ACETALDEHYDE

Data were last reviewed in IARC (1985) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

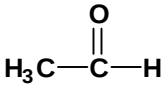
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 75-07-0
Chem. Abstr. Name: Acetaldehyde
IUPAC Systematic Name: Acetaldehyde
Synonyms: Acetic aldehyde; 'aldehyde'; ethanal; ethylaldehyde

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2H_4O Relative molecular mass: 44.05

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid or gas with a characteristic pungent odour (Budavari, 1996; Verschueren, 1996)
(*b*) *Boiling-point*: 20.1°C (Lide, 1997)
(*c*) *Melting-point*: –123°C (Lide, 1997)
(*d*) *Solubility*: Miscible with water, benzene, diethyl ether and ethanol (Budavari, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 98 kPa at 20°C; relative vapour density (air = 1), 1.52 (Verschueren, 1996)
(*f*) *Reactivity*: Flammable; polymerizes violently in the presence of trace amounts of metals or acids; can react violently with acid anhydrides, alcohols, ketones, phenols, ammonia, hydrocyanic acid, hydrogen sulfide, halogens, phosphorus, isocyanates, strong alkalis and amines (American Conference of Governmental Industrial Hygienists, 1991)
(*g*) *Flash-point*: –38°C, closed cup; –40°C, open cup (American Conference of Governmental Industrial Hygienists, 1991; Budavari, 1996)

(*h*) *Explosive limits*: Upper, 57%; lower, 4% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
(*i*) *Octanol/water partition coefficient (P)*: log *P*, 0.43 (Verschueren, 1996)
(*j*) *Conversion factor*: mg/m^3 = 1.80 × ppm

1.2 Production and use

Production capacity for acetaldehyde in the United States in 1989 was 443 000 tonnes/year (Hagemeyer, 1991). Information available in 1995 indicated that it was produced in 16 countries (Chemical Information Services, 1995).

Acetaldehyde is used as an intermediate in the production of acetic acid, acetic anhydride, cellulose acetate, vinyl acetate resins, acetate esters, pentaerythritol, synthetic pyridine derivatives, terephthalic acid and peracetic acid. Synthetic pyridine derivatives, peracetic acid, acetate esters and pentaerythritol account for 40% of acetaldehyde demand (Hagemeyer, 1991). Other uses of acetaldehyde include: in the silvering of mirrors; in leather tanning; as a denaturant for alcohol; in fuel mixtures; as a hardener for gelatin fibres; in glue and casein products; as a preservative for fish and fruit; in the paper industry; as a synthetic flavouring agent; and in the manufacture of cosmetics, aniline dyes, plastics and synthetic rubber (American Conference of Governmental Industrial Hygienists, 1991; United States National Library of Medicine, 1998).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 220 000 workers in the United States were potentially exposed to acetaldehyde (see General Remarks). Occupational exposure to acetaldehyde may occur in its production, in the production of acetic acid, acetate esters and other chemicals and in other applications.

1.3.2 *Environmental occurrence*

Acetaldehyde is a natural product of combustion and photo-oxidation of hydrocarbons commonly found in the atmosphere. It is an important industrial chemical and may be released into the air or in wastewater during its production and use. It has been detected at low levels in drinking-water, surface water, rainwater, effluents, engine exhaust and ambient and indoor air samples. It is also photochemically produced in surface water. Acetaldehyde is an intermediate product in the metabolism of ethanol and sugars and therefore occurs in trace quantities in human blood. It is present in small amounts in all alcoholic beverages, such as beer, wine and spirits and in plant juices and essential oils, roasted coffee and tobacco smoke (Jira *et al*., 1985; Hagemeyer, 1991; United States National Library of Medicine, 1998).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not recommended an 8-h time-weighted average threshold limit value but has recommended 45 mg/m^3 as the ceiling value for occupational exposures to acetaldehyde in

workplace air. Values of 5–200 mg/m^3 for time-weighted averages have been used as standards or guidelines in other countries (International Labour Office, 1991).

No international guideline for acetaldehyde in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Case series

In a survey of chemical plants (without prior hypothesis) in the German Democratic Republic, nine cancer cases were found in a factory where the main process was dimerization of acetaldehyde and where the main exposures were to acetaldol (3-hydroxybutanal), acetaldehyde, butyraldehyde, crotonaldehyde (IARC, 1995) and other higher, condensed aldehydes, as well as to traces of acrolein (IARC, 1985). Of the cancer cases, five were bronchial tumours and two were carcinomas of the oral cavity. All nine patients were smokers. The relative frequencies of these tumours were reported to be higher than those expected in the German Democratic Republic. [The Working Group noted the mixed exposure, the small number of cases and the poorly defined exposed population.]

2.2 Case–control studies

Acetaldehyde is the main metabolite of ethanol and this reaction is catalysed by alcohol dehydrogenases (ADH). Five ADHs have been characterized in humans, two of which (ADH2 and ADH3), are known to be polymorphic. In particular, polymorphism for ADH3 seems to strongly influence the metabolism of ethanol to acetaldehyde, with ADH_3^1 allele carriers being faster metabolizers than ADH_3^2 carriers. Acetaldehyde is metabolized by phase II enzymes, including aldehyde dehydrogenases (ALDH) and glutathione *S*-transferases (GST). ALDH2 is polymorphic; its mutant allele, $ALDH_2^2$, which leads to enzyme inactivity, is prevalent in Asian populations. GSTM1 is also polymorphic, with a null genotype $GSTM_1^0$ present mainly in European populations (Coutelle *et al.*, 1997). Therefore, carriers of ADH_3^2, $ALDH_2^2$ and $GSTM_1^0$ alleles are likely to be exposed to higher levels of acetaldehyde than are other people, following intake of a comparable amount of alcohol.

A Japanese case–control study (Yokoyama *et al.*, 1996) of ALDH2-related risk for oesophageal squamous-cell carcinoma in alcoholics (40 cases and 55 controls) and non-alcoholic drinkers (29 cases and 28 controls) during 1991–95 showed a higher risk for oesophageal cancer in those with one $ALDH_2^2$ allele in both alcoholics (crude odds ratio, 7.6; 95% confidence interval (CI), 2.8–20.7) and non-alcoholic drinkers (odds ratio, 12.1; 95% CI, 3.4–42.8). Mantel–Haenszel adjustment for age and daily alcohol consumption had virtually no influence on the risk estimates [adjusted odds ratios not given]. As persons who have the mutant $ALDH_2^2$ allele have a high concentration of blood acetaldehyde after drinking alcohol, the results of this study were interpreted as strongly suggesting a carcinogenic role of acetaldehyde in humans.

As part of a population-based study of oral cancer (oral cavity and pharynx) in Puerto Rico in 1992–95, the alcohol dehydrogenase type 3 (ADH3) genotype was determined in 137 patients and 146 controls without cancer by molecular genetic analysis of oral epithelial cell samples (Harty *et al*., 1997). Participation rates were 48% among cases and 57% among controls. After adjustment for tobacco smoking, diet and alcohol drinking, the odds ratio for the ADH_3^{1-2} genotype was 0.7 (95% CI, 0.4–1.3) and that for the ADH_3^{2-2} genotype was 0.6 (95% CI, 0.3–1.6), using the ADH_3^{1-1} genotype as reference category. When non-drinkers with the ADH_3^{1-1} genotype were used as reference, the risk among drinkers of 57 or more drinks per week was modified by the ADH3 genotype: odds ratios were 40.1 (95% CI, 5.4–296), 7.0 (95% CI, 1.4–35.0) and 4.4 (95% CI, 0.7–33.3) for ADH_3^{1-1}, ADH_3^{1-2} and ADH_3^{2-2}, respectively. For lower alcohol consumption, the risks were not or only moderately elevated, without a clear pattern according to genotype. [The Working Group noted the low participation rate.]

Coutelle *et al*. (1997) conducted a case–control study in France among male heavy drinkers (more than 100 g of alcohol per day for more than 10 years). They included 21 cases of oral and pharyngeal cancer, 18 cases of laryngeal cancer and 37 heavy drinkers recruited in an alcoholism clinic. As compared to ADH_3^{1-1} or ADH_3^{2-2}, the ADH_3^{1-2} genotype was associated with an age-adjusted odds ratio of 2.6 (95% CI, 0.7–10.0) for oropharyngeal cancer and 6.1 (95% CI, 1.3–28.6) for laryngeal cancer. The GSTM1 null genotype had an odds ratio of 1.8 (95% CI, 0.5–6.2) for oropharyngeal cancer and 4.7 (95% CI, 1.0–21.8) for laryngeal cancer. The combination of ADH_3^{1-1} and GSTM1 null genotypes, as compared to the combination of ADH_3^{1-2} or ADH_3^{2-2} and GSTM1 non-null, gave an odds ratio of 4.3 (95% CI, 0.6–28.8) for oropharyngeal cancer and 12.9 (95% CI, 1.8–92.0) for laryngeal cancer.

In an abstract, Freudenheim *et al*. (1997) presented the results of a study conducted in western New York, United States, on 134 premenopausal and 181 postmenopausal cases of breast cancer and 356 population controls. Heavy alcohol intake was associated with an increased risk for premenopausal breast cancer (odds ratio, 3.5; 95% CI, 1.3–9.2) among ADH_3^{1-1} subjects but not among women with ADH_3^{1-2} or ADH_3^{2-2} genotypes. This association was not observed for postmenopausal breast cancer.

3. Studies of Cancer in Experimental Animals

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and intratracheal instillation. Following inhalation exposure, an increased incidence of carcinomas was induced in the nasal mucosa of rats, and laryngeal carcinomas were induced in hamsters. In another inhalation study in hamsters, using a lower exposure level, and in an intratracheal instillation study, no increased incidence of tumours was observed. In hamsters, inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[*a*]pyrene (IARC, 1985).

3.1 Inhalation exposure

Rat: In a study summarized from a preliminary report in the previous monograph, four groups of 105 male and 105 female Cpb:WU albino Wistar rats, six weeks of age, were exposed by whole-body inhalation to concentrations of 0, 750, 1500 or 3000 (reduced progressively over a period of 11 months to 1000 ppm due to toxicity) ppm [0, 1350, 2700 or 5400–1800 mg/m^3] acetaldehyde vapour [purity unspecified] for 6 h per day on five days per week for a maximum of 27 months. Each group comprised five subgroups, three of which were used for interim kills at weeks 13, 26 and 52, respectively. Of the animals killed at these intervals, only one had a tumour of the respiratory tract: a female in the high-dose group killed in week 53, bearing a nasal squamous-cell carcinoma. At day 468, the mortality rate in the high-dose group was 50% (28/55) for males and 42% (23/55) for females. By day 715, all high-dose rats had died and, at termination of the study at day 844, only a few animals were still alive in the mid-dose group. At the end of the study, the incidences of nasal carcinomas (carcinomas *in situ*, squamous-cell carcinomas and adenocarcinomas) were in males: 1/49, 17/52, 41/53 and 37/49 in the control, low-, mid- and high-dose groups, respectively; and in females: 0/50, 6/48, 34/53 and 43/53 in the control, low-, mid- and high-dose groups, respectively. One carcinoma *in situ* of the larynx was found in a female of the mid-dose group and one female of the low-dose group developed a poorly differentiated adenocarcinoma in the lung (Woutersen *et al*., 1986).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Human subjects retained 45–70% of acetaldehyde inhaled either orally or nasally.

N-Nitroso-2-methylthiazolidine 4-carboxylic acid (*cis*- and *trans*-isomers) was frequently detected in the urine of human subjects; a fraction of this may be formed as a two-step synthesis *in vivo* from acetaldehyde and L-cysteine to yield 2-methylthiazolidine 4-carboxylic acid, which is easily nitrosated (IARC, 1985).

4.1.2 *Experimental systems*

Acetaldehyde is oxidized to acetic acid by NAD^+-dependent aldehyde dehydrogenases (ALDH) in liver and nasal mucosal preparations. Its administration to rats causes an increase in urinary excretion of sulfur metabolites and it is known to react with cysteine to produce a thiazolidine 4-carboxylic acid derivative that can be *N*-nitrosated *in vivo* upon co-administration of nitrite (IARC, 1985). Many studies have been published subsequently, but these have been mainly in the context of ethanol metabolism.

Six dogs were each given a single 600 mg/kg bw dose of acetaldehyde by stomach tube. In two dogs, the maximum plasma concentration was reached after 15 min, while in

the others plasma acetaldehyde was either close to the limit of detection (2 ng/μL) or was not detectable. Urinary recovery of acetaldehyde was < 0.02% of the dose (Booze & Oehme, 1986).

The oxidation of acetaldehyde to acetic acid has been studied with NAD-linked ALDH purified from human, rat and Syrian hamster liver (Klyosov *et al*., 1996). The mitochondrial enzymes from these species have very similar kinetic properties, whereas human cytosolic ALDH1 has a K_m value of about 180 μM, compared with 15 μM and 12 μM for rats and hamsters, respectively. Apparently, in human liver, only mitochondrial ALDH oxidizes acetaldehyde at physiological concentrations, whereas both mitochondrial and cytosolic ALDHs of rodents can participate in acetaldehyde metabolism. The rodent cytosolic ALDHs are at least 10 times more sensitive that the human enzyme to inhibition by disulfiram.

In addition to forming adducts with cytosine and purine-containing nucleotides (IARC, 1985), acetaldehyde has been shown to form stable, cyclic imidazolidinones with the N-terminal valine of the α and β chains of haemoglobin (San George & Hoberman, 1986).

4.2 Toxic effects

4.2.1 *Humans*

The irritant effect of acetaldehyde vapour, which is reported to cause coughing and a burning sensation in the nose, throat and eyes, usually prevents exposure to a level sufficient to cause depression of the central nervous system. A splash of liquid acetaldehyde was reported to cause a burning sensation, lachrymation and blurred vision. Prolonged periods of contact with the skin result in erythema and burns; repeated contact may result in dermatitis, due either to primary irritation or to sensitization.

Intravenous infusion of 5% acetaldehyde [purity unspecified] at a rate of 20.6–82.4 mg/min for up to 36 min into normal human subjects caused an increase in heart rate, ventilation and dead space, and a decrease in alveolar carbon dioxide levels. These symptoms are qualitatively and quantitatively similar to those seen after ethanol intake in subjects previously treated with disulfiram (Antabuse), a known inhibitor of ALDH (IARC, 1985).

4.2.2 *Experimental systems*

Inhalation of acetaldehyde for four weeks by rats caused some degeneration of the nasal epithelium; a concentration of 400 ppm [720 mg/m^3] produced a slight degeneration of the olfactory epithelium. A similar concentration had no effect upon Syrian hamsters (IARC, 1985). The toxicology of acetaldehyde has been reviewed (Von Burg & Stout, 1991).

In the study by Booze and Oehme (1986) described above, all the dogs given a single 600 mg dose of acetaldehyde by stomach tube vomited and this condition lasted for several hours. The two dogs with the highest plasma levels of acetaldehyde developed slight tremors, but all dogs appeared to be normal 24 h after dosing.

Groups of weanling male and female Wistar rats were given acetaldehyde in the drinking-water to provide doses of 0, 25, 125 and 675 mg/kg bw per day for four weeks.

Food and water consumption was reduced and slight to moderate hyperkeratosis of the forestomach was observed in both sexes at the highest dose level (Til *et al*., 1988).

Male Wistar rats exposed to 243 ppm [437 mg/m^3] acetaldehyde atmospheres for 8 h per day on five days per week for five weeks showed increases in functional residual capacity, residual volume, total lung capacity and respiratory frequency. These changes were interpreted as being caused by damage to the peripheral regions of the lung parenchyma (Saldiva *et al*., 1985).

The progression and regression of nasal lesions were studied in groups of 30 male and 30 female Wistar rats exposed to acetaldehyde by inhalation for 6 h per day on five days per week at concentrations of 0, 750, 1500 and 3000 ppm [0, 1350, 2700 and 5400 mg/m^3] (the last dose was gradually reduced to 1500 ppm from week 20 to week 44) for 52 weeks. The animals were killed after recovery periods of 26 or 52 weeks. The main treatment-related effects included (1) focal basal cell hyperplasia of the olfactory epithelium in 750- and 1500-ppm group rats, (2) hyperplasia and metaplasia of the respiratory epithelium, often accompanied by keratinization and sometimes by proliferation of atypical basal cells, in 3000-/1500-ppm group rats and (3) rhinitis in some of 3000-/1500-ppm group rats. There was no restoration of the respiratory epithelium among 3000-/1500-ppm group rats, even after a recovery period of 52 weeks. Progression of the hyperplasia and metaplasia in the respiratory epithelium to squamous-cell carcinomas occurred during the first 26 weeks in 11 males and four females, but degeneration of the epithelium was less pronounced in the succeeding 26 weeks. Regeneration of the olfactory epithelium occurred in the 750- and 1500-ppm groups, but not in the 3000-/1500-ppm group (Woutersen & Feron, 1987).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

It is not known whether acetaldehyde, the primary metabolite of ethanol, is involved in the etiology of the human fetal alcohol syndrome (IARC, 1985).

4.3.2 *Experimental systems*

Fetal malformations were found in mice and rats treated with acetaldehyde *in vivo* and *in vitro*, and resorptions were observed in both species *in vivo* (IARC, 1985; WHO, 1995).

4.4 Genetic and related effects

The toxicity (including genotoxicity) of acetaldehyde has been reviewed (Dellarco, 1988; Feron *et al*., 1991; WHO, 1995).

4.4.1 *Humans*

Acetaldehyde–DNA adducts have been observed in granulocytes and lymphocytes of human alcohol abusers (Fang & Vaca, 1997).

4.4.2 *Experimental systems* (see Table 1 for references)

Acetaldehyde did not cause differential killing of repair-deficient *Escherichia coli* K-12 *uvrB*/*recA* cells and was not mutagenic to *Salmonella typhimurium* or *E. coli* WP2 *uvrA* after vapour exposure, with or without metabolic activation. It induced chromosome malsegregation in *Aspergillus nidulans* and was mutagenic in *Drosophila melanogaster* after injection but not after feeding.

In vitro and without exogenous metabolic activation, acetaldehyde induced gene mutations in mouse lymphoma L5178T cells, sister chromatid exchanges in Chinese hamster ovary cells and aneuploidy in embryonic Chinese hamster diploid fibroblasts. In human lymphocytes it also induced gene mutations and sister chromatid exchanges and, in addition, chromosomal aberrations and both positive- and negative-centromere-staining micronuclei. It did not cause morphological transformation in cultured mammalian cells when tested alone, but positive results were obtained when it was used in combination with the tumour promoter 12-*O*-tetradecanoylphorbol 13-acetate. It did not induce micronuclei in early spermatids of mice.

Acetaldehyde caused DNA strand breaks and cross-links in human lymphocytes *in vitro* without metabolic activation, but not in human bronchial epithelial cells and in human leukocytes. It has been shown to bind covalently to deoxynucleotides *in vitro* to form DNA–protein cross-links in rat nasal mucosa. Acetaldehyde–DNA adducts have been found *in vitro* in calf thymus DNA, in 2′-deoxyguanosine-3′-monophosphate and in liver from mice treated with ethanol (Fang & Vaca, 1995). Abnormal sperm morphology or spermocyte micronuclei were not observed in mice treated with an intraperitoneal injection of acetaldehyde.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to acetaldehyde may occur in its production, and in the production of acetic acid and various other chemical agents. It is a metabolite of sugars and ethanol in humans and has been detected in plant extracts, tobacco smoke, engine exhaust, ambient and indoor air, and in water.

5.2 Human carcinogenicity data

An increased relative frequency of bronchial and oral cavity tumours was found among nine cancer cases in one study of chemical workers exposed to various aldehydes. Oesophageal tumours have been associated with genetically determined, high metabolic levels of acetaldehyde after drinking alcohol.

Three case–control studies assessed the risk of oral, pharyngeal, laryngeal and oesophageal cancer following heavy alcohol intake, according to genetic polymorphism of enzymes involved in the metabolism of ethanol to acetaldehyde (alcohol dehydrogenase 3) and in the further metabolism of acetaldehyde (aldehyde dehydrogenase 2 and

Table 1. Genetic and related effects of acetaldehyde

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECD, *Escherichia coli pol*A, differential toxicity (spot test)	–	NT	7800	Rosenkranz (1977)
ERD, *Escherichia coli* K-12 *uvrB/recA*, differential toxicity	–	NT	16317	Hellmér & Bolcsfoldi (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Mortelmas *et al*. (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	NT	2515	Marnett *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	7800	Rosenkranz (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	7800	Rosenkranz (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1% in air	JETOC (1997)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	0.5% in air	JETOC (1997)
SCF, *Saccharomyces cerevisiae*, forward mutation	(+)	NT	23400	Bandas (19892)
ANN, *Aspergillus nidulans*, aneuploidy (chromosome malsegregation)	+	NT	200	Crebelli *et al*. (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		22500 ppm inj × 1	Woodruff *et al*. (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		25000 ppm feed	Woodruff *et al*. (1985)
DIA, DNA–protein cross-links, Fischer 344 rat nasal mucosa cells *in vitro*	+	NT	4410	Lam *et al*. (1986)

Table 1 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	176	Wangenheim & Bolcsfoldi (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	3.9	Obe & Ristow (1977)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	3.9	Obe *et al*. (1978)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.9	Obe & Beek (1979)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	7.8	De Raat *et al*. (1983)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.3	Brambilla *et al*. (1986)
MIA, Micronucleus test, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	4.4	Bird *et al*. (1982)
CIR, Chromosomal aberrations, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	44.1	Bird *et al*. (1982)
AIA, Aneuploidy, Chinese hamster embryonic diploid fibroblasts *in vitro*	+	NT	15.6	Dulout & Furnus (1988)
TCM, Cell transformation, C3H 10T½ mouse cells *in vitro*	–	NT	100	Abernathy *et al*. (1982)
TCL, Cell transformation, mammalian cells	–[c]	NT	0.44	Eker & Sanner (1986)
DIH. DNA strand breaks, human leukocytes *in vitro*	–	NT	441	Lambert *et al*. (1985)
DIH, DNA cross-links, human lymphocytes *in vitro*	+	NT	411	Lambert *et al*. (1985)
DIH, DNA strand breaks, human bronchial epithelial cells *in vitro*	–	NT	44	Saladino *et al*. (1985)
DIH, DNA–protein cross-links, human bronchial epithelial cells *in vitro*	–	NT	44	Saladino *et al*. (1985)
DIH, DNA strand breaks, human lymphocytes *in vitro*	+	NT	68.8	Singh & Khan (1995)
GIH, Gene mutation, human lymphocytes, *hprt* locus *in vtro*	+	NT	13	He & Lambert (1990)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	7.8	Obe *et al*. (1978)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	7.8	Ristow & Obe (1978)

Table 1 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	5.8	Jansson (1982)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	8	Bohlke *et al*. (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	He & Lambert (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Knadle (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	11	Norppa *et al*. (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	15.6	Obe *et al*. (1986)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Helander & Lindahl-Kiessling (1991)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	11	Sipi *et al*. (1992)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	20	Badr & Hussain (1977)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	NT	7.8	Obe *et al*. (1978)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	15.6	Obe *et al*. (1979)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	15.9	Böhlke *et al*. (1983)
CIH, Chromosomal aberrations, human Fanconi's anaemia lymphocytes *in vitro*	+	NT	7.8	Obe *et al*. (1979)
MIH, Micronucleus test, human lymphocytes *in vitro*	+[d]		26.5	Migliore *et al*. (1996)
DVA, DNA–protein cross-links, Fischer 344 rat nasal mucosa *in vivo*	+		1000 ppm inh 6 h/d × 5 d	Lam *et al*. (1986)
SVA, Sister chromatid exchange, male C3A mouse bone-marrow cells *in vivo*	+		0.4 µg/mouse ip × 1	Obe *et al*. (1979)
SVA, Sister chromatid exchange, Chinese hamster bone-marrow cells *in vivo*	+		0.5 ip × 1	Korte *et al.* (1981)
MVM, Micronucleus test, C57BL/6J × C3H/He mouse spermatocytes *in vivo*	–		375 ip × 1	Lähdetie (1988)

Table 1 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
COE, Chromosomal aberrations, rat embryos *in vivo*	+		7800 iam × 1	Bariliak & Kozachuk (1983)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	44100	Ristow & Obe (1978)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	78800	Fang & Vaca (1995)
BID, Binding (covalent) to deoxynucleosides *in vitro*	+	NT	7880	Vaca *et al*. (1995)
SPM, Sperm morphology, C57BL/6J × C3H/He mouse early spermatids *in vivo*	–		250 ip × 5	Lähdetie (1988)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; inj, injection; inh, inhalation; ip, intraperitoneal; iam, intra-amniotic

[c] Positive results when acetaldehyde treatment was followed by exposure of the cells to 12-*O*-tetradecanoylphorbol 13-acetate

[d] A dose-related increase in centromere-positive micronuclei was observed with fluorescence in-situ hybridization but it was not significantly different from the negative control

glutathione *S*-transferase M1). Despite limitations in the study design and the small size of most of the studies, these studies consistently showed an increased risk of alcohol-related cancers among subjects with the genetic polymorphisms leading to higher internal doses of acetaldehyde following heavy alcohol intake as compared to subjects with other genetic polymorphisms.

5.3 Animal carcinogenicity data

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and by intratracheal instillation. It produced tumours of the respiratory tract following inhalation, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters. In hamsters, it did not cause an increased incidence of tumours following intratracheal instillation. Inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[*a*]pyrene.

5.4 Other relevant data

Acetaldehyde is metabolized to acetic acid. During inhalation exposure of rats, degeneration of nasal epithelium occurs and leads to hyperplasia and proliferation.

Acetaldehyde causes gene mutations in bacteria and gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells, without metabolic activation. *In vivo*, it causes mutations in *Drosophila melanogaster* but not micronuclei in mouse germ cells. It causes DNA damage in cultured mammalian cells and in mice *in vivo*. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde.

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

Overall evaluation

Acetaldehyde is *possibly carcinogenic to humans (Group 2B)*.

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