehyde cause the toxicity of repeated administration of ethanol and that the changes of membrane component and fluidity, which involves acetaldehyde, cause the ethanol tolerance (Ortiz et al., 1974; Shiohara et al., 1985; Latge et al., 1987; Roumec et al., 1988).

Hamsters exposed to acetaldehyde at doses of 0, 390, 1,340 and 4,560 ppm (0, 700, 2400 and 8,200 mg/m^3) for 13 weeks (6 hours/day, 5 days/week). Focal hyperplasia of the respiratory tract was observed at 1,340 ppm and above, and the following symptoms were found at 4,560 ppm: suppression of body weigh gain, rhinitis, nasal effusion, salivation, increased relative weights of lungs, kidney and heart, degeneration, hyperplasia and metaplasia of the respiratory and olfactory epithelium of nasal cavity, disappearance of subepithelial gland of nasal cavity, severe degeneration, hyperplasia and metaplasia of the epithelium of turbinate, and focal hyperplasia and metaplasia of the larynx, trachea and lungs (Kruysse et al., 1975). From these results, the NOAEL is considered to be 390 ppm (700

mg/m^3) in this assessment.

c. Intravenous administration

In a 20 days intravenous administration study of acetaldehyde in rats at doses of 24 and 26 mg/kg/day, the brain salsolinol concentration was increased (Myers et al., 1985).

In summary, oral administration of acetaldehyde to rats for 4 weeks caused slight hyperkeratosis in the forestomach at a dose of 675 mg/kg/day. The NOAEL is 125 mg/kg/day. Inhalation exposure damaged the epithelium of the respiratory tract in rats and hamsters, showing that a target tissue of inhalation exposure to rats and hamsters is the upper respiratory tract. The NOAELs are 150 ppm (270 mg/m^3) for rats exposed for 4 weeks and 390 ppm (700 mg/m^3) for hamsters exposed for 13 weeks.

Table 7-3 Repeated dose toxicity of acetaldehyde

Species/strain /sex/age/number of animals	Route	Period	Dose	Results	Reference
Rat Wistar Male and Female	Oral administration (drinking water)	4 weeks	Equivalent to 0, 25, 125, 675 mg/kg/day	675 mg/kg/day Male: focal hyperkeratosis of forestomach (slight to moderate: 8/10) Female: focal hyperkeratosis of forestomach (slight to moderate: 8/10) LOAEL: 675 mg/kg/day NOAEL: 125 mg/kg/day	Til et al., 1988
Rat	Oral administration (drinking water)	6 months	0 and 0.05% (equivalent to 0 and 40 mg/kg/day)	0.05% Increase in collagen synthesis in the liver	Bankowski et al., 1993
Mouse ICR 4-5 weeks 17-18 animals /group	Inhalation exposure	5 days 3 hours/day	0, 324 mg/m^3 (0, 180 ppm)	324 mg/m^3 Decrease in bactericidal activity of alveolar macrophages by 11.2%, no change in mortality by streptococcal infection	Aranyi et al., 1986
Rat SD Male Age unknown 6 animals /group	Inhalation exposure	22 days	750-2,500 mg/m^3	No death following phased increases of exposure concentrations. The authors consider that the reason is due to metabolic adaptation.	Lamboeuf et al. 1987; Latge et al., 1987

Species/strain /sex/age/number of animals	Route	Period	Dose	Results	Reference
Rat Wistar Male and female 10 animals /group	Inhalation exposure	4 weeks 6 hours/day 5 days/week	0, 400, 1,000, 2,200, 5,000 ppm (0, 720, 1,800, 3,950, 9,000 mg/m^3)	400 ppm and above Degeneration of the nasal mucosa 1,000 ppm and above Male: suppression of body weight gain 2,200 ppm and above Hyperplasia and metaplasia of the nasal mucosa, increase in mortality 5,000 ppm Male: increase in relative weight of lung, decrease in relative weight of liver Female: suppression of body weight gain, decrease in relative weight of liver LOAEL: 400 ppm (720 mg/m^3)	Appelman et al., 1982
Rat Wistar Male 10 animals /group	Inhalation exposure	4 weeks 6 hours/day 5 days/week	At basic concentrations of 0, 150, 500 ppm (0, 270, 900 mg/m^3) (1) Continuous exposures of 6 hours/day at basic concentrations (2) Exposures at 0, 110, 500 ppm for two periods of 3 hrs/day interrupted by a non-exposure period of 1.5 hrs (3) An exposure profile as (2) superimposed with 5-min periods of six times the basic concentration with a frequency of four peak exposures per 3-hr period.	(1) 6-hr uninterrupted 500 ppm: degeneration of the olfactory epithelium NOAEL: 150 ppm (270 mg/m^3) (2) 6-hr interrupted 500 ppm: degeneration of the olfactory epithelium (3) 6-hr interrupted with peak (6 times the basic concentration) 500 ppm:eye irritation , nervously running around, suppression of body weight gain	Appelman et al., 1986
Rat Wistar Male 12 animals /group	Inhalation exposure	5 weeks 8 hours/day 5 days/week	0, 243 ppm (0, 437 mg/m^3)	243 ppm Degradation of the olfactory epithelium, inflammation of the nasal mucosa, increases in residual volume and functional residual capacity in pulmonary function test	Saldiva et al., 1985

Species/strain /sex/age/number of animals	Route	Period	Dose	Results	Reference
Syrian hamster 20 animals /group	Inhalation exposure	13 weeks 6 hours/day 5 days/week	0, 390, 1,340, 4,560 ppm (0, 700, 2,400, 8,200 mg/m^3)	1,340 ppm Focal hyperplasia, metaplasia of the respiratory tract 4,560 ppm Suppression of body weigh gain, rhinitis, nasal effusion, salivation, increased relative weights of lung, kidney and heart, degeneration, hyperplasia and metaplasia of respiratory and olfactory epithelium of nasal cavity, disappearance of sub epithelial gland of nasal cavity, severe degeneration, hyperplasia and metaplasia of the epithelium of nasal turbinate, and focal hyperplasia and metaplasia of the larynx, trachea and lung NOAEL: 390 ppm (in this assessment)	Kruysse et al., 1975
Rat	Intra-venous injection	20 days	24-26 mg/kg/day	Increase in the brain salsolinol concentration	Myers et al., 1985

7.3.5 Reproductive and developmental toxicity

Studies on reproductive and developmental toxicity of acetaldehyde to experimental animals are summarized in Table 7-4.

In a developmental study, an oral administration of acetaldehyde to pregnant female SD rats is reported to cause skeletal defects in fetuses. Pregnant rats were treated with a dose of 200 mg/kg/day (3% water solution) on gestation days 6 to 18. Anomaly of the ribs and vertebrae as well as delayed ossification and hypoplasia of the cranial bones and sternum were observed in fetuses (Fadel and Perasud, 1990). However, this report is abstract only, which detailed data are not decribed.

Female CFLP mice were injected intravenously 1% and 2% acetaldehyde (approximately 31 and 62 mg/kg/day) on gestation day 7-9. A dose-dependent increase in fetal resorptions, body weight loss/ neural tube defect and malformation (no detailed description) were found in fetuses (O'Shea and Kaufman, 1979, 1981).

Female C57BL/6J mice were injected intraeritoneally acetaldehyde at a single dose of 320 mg/kg (4% water solution) in on gestation day 7, 8, 9 or 10. Exencephaly and maxillary and mandibular hypoplasia were observed in the groups administered on gestation day 7 and 8, and polydactyly and club foot in the groups administered on gestation day 9 and 10 (Webster et al., 1983).

Intraperitoneal injection of acetaldehyde was given to female ICR mice at 200 mg/kg (0.69% water solution) with repeated administrations for 5 times at a 2-hour interval on gestation day 10. No effects were found in the fetuses (Blakley and Scott, 1984a).

Female CF rats were injected intraperitoneally acetaldehyde at a single dose of 0, 50, 75, 100 mg/kg/day on gestation day 10, 11 or 12, and with repeated doses at 0, 50, 75, 100 mg/kg/day on gestation days 10 to 12. Fetal resorptions, malformation (edema, microcephaly, micrognathia, exencephaly and hydrocephaly), retarded development, and decreases in fetal body and placenta weight were observed in the groups given 50 mg/kg and above (Sreenathan et al., 1982).

In summary, the effects of acetaldehyde on fetuses were observed in all routes of administration in the reproductive and developmental toxicity studies. In mice, intravenous administration of 31 mg/kg/day and intraperitoneal administration of 320 mg/kg caused malformation in fetuses.

Table 7-4 Reproductive and developmental toxicity of acetaldehyde

Species sex/number of animals	Route	Period	Dose	Results	Reference
Rat SD Female	Oral administration	On gestation days 6-18 Caesarian section on gestation day 20	0, 200 mg/kg/day	F_0 : No description F_1 : Effect on skeleton (no detailed description)	Fadel & Perasud, 1990
Mouse CFLP Female 7-11 animals	Intra-venous injection	On gestation day 7-9 Caesarian section on gestation day 10 or 19	0, 1, 2% (v/v) (approximately 31, 62 mg/kg/day)	F_0: No effect NOAEL : 62 mg/kg/day F_1: Dose-dependent increase in fetal resorptions, body weight loss 2.0%: neural tube defect, malformation (head and tail)	O'Shea & Kaufman, 1979, 1981
Mouse Female C57BL/6J 4-14 animals	Intra-peritoneal injection	On gestation day 7, 8, 9 or 10 Caesarian section on gestation day 18	320 mg/kg	F_0: No description F_1 : Group given on gestation day 7 or 8: exencephaly, maxillary and mandibular hypoplasia Group given on gestation day 9 or 10: polymelia, valgus foot	Webster et al., 1983
Mouse ICR Female 8 animals	Intra-peritoneal injection	On gestation day 10 Caesarian section on gestation day 18	0.69% (200mg/kg) × 5 at a 2-hour interval	F_0: No description F_1 : No effect	Blakley & Scott, 1984a
Rat CF Female Control: 13 animals Treated: 5-10 animals	Intra-peritoneal injection	On gestation day 10, 11 or 12 or 10-12 Caesarian section on gestation day 21	0, 50, 75, 100 mg/kg/day	F_0 : No effect NOAEL: 50 mg/kg F_1 : Group given on gestation day 10 50 mg/kg and above: fetal resorptions, decreases in fetal body and placenta weight 100 mg/kg: syndactyly, cataract Group given on gestation day 11 50 mg/kg and above: fetal resorptions, decreases in fetal body and placenta weight	Sreenathan et al., 1982

Species sex/number of animals	Route	Period	Dose	Results	Reference
				75 mg/kg: hydrocephaly, exencephaly, syndactyly, cataract 100 mg/kg: cataract Group given on gestation day 12 50 mg/kg and above: fetal resorptions, decreases in fetal body and placenta weight, syndactyly, low set ears, cataract 75 mg/kg and above: micrognathia, hemorrhage, hydrocephaly 100 mg/kg: edema Group given on gestation days 10-12 50 mg/kg/day and above: fetal resorptions, decreases in fetal body and placenta weight, syndactyly, low set ears, micrognathia, microcephaly, hemorrhage, edema, cataract 75 mg/kg and above: hydrocephaly	

7.3.6 Genotoxicity

In vitro and *in vivo* studies on genotoxicity of acetaldehyde are summarized in Table 7-5.

Acetaldehyde showed positive responses in various *in vitro* studies. Acetaldehyde without metabolic activation induced gene mutation in mouse lymphoma L5178Y cells, chromosomal aberration and micronucleus in SD rat primary skin fibroblasts. The induction of these gene mutation and chromosomal aberration was dose-dependent. Acetaldehyde also induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells, aneuploid in embryonic diploid fibroblasts of Chinese hamster, and nondisjunction in *Aspergillus nidulans*. In human lymphocytes, dose-dependent gene mutation, sister chromatid exchange and chromosomal aberration were induced. In mammalian cultured cells, acetaldehyde alone did not induce morphological transformation, but acetaldehyde combined with TPA, tumor promoter, showed positive results (Eker and Sanner, 1986). Acetaldehyde induced DNA strand breaks and DNA cross-links in human lymphocytes, and DNA protein cross links in rat nasal mucosa cells. In addition, in a DNA binding study using calf thymus DNA, positive results were obtained, while in a reverse mutation study using *Salmonella typhimurium* and *Escherichia coli*, and a transformation study using mouse C3H/10T1/2 cells, negative results were reported.

In *in vivo* studies, acetaldehyde induced sister chromatid exchanges in Chinese hamster and mouse bone marrow. In a chromosomal aberration study using rat embryo cells given acetaldehyde through the amnion, positive results were obtained. In intraperitoneal studies of acetaldehyde in rats and mice, micronucleus was induced in rat bone marrow cells and peripheral lymphocytes, and mouse bone marrow cells, however, neither micronucleus nor morphological abnormalities was found in mouse spermatids.

In summary, acetaldehyde showed positive results in many *in vitro* studies including gene mutation,

chromosomal aberration, sister chromatid exchanges. In *in vivo* studies, the frequency of sister chromatid exchange was increased in intraperitoneal studies using hamsters and mice, and positive results were observed in a micronucleus assay. From the overall evaluation of these data, acetaldehyde is considered to be genotoxic.

Table 7-5 Genotoxicity of acetaldehyde

Test system		Species (Organisms) /Strain	Experimental Condition	Concentration / Dose[a)] (μg/mL)	Results[b)] - S9 +S9	Reference
In vitro	Reverse mutation	*Salmonella typhimurium* TA100, TA1535, TA1537, TA98	ND	5,000	- -	Mortelmans et al., 1986
		Salmonella typhimurium TA100, TA1535, TA1537	ND	0.5% (in air)	- -	JETOC, 1997
		TA98		1% (in air)	- -	
		E. coli. WP2 *uvr*A		0.5% (in air)	- -	
		Salmonella typhimurium TA104	ND	2,515	- ND	Marnett et al., 1985
		Salmonella typhimurium TA1535	ND	7,800	- ND	Rosenkranz, 1977
		Salmonella typhimurium TA100, TA102 TA104	Vapor exposure	0.1-1.0 μg/plate	- -	Dillon et al.,1998
	Forward mutation	Yeast	No description	23,400	W+ ND	Bandas, 1982
	Gene mutation	Mouse lymphoma L5178Y cells *tk* gene locus	4 hours treatment	176-353	+ ND Dose-dependent	Wangenheim &Bolcsfoldi, 1988
		Human lymphocytes *hprt* gene locus		13	+ ND	He & Lambert, 1990
	Chromosomal aberration	SD rat primary skin fibroblasts	ND	44.4	+ ND	Bird et al., 1982
		Human lymphocytes	ND	20-40	+ ND Dose-dependent	Badr & Hussain, 1977
		Human lymphocytes	ND	7.8	W+ ND	Obe et al., 1978
		Human lymphocytes	ND	15.6	- ND	Obe et al., 1979
		Human lymphocytes	ND	15.9	+ ND	Bohlke et al., 1983
		Human (Fanconi's anemia), lymphocytes	ND	7.8-15	+ ND Dose-dependent	Obe et al., 1979
	Chromosome aberration (nondisjunction)	*Aspergillus nidulans*	ND	200	+ ND	Crebelli et al., 1989
	Chromosome aberration (Aneuploid)	Chinese hamster embryonic diploid fibroblasts	ND	15.6	+ ND	Dulout & Furnus, 1988
	Micronucleus	SD rat primary skin fibroblasts	12 hours treatment	4.4-44	+ ND Dose-dependent	Bird et al., 1982

Test system		Species (Organisms) /Strain	Experimental Condition	Concentration / Dose[a] (μg/mL)	Results[b] - S9	Results[b] +S9	Reference
		Human lymphocytes	ND	26.5	+		Migliore et al., 1996
	Sister chromatid exchange	CHO cells [c]	ND	1.9, 3.9	+	ND	Obe & Listow, 1977 Obe et al., 1978 Obe & Beek, 1979
		CHO cells	ND	7.8	+	+	De Raat et al., 1983
		CHO cells	ND	1.3-13	+	ND	Brambilla et al.,1986
		Human lymphocytes	ND	7.8	+	ND	Obe et al., 1978
		Human lymphocytes	ND	7.8	+	ND	Ristow & Obe, 1978
		Human lymphocytes	ND	5.8	+	ND	Jansson, 1982
		Human lymphocytes	90 hours treatment	4-8	+ Dose-dependent	ND	Bohlke et al., 1983
		Human lymphocytes	1-70 hours treatment	4.4-106	+	ND	He& Lambert, 1985
		Human lymphocytes	70 hours treatment	4.4-13	+	ND	Knadle, 1985
		Human lymphocytes	ND	11, 15.6	+	ND	Norppa et al., 1985 Sipi et al., 1992 Obe et al., 1986
		Human lymphocytes	48 hours treatment	4.4-22	+	ND	Helander & Lindahl-Kiessling, 1991
	Cell transformation	Mouse C3H 10T1/2 cells	ND	10-100	-	ND	Abernathy et al., 1982
		Mammalian cells	3 hours treatment	0.44	-	ND	Eker & Sanner, 1986
	DNA damage	*E. coli.* polA	ND	7,800	-	ND	Rosenkranz, 1977
		E. coli. K-12 *uvr*B/recA	ND	16,317	-	ND	Hellmer & Bolcsfoldi, 1992
	DNA strand breaks	Human leukocytes	ND	441-882	-	ND	Lambert et al., 1985
		Human bronchial epithelial cells	6 hours treatment	44	-	ND	Saladino et al., 1985
		Human lymphocytes	ND	68.8	+	ND	Singh & Khan, 1995
	DNA-DNA cross-links	Human lymphocytes	ND	411	+	ND	Lambert et al.,1985

Test system		Species (Organisms) /Strain	Experimental Condition	Concentration / Dose[a] (μg/mL)	Results[b] - S9 +S9	Reference
	DNA-protein cross-links	Fischer 344 rat nasal mucosa cells, calf thymus histone		4,410-44,100	+ ND	Lam et al., 1986
		Human bronchial epithelial cells	ND	44	- ND	Saladino et al., 1985
	DNA binding	Calf thymus DNA	ND	7,880-78,800 mg/kg	+ ND	Ristow & Obe, 1978 Fang & Vaca, 1995 Vaca et al., 1995
In vivo	Sex-linked recessive lethal	*Drosophila melanogaster*	Oral (fed)	25,000 ppm	-	Woodruff et al., 1985
		Drosophila melanogaster	Intraperitoneal once	22,500 ppm	+	Woodruff et al., 1985
	Micronucleus	Rat bone marrow cells	Intraperitoneal	250 mg/kg	+	Wakata et al., 1998
		Rat peripheral blood cells	Intraperitoneal	250 mg/kg	+	
	Micronucleus	CD-1 male mouse bone marrow cells	Intraperitoneal	400 mg/kg	+	Morita et al., 1997
	Micronucleus	C57BL/6J×C3H/He mouse early spermatid	Intraperitoneal once	375 mg/kg	-	Lahdetie, 1988
	Chromosomal aberration	Rat embryo cells	Administration through the amnion (On gestation day 13), once	7,800 mg/kg	+	Barilak & Kozachuk, 1983
	Sister chromatid exchange	Male C3A mouse bone marrow cells	Intraperitoneal once	0.4 μg/ animals	+	Obe et al., 1979
		Chinese hamster bone marrow cells	Intraperitoneal once	0.5 mg/kg	+	Korte et al., 1981
	Comet	Human lymphocyte	37°C, 1 hourtreatment	3-100 mM	+	Blasiak et al., 1999
	DNA-protein cross-links	Fischer 344 rat nasal mucosa	Inhalation exposure, 6 hours/day, 5 days	1,000 ppm	+	Lam et al., 1986
	Sperm abnormality	C57BL/6J×C3H/He mouse early spermatid	Intraperitoneal 5 times	250 mg/kg	-	Lahdetie, 1988

ND: No data available

a) When a single dose value is described, it indicates the lowest positive concentration in the positive result and the highest negative concentration in the negative result.

b) -: Negative, +: Positive, W+: Weak positive c) CHO cells: Chinese hamster ovary cells.

7.3.7 Carcinogenicity

Studies on carcinogenicity of acetaldehyde in experimental animals are summarized in Table 7-6.

In an inhalation study, male and female Wistar rats were exposed to acetaldehyde at concentrations of 0, 750, 1,500 and 3,000 to 1,000 ppm (equivalent to 0, 1,350, 2,700 and 5,400 to 1,800 mg/m^3; the exposure concentration of 3,000 ppm at week 20 was gradually reduced to 1,000 ppm at week 52) for 6 hours/day, 5 days/week, for 28 months. Carcinoma (carcinoma *in situ*, squamous cell carcinoma and adenocarcinoma) was induced in the nasal cavity of the male and female rats at 750 ppm and above (Woutersen and Appelman,1984; Woutersen et al.,1985; Woutersen et al., 1986).

Inhalation exposure of acetaldehyde to male and female Syrian hamsters was given at concentrations of 0 and 2,500 to 1,650 ppm (0 and 4,500 to 2,970 mg/m^3; in the acetaldehyde-treated group, the exposure concentration was gradually reduced to 1,650 ppm during the study period) for 7 hours/day, 5 days/week, for 52 weeks. Tumors (mainly laryngeal cancer and others including laryngeal polyp, carcinoma and polyp in the nasal cavity) in the respiratory tract were induced (Feron, 1982).

To investigate a promoter activity of acetaldehyde, male and female Syrian hamsters were exposed with acetaldehyde at concentrations of 0 and 2,500 to 1,650 ppm (0 and 4,500 to 2,970 mg/m^3; in the acetaldehyde-treated group, the exposure concentration was gradually reduced to 1,650 ppm during the study period) for 7 hours/day, 5 days/week, for 52 weeks, and the additional intratracheal administration of 0.175% and 0.35% benzo(*a*)pyrene at a dose of 0.2 mL once a week or subcutaneous administration of 0.0625% diethylnitrosamine at a dose of 0.2 mL every 3 weeks. The incidences of respiratory tumors (papilloma, adenoma, squamous cell carcinoma, adenocarcinoma, carcinoma *in situ*) were significantly higher in the acetaldehyde plus 0.175% benzo(*a*)pyrene-treated group than that in the group of benzo(*a*)pyrene alone. The incidence in the acetaldehyde plus 0.35% benzopyrene-treated group was not higher than that in the group of 0.35% benzo(*a*)pyrene alone, which is considered to be because of the fact that benzo(*a*)pyrene itself induced tumors at a sufficiently high rate. In the acetaldehyde plus diethylnitrosamine group, the tumor incidence was not increased. These results show no promoter action of acetaldehyde (Feron, 1982).

In a mid-term hepatic carcinogenesis study using Ito Model, male F344 rats received an intraperitoneal injection of diethylnitrosamine as initiator and then 0, 2.5 and 5% of acetaldehyde (equivalent to 0, 1.66 and 2.75 mg/kg/day) orally (via drinking water) for 4 weeks from 2 weeks after the beginning of the study. During the study period, rats had a two-thirds partial hepatectomy. At the completion of the study, no increase was found in the glutathione *S*-transferase (placental type) (GST-P)-positive cell foci (Ikawa et al., 1986).

In summary, an inhalation study in Wistar rats shows dose-dependent increases in nasal adenocarcinoma and squamous cell carcinoma at 750 ppm (1,350 mg/m^3) and above for 28 months. In hamsters, exposure of acetaldehyde for 52 weeks causes significant increases in the incidence of respiratory tract tumors (including primarily laryngeal cancer, and also laryngeal polyp and carcinoma in the nasal cavity). Acetaldehyde is considered a carcinogenic substance in experimental animals in this assessment.

There is a study suggesting the promoter activity of acetaldehyde to respiratory tumor. However, the data are insufficient and inconclusive.

The evaluation of carcinogenicity of acetaldehyde by the international and national organizations is shown in Table 7-7.

The IARC has categorized acetaldehyde as Group 2B (the agent is possibly carcinogenic to humans). The U.S. EPA (2002) estimated the inhalation cancer unit risk of acetaldehyde as 2.2×10^{-6}/ ($\mu g/m^3$) based on the results of an inhalation study in Wistar rats, and has indicated the air concentrations for the excess lifetime cancer risk of 10^{-6} and 10^{-5} as 0.5 and 5 $\mu g/m^3$, respectively.

Table 7-6 Carcinogenicity of acetaldehyde

Species/strain/ sex/age/number of animals	Route	Period	Dose	Results	Reference
Rat Wistar Male and female The number unknown	Inhalation exposure	28 months 6 hours/day 5 days/week	0, 750, 1,500, 3,000-1,000 ppm (equivalent to 0, 1,350, 2,700, 5,400-1,800 mg/m^3, in administering a high dose, the exposure concentration was gradually reduced to 1,000 ppm from Week 20 to 52)	750 ppm and above Male and female: carcinoma in the nasal cavity (carcinoma in situ, squamous cell carcinoma, adenocarcinoma)	Woutersen et al., 1986; Woutersen & Appelman, 1984; Woutersen et al.,1985
Rat F344 Male 19-20 animals/ group	Mid-term hepatic carcino-genesis (Ito Model) oral (drinking water)	Intraperi-toneal injection of DEN[1)] as initiator, followed by acetaldehyde administratio n for 4 weeks from 2 weeks after the start of study	2.5 and 5% (equivalent to 1.66 and 2.75 mg/kg/day)	No increase in the GST-P positive cell foci in the liver	Ikawa et al., 1986
Syrian hamster Male and female 6-week age 30 animals/ group	Inhalation exposure (sys-temic)	52 weeks 7 hours/day 5 days/week	0, 2,500-1,650 ppm (0, 4,500-2,970 mg/m^3) The exposure concentration was gradually reduced from 2,500 to 1,650 ppm during the study period.	Respiratory tract tumors (laryngeal cancer in main, laryngeal polyp, carcinoma and polyp in the nasal cavity) (ppm) Male Female 0 0/30 0/28 2,500-1,650 8/29* 5/29* * Statistical significance (Fisher's exact test) (conducted by CERI)	Feron, 1982

Species/strain/ sex/age/number of animals	Route	Period	Dose	Results	Reference
Syrian hamster Male and female 6-week age 30 animals /group	Inhalation exposure (sys-temic) + Intra-tracheal administ-ration of BZ [2)] or sub-cutaneous administ-ration of DEN	52 weeks 7 hours/day 5 days/week Autopsy at Week 82 BZ:once/week DEN: once/3 weeks	0, 2,500-1,650 ppm (0, 4,500-2,970 mg/m^3) The exposure concentration was gradually reduced from 2,500 to 1,650 ppm during the study period. 0.175% and 0.35% of BZ at a dose of 0.2 mL (total amounts: 18.2 and 36.4 mg/ animals) 0.0625% of DEN at a dose of 0.2 mL (total amount: 2.1 μg/ animals)	Respiratory tract tumors (papilloma, adenoma, squamous cell carcinoma, adenocarcinoma, carcinoma in situ, no specific organ) Acetaldehyde (ppm)+ BZ (%) Male Female 0 + 0.175 4/29 3/27 2,500-1,650 + 0.175 12/29* 11/29* 0 + 0.35 19/30 7/24 2,500-1,650 + 0.35 22/27 16/29 Acetaldehyde (ppm) + DEN (%) Male Female 0 + 0.0625 12/29 11/27 2,500-1,650 + 0.0625 11/30 8/20 *Statistical significance (Fisher's exact test, CERI test) (conducted by CERI)	Feron, 1982

[1)] DEN, diethylnitrosamine; [2)] BZ, benzo(*a*)pyrene.

Table 7-7 Evaluation of carcinogenicity of acetaldehyde by the international and national organizations

Organization/Source	Classification	Classification criteria
IARC (2002)	Group 2B	The agent is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.
ACGIH (2002)	A3	Confirmed animal carcinogen with unknown relevance to humans.
The Japan Society for Occupational Health (2002)	Group 2B	The substance with less evidence (possibly carcinogenic to humans).
U.S.EPA (2002)	Group B2	Probable human carcinogen
U.S. NTP (2002)	R	Reasonably anticipated to be human carcinogens.

7.4 Summary of effects on human health

Acetaldehyde is an exogenous chemical substance to which humans are exposed as well as an endogenous substance that is internally generated within humans and animals. Acetaldehyde is generated from ethanol metabolism by liver alcohol dehydrogenase (ADH) and is further metabolized into acetic acid by aldehyde dehydrogenase (ALDH), and finally degraded to carbon dioxide and water. Acetaldehyde is absorbed through the lung and gastrointestinal tract. Absorption through the skin is probable considering its physico-chemical properties. Absorbed acetaldehyde is distributed in the blood, liver, kidney, spleen, heart and muscle, and the possibility that acetaldehyde can enter the fetal

environment through the placenta is suggested.

Acetaldehyde causes moderate irritation in the eyes and respiratory tract including the throat and nose. In a patch test with Oriental subjects, erythema was observed in the skin, but no sufficient data are obtained to evaluate sensitization of acetaldehyde. There are no sufficient data to assess reproductive/developmental, neurological and immunological effects of acetaldehyde in the general population, and in the workers who were occupationally exposed to acetaldehyde.

In experimental animals, moderate irritation in the skin and eyes has been reported in the studies with rabbits. No reports were obtained on sensitization of acetaldehyde in this investigation.

The acute toxicity of acetaldehyde in experimental animals with oral administration is lower than that with inhalation exposure. Oral LD_{50} values are 1,230 mg/kg in mice and 660 to 1,930 mg/kg in rats. The LC_{50}s following inhalation exposure in rats range 13,100 (4 hours) to 20,200 (0.5 hours) ppm. The symptoms caused by acetaldehyde are increases in heart rate and blood pressure, pulmonary edema and effects on the central nervous system.

Regarding repeated dose toxicity of acetaldehyde, oral administration of acetaldehyde to rats for 4 weeks caused slight hyperkeratosis in the forestomach at a dose of 675 mg/kg/day. The NOAEL is 125 mg/kg/day. Inhalation exposure damaged the epithelium of the respiratory tract in rats and hamsters, showing that a target tissue of inhalation exposure to rats and hamsters is the upper respiratory tract. The NOAELs are 150 ppm (270 mg/m^3) for rats exposed for 4 weeks and 390 ppm (700 mg/m^3) for hamsters exposed for 13 weeks.

Regarding reproductive and developmental toxicity, intravenous and intraperitoneal injections of acetaldehyde caused malformation in fetuses. Oral administration of acetaldehyde at dose of 200 mg/kg/day on gestation days 6 to 18 to rats showed in skeletal defects in fetuses. However, this report is an abstract only, which detailed data are not described.

In genotoxicity studies of acetaldehyde, there are many positive results in *in vitro* studies including gene mutation, chromosomal aberration, sister chromatid exchanges. Also, in *in vivo* studies, the frequency of sister chromatid exchange was increased in intraperitoneal studies using hamsters and mice, and positive results was observed in a micronucleus assay. The overall evaluation of these results indicates that acetaldehyde is genotoxic.

There are no reliable epidemiological data for carcinogenicity of acetaldehyde in humans. In rats, acetaldehyde by inhalation exposure causes dose-dependent increases in nasal adenocarcinoma and squamous cell carcinoma, and significant increases in laryngeal and nasal tumors in hamsters. Therefore, acetaldehyde is considered to be carcinogenic in experimental animals. Some data suggest promoter activity of acetaldehyde in respiratory tract tumorigenesis, but the data are insufficient to make a definitive conclusion. Acetaldehyde is categorized as Group 2B (the agent is possibly carcinogenic to humans) by the IARC.

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ABBREVIATIONS

ACGIH : American Conference of Governmental Industrial Hygienists
ADH : alcohol dehydrogenase
ALDH : aldehyde dehydrogenase
ALP : alkaline phosphatase
ALT : alanine aminotransferase
ASAT : aspartate aminotransferase
AST : aspartate aminotransferase
ATSDR : Agency for Toxic Substances and Disease Registry
BCF : Bioconcentration Factor
BHK : Syrian hamster kidney culture cells
BOD : Biological Oxygen Demand
BUN : blood urea nitrogen
CAS : Chemical Abstract Services
CAS Online : Chemical Abstract Services Online
CEPA : Commonwealth Environment Protection Agency
CERHR : Center for the Evaluation of Risks to Human Reproduction
CERI : Chemicals Evaluation and Research Institute, Japan
CHL : Chinese hamster lung cells
CHO : Chinese hamster ovary cells
CICAD : Concise International Chemical Assessment Document
Cmax : the maximum concentration of a compound in the blood, etc.
COD : Chemical Oxygen Demand
CPK : Creatinine phosphokinase
DDT : dichlorodiphenyltrichloroethane
DOC : Dissolved Organic Carbon
EA : Environment Agency of Japan
EC : European Communities
EC_{10} : Effect Concentration measured as 10% effect
EC_{50} : median Effect Concentration
ECB : European Chemicals Bureau
ECETOC : European Centre for Ecotoxicology and Toxicology of Chemicals
EEC : European Economic Communities
EHC : Environmental Health Criteria
EHI : Estimated Human Intake
EPA : Environmental Protection Agency (USA)
EU : European Union
EUSES : Europian Union System for the Evaluation of Substances
FAD : flavin adenine dinucleotide
FAO : Food and Agriculture Organisation of the United Nations
GABA : g-aminobutyric acid
GC : gas chromatography
GGT : gamma-glutamyl transpeptidase
GLP : Good Laboratory Practice
hr : hour
HSDB : Hazardous Substances Data Bank
IARC : International Agency for Research on Cancer
IC : Industrial Category
IC_{50} : median Immobilisation Concentration or median Inhibitory Concentration
ILO : International Labour Organisation
IPCS : International Programme on Chemical Safety
IRIS : Integrated Risk Information System
IUCLID : International Uniform Chemical Information Database (existing substances)
Koc : Soil adsorption coefficient Koc
Kow : octanol/water partition coefficient
LC_{50} : median Lethal Concentration

LD_{50} : median Lethal Dose
LDH : lactate dehydrogenase
LLNA : Local Lymph Node Assay
LOAEL : Lowest Observed Adverse Effect Level
LOEC : Lowest Observed Effect Concentration
LOEL : Lowest Observed Effect Level
MAO : monoamineoxydase
MATC : Maximum Acceptable Toxic Concentration
MCH : mean corpuscular hemoglobin
MCV : mean corpuscular volume
METI : Ministry of Economy, Trade and Industry, Japan
MHLW : Ministry of Health, Labour and Welfare
min : minute
MITI : Ministry of International Trade and Industry, Japan
MNLD : maximum non lethal dose
MOE : Ministry of the Environment, Japan
MOF : Ministry of Finance, Japan
MOS : Margin of Safety
MTD : maximum tolerance dose
NAT2 : N-acetyltransferase
NCI : National Cancer Institute
NICNAS : Australia's National Industrial Chemicals Notification and Assessment Scheme
NIES : National Institute for Environmental Studies, Japan
NITE : National Institute of Technology and Evaluation, Japan
NMR : nuclear magnetic resonance analysis
NOAEL : No Observed Adverse Effect Level
NOEC : No Observed Effect Concentration
NOEL : No Observed Effect Level
NTE : neurotoxic esterase
NTP : National Toxicology Program (USA)
NZW : New Zealand White
OECD : Organisation for Economic Cooperation and Development
OPIDN : Organophosphate-induced delayed neuropathy
OR : odds ratios
ppm : parts per million
$polA^-$: DNA $polymerase^-$
$polA^+$: DNA $polymerase^+$
pKa : negative log of the acid dissociation constant
PRTR : Pollutant Release and Transfer Register
RBC : Radiation Biology Center
RAR : Risk Assessment Report
RC : Risk Characterisation
RfC : Reference Concentration
RfD : Reference Dose
RTECS : Registry of Toxic Effects of Chemical Substances
SCE : Sister chromatid exchange
SDH : sorbitol dehydrogenase
SER : smooth endoplasmic reticulum
SG : Syrian golden
SIDS : Screening Information Data Set
SLRL-test : sex-linked recessive lethal test
SOD : superoxide dismutase
TDI : Tolerable Daily Intake
TE : toxic equivalent
TLV : Threshold Limit Value
Tmax : time until a concentration reaches Cmax.
TOXLINE : Toxicology Literature Online
UV : ultraviolet

v/v : volume per volume ratio
w : week
w/w : weight per weight ratio
WHO : World Health Organization
γ-GTP : γ-glutamyl transpeptidase
δALS : δ-aminolevulinic acid synthetase