Overview information for

Acetaldehyde

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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Acetaldehyde

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PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Acetaldehyde

Environment Canada
Health Canada

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LIST OF ACRONYMS AND ABBREVIATIONS

BMC	benchmark concentration
BMC_{05}	the concentration associated with a 5% increase in the benchmark endpoint
$BMCL_{05}$	the lower 95% confidence limit for the BMC_{05}
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CTV	Critical Toxicity Value
EC_{50}	median effective concentration
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
MIR	maximum incremental reactivity
NAPS	National Air Pollution Surveillance
NOEL	No-Observed-Effect Level
ODP	Ozone Depletion Potential
POCP	photochemical ozone creation potential
NO_x	nitrogen oxides
PSL	Priority Substances List
TC	Tolerable Concentration
TC_{05}	Tumorigenic Concentration
TCL_{05}	lower 95% confidence limit of the TC_{05}
VOC	volatile organic compounds

SYNOPSIS

In Canada, the major use of acetaldehyde is in the production of pentaerythritol for use in alkyd resin production, fatty acid esters (synthetic lubricants), rosin and tall oil esters, and other smaller-volume applications. The Canadian domestic demand for acetaldehyde was under 10 000 tonnes in 1996.

Acetaldehyde enters the Canadian environment from natural sources (including forest and brush fires), from human sources such as fuel combustion and industrial on-site releases, and through secondary formation as a result of the atmospheric oxidation of natural and anthropogenic organic compounds. Although there are no quantitative estimates of releases from natural and secondary sources in Canada, it is believed that these sources are very large. However, the highest concentrations measured in the environment are present near anthropogenic sources. On-road motor vehicles are the largest human source of acetaldehyde emissions to the Canadian environment, releasing about 3290 tonnes per year into the air. The amount of acetaldehyde estimated to have been released into the Canadian environment from industrial processes in 1996 was 478 tonnes.

When acetaldehyde is released to or formed in air, most will undergo various degradation processes in air, and a very small amount will move into water. When acetaldehyde is released into water, it degrades there and does not move into other media. Acetaldehyde does not persist in the environment, but its continuous release and formation result in chronic exposure of biota near sources of release or formation.

Extensive recent data are available on concentrations of acetaldehyde in urban, suburban and rural air in Canada, and data are available on concentrations in air at the largest industrial emitter of acetaldehyde in Canada. Limited data are available on concentrations in surface water in four rivers and in groundwater at the industrial site that is the largest single emitter of acetaldehyde. Environmental toxicity data are available for a range of terrestrial and aquatic organisms, although mostly only for acute exposure. Based on the highest concentrations measured in air and in surface water and groundwater in Canada and on the Estimated No-Effects Values derived from experimental data for terrestrial and aquatic biota, it is unlikely that organisms are exposed to harmful levels of acetaldehyde in the Canadian ambient environment.

Acetaldehyde is not involved in the depletion of stratospheric ozone or in climate change. Because of its photo-reactivity and its moderate concentrations in the air in Canadian cities, acetaldehyde plays a role, along with other reactive volatile organic chemicals in air, in the photochemical formation of ground-level ozone.

The focus of the human health assessment is airborne exposure. Based on short-term and long-term inhalation studies conducted in experimental animals, the upper respiratory tract is the principal target site for effects of inhaled acetaldehyde. In short-term studies, acetaldehyde causes degenerative non-neoplastic effects. Although it is genotoxic both *in vitro* and *in vivo*, tumours have been observed following inhalation only at concentrations that have produced significant cytotoxicity, and it is likely that both the genotoxicity and irritancy of acetaldehyde play a role in its carcinogenicity.

Therefore, a Tolerable Concentration (based on a benchmark concentration or an Effect Level) and a Tumorigenic Concentration have been derived for this substance.

Based on the information available, it is concluded that acetaldehyde is not entering the environment in a quantity or concentration or under conditions that have or may have a

harmful effect on the environment or its biological diversity. Acetaldehyde may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends or a danger to human life or health in Canada. Therefore, acetaldehyde is considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

Since acetaldehyde contributes to the formation of ground-level ozone, it is recommended that key sources of acetaldehyde be addressed as part of management plans for volatile organic chemicals associated with the formation of ground-level ozone.

Based on the comparison of the carcinogenic potency of acetaldehyde with estimates of population exposure, the priority for investigation of options to reduce exposure of the general population in the ambient environment is considered to be moderate only. Additional work on characterization of exposure of populations in the vicinity of industrial point sources and of sources in indoor air may be warranted.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or are capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing acetaldehyde provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> This compound is used in Canada primarily in the manufacture of other chemical substances and as a finishing agent. Humans are likely to be exposed to acetaldehyde from airborne pollution. Direct human exposure may also result from other uses. Acetaldehyde is not persistent or bioaccumulative. Under laboratory conditions, it is carcinogenic when inhaled by rats and hamsters. It induces chromosome abnormalities in rodents. Information on this substance has been gathered, reviewed and evaluated by an international group of experts. An assessment is required to determine human exposure to acetaldehyde in the Canadian environment and its associated risks.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances"

(Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis and Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to the assessment of potential effects on the environment (prior to January 1999) and human health (prior to April 1998) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether acetaldehyde is "toxic" under CEPA have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Preparation of the environmental components of the assessment was led by R. Chénier with support from M. Eggleton and was coordinated by A. Bobra on behalf of Environment Canada. Sections of the Assessment Report and the supporting documentation (Environment Canada, 1999) related to the environmental assessment of acetaldehyde were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

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Environmental sections of the Assessment Report and supporting documentation (Environment Canada, 1999) were also reviewed by S. Abernethy (Ontario Ministry of the Environment), D. Ames (California Environmental Protection Agency), G. Bird (Natural Resources Canada), L. Brownlee (Environment Canada), J. Collins (California Environmental Protection Agency), A. Day (Celanese Canada Inc.), S. Dungey (United Kingdom Environment Agency), L. McCarty (L.S. McCarty Scientific Research and Consulting), G. Obe (Essen Polytechnic University), L. Seed (Health Canada) and P. Shepson (Purdue University).

The health-related sections of this Assessment Report and supporting documentation were prepared by the following staff of Health Canada:

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Sections of the supporting documentation on genotoxicity were reviewed by D. Blakey of the Environmental and Occupational Toxicology Division of Health Canada. Sections of the supporting documentation pertaining to human health were reviewed externally by R. Keefe (Imperial Oil) and C. Chopra (Bio-Tox Research Limited), primarily to address adequacy of coverage. Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analyses were considered in written review by staff of the Information Department of BIBRA International and at a panel meeting of the following members, convened by Toxicology Excellence in Risk Assessment (TERA) on September 30, 1997, in Cincinnati, Ohio:

K. Blackburn, Procter & Gamble
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K. Poirier, Procter & Gamble
A. Renwick, University of Southampton
L. Rosato, Millennium Petrochemical
L. Sirinek, Ohio Environmental Protection Agency

Helpful written comments were also received from A. Jarabek of the U.S. Environmental Protection Agency.

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (August 14 to October 13, 1999) (Environment Canada and Health Canada, 1999). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and their responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation
Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

2.1 Identity and physical/chemical properties

Acetaldehyde is also known as ethanal, acetic aldehyde, acetylaldehyde, ethylaldehyde and methyl formaldehyde. Its Chemical Abstracts Service (CAS) registry number is 75-07-0. Acetaldehyde's empirical formula is CH_3CHO.

At room temperature, acetaldehyde is a colourless, volatile liquid with a pungent, sharp, fruity odour (CARB, 1993; IPCS, 1995). It is a highly reactive compound that undergoes numerous condensation, addition and polymerization reactions. It decomposes at temperatures above 400°C. It is highly flammable when exposed to heat or flame, and it can be explosive in air. It is miscible in all proportions with water and most common organic solvents (Hagemeyer, 1978; IPCS, 1995). In aqueous solutions, acetaldehyde exists in equilibrium with the hydrate, $CH_3CH(OH)_2$. Its degree of hydration is fairly small (1.4) (CARB, 1993). The enol form, vinyl alcohol (CH_2CHOH), exists in equilibrium with acetaldehyde to the extent of approximately 1 molecule per 30 000 (Hagemeyer, 1978; IPCS, 1995). Values for the physical and chemical properties of acetaldehyde are given in Table 1.

2.2 Entry characterization

2.2.1 Production, importation, exportation and uses

In Canada, acetaldehyde is recovered from a vinyl acetate facility, as a reactor off-gas from continuous polymerization and from the production of acetic acid by the liquid-phase oxidation of n-butane (Environment Canada, 1997c). In 1996, between 2000 and 3000 tonnes of acetaldehyde were produced in Canada. A further 6000–7000 tonnes of acetaldehyde were imported into Canada, while fewer than 10 tonnes were exported (Environment Canada, 1997c).

Acetaldehyde is used primarily as a feedstock in the production of pentaerythritol, which is used in alkyd resin production, fatty acid esters (synthetic lubricants), rosin and tall oil esters, and other smaller-volume applications (Camford Information Services, 1994; SRI International, 1995). Total Canadian consumption of acetaldehyde was reported at less than 10 000 tonnes for 1996, almost all being used for pentaerythritol production (Environment Canada, 1997c). Much smaller amounts have been used as a fragrance, deodorizer or flavouring agent, as a finishing agent, as an analytical reagent and in research and development (Environment Canada, 1996b). Acetaldehyde is also used as a feed; this use is regulated under the *Feeds Act* in Canada and is not considered further in this assessment.

2.2.2 Sources and releases

Acetaldehyde is formed and released by the combustion of organic materials and by a variety of natural processes and human activities. In addition, secondary formation of acetaldehyde occurs in the atmosphere through the oxidation of natural and anthropogenic volatile organic compounds. While there are major uncertainties associated with estimated releases from natural sources and from secondary atmospheric formation, these may be expected to be much larger than direct emissions from anthropogenic activities. However, the highest concentrations in the environment have been measured near key anthropogenic sources (see below), such as

TABLE 1 Physical and chemical properties of acetaldehyde

Property	Reported values [1]
molecular weight (g/mol)	44.05
melting point (°C)	–123.5 to –121 (–123) [2]
boiling point (°C)	20.2 to 20.8 (20.8)
vapour pressure (kPa)	98.642 to 134.018 (121.3)
water pseudo-solubility (mg/L) [3]	147,570 to 920,335 (668,000)
Henry's law constant ($Pa \cdot m^3/mol$)	5.423 to 10.18 (8.0)
log octanol/water partition coefficient (log K_{ow})	–0.53 to 0.52 (0.45)
log organic carbon/water partition coefficient (log K_{oc})	0.063

[1] Includes experimental and calculated values from Palit, 1947; Stull, 1947; Buttery *et al.*, 1969; Hoy, 1970; Hine and Mookerjee, 1975; Rekker, 1977; Karickhoff, 1981; Wasik *et al.*, 1981; Tewari *et al.*, 1982; Weast, 1982–83; Verschueren, 1983; Boublik *et al.*, 1984; Dean, 1985; Snider and Dawson, 1985; Leahy, 1986; Riddick *et al.*, 1986; Yoshida *et al.*, 1986; Gaffney *et al.*, 1987; Kamlet *et al.*, 1987; Betterton and Hoffmann, 1988; Nirmalakhandan and Speece, 1988; Sangster, 1989; Zhou and Mopper, 1990; Yaws *et al.*, 1991; Benkelberg *et al.*, 1995; Mackay *et al.*, 1995; DMER and AEL 1996; most values measured or calculated at 25°C and 101.3 kPa.

[2] Values in parentheses are those selected by Mackay *et al.* (1995) as being the "most reliable" data.

[3] For a substance that is fully miscible in water, a pseudo-solubility can be calculated for modelling purposes.

automotive and industrial emissions. Detailed information on sources and emission rates is discussed in Environment Canada (1999).

2.2.2.1 Natural sources

Acetaldehyde is a product of many natural processes and is naturally present in the environment. It is released during biomass combustion, such as forest and brush fires (Howard, 1990). There are no reliable estimates of amounts released from forest and brush fires, although total releases can be expected to be large. Acetaldehyde is formed by the irradiation of humic substances in water by sunlight (Kieber *et al.*, 1990).

Acetaldehyde is a metabolic intermediate in humans and other animals, in the respiration of higher plants and in alcohol fermentation (U.S. EPA, 1993; IPCS, 1995). As such, it has been found in a variety of plant and animal tissues (Collins and Bean, 1963; Furia and Bellanca, 1975; Berni and Stanley, 1982; Kami, 1983; U.S. NRC, 1985; Graedel *et al.*, 1986; Adkins *et al.*, 1990; Righetti *et al.*, 1990; Isidorov, 1992; Osborn and Young, 1993).

2.2.2.2 Anthropogenic sources

While acetaldehyde is not found in gasoline, it is a product of incomplete combustion, and all internal combustion engines have the potential to produce it. The amount generated depends primarily on the composition of the fuel, the type of engine, the emission control system, the operating temperature, and the age and state of repair of the vehicle. Therefore, release estimates are variable (see Environment Canada, 1999, for specific emission rates).

Based on the National Pollutant Release Inventory (NPRI) for 1994, on-road motor vehicles were the largest direct anthropogenic source of acetaldehyde into the environment (Environment Canada 1996a). Data on releases from on-road motor vehicles in 1994 were estimated by modelling (Mobile 5C model), using assumptions outlined in Environment Canada (1996a). It can be expected that the rates of release of acetaldehyde from automotive sources have and will continue to change; most current and planned modifications to automotive emission control technology and gasoline quality would lead to decreases in the releases of acetaldehyde

and other volatile organic compounds (VOCs), while possible increases in the use of ethanol or other oxygenated fuels could result in increases in releases of acetaldehyde (Environment Canada, 1999). The amount of acetaldehyde estimated to be released in 1994 from on-road motor vehicles in Canada was 3290 tonnes, and 677 tonnes from aircraft; other off-road gasoline-powered and diesel-powered engines also release acetaldehyde, but no reliable estimates are available. While Environment Canada (1996a) did not distinguish between gasoline-powered and diesel-powered on-road vehicles, it has been estimated, based on emission data from gasoline-powered vehicles, that the emission of acetaldehyde from gasoline-powered vehicles in 1994 was 1903 tonnes and 1387 tonnes from diesel-powered vehicles (Environment Canada, 1999).

Other anthropogenic combustion sources (covering a range of fuels from wood to plastics, polycarbonate foams and polyurethane foams) include wood-burning stoves, fireplaces, furnaces, power plants, agricultural burns, waste incinerators, cigarette smoking, coffee bean roasting and the cooking of food (Rudling *et al.*, 1981; Ramdahl *et al.*, 1982; Lipari *et al.*, 1984; MRI, 1987; Garcia *et al.*, 1992; CARB, 1993; Ryan and McCrillis, 1994; IPCS, 1995). Cigarette smoking alone in Canada is estimated to account for 5–76 tonnes per year, based on estimated emission rates (IPCS, 1995) and a Canadian consumption rate of 56 billion cigarettes per year. Canadian coal-based electricity generating plants are estimated to emit at least 28 tonnes per year, based on U.S. emission factors (Lipari *et al.*, 1984; Sverdrup *et al.*, 1994), the high heating value of fuel and Canadian coal consumption in 1995 (Rose, 1998). A gross estimate of acetaldehyde emissions from municipal, hazardous and biomedical waste in Canada is 2.6 tonnes per year, based on measured emission rates from one municipal incinerator in Ontario (Environment Canada, 1999).

Industrial releases of acetaldehyde can occur at any stage during the production, use, storage, transport or disposal of products with residual acetaldehyde. Acetaldehyde has been detected in emissions from chemical manufacturing plants (Environment Canada, 1997c), pulp and paper mills and forestry product plants (Environment Canada, 1997c; O'Connor and Voss, 1997), tire and rubber plants (Environment Canada, 1997c), petroleum refining and coal processing plants (IARC, 1985), textile mills (Kotlovoi, 1974) and food processing facilities (CARB, 1993). The total release from Canadian industry in 1996 was reported at 478 tonnes, with 69% going to air, 30% injected into deep wells and 1% released to water bodies (Environment Canada, 1997c). Acetaldehyde disposed of through deep-well injection is not considered to interact with biologically active soil strata. From 1979 to 1989, about 2.2 tonnes of acetaldehyde were reported to have been released to the environment as a result of two spills (NATES, 1996).

Acetaldehyde is a product of the degradation of sewage and solid biological wastes (U.S. EPA, 1975; Shackelford and Keith, 1976). Weschler *et al.* (1992) detected acetaldehyde released from carpets, with concentrations increasing with increasing levels of ozone. Acetaldehyde has also been detected following the exposure of interior latex paint to ozone (Reiss *et al.*, 1995).

2.2.2.3 Secondary formation

Acetaldehyde is formed in the troposphere by the photochemical oxidation of many types of organic compounds, including naturally occurring compounds (e.g., terpenes) as well as pollutants from mobile and stationary sources, such as alkenes (e.g., propene), alkanes (e.g., ethane, propane), alkylbenzenes, alcohols (e.g., allyl alcohol, ethanol, butenol, hexanol), aldehydes (e.g., propionaldehyde, acrolein), phenols, aromatic compounds, ethyl-containing compounds (e.g., ethyl peroxide) and chlorinated organics (e.g., chloroethylene, 1,1-dichloroethylene) (CARB, 1993; Grosjean *et al.*, 1993, 1994; U.S. EPA, 1993; Kao, 1994; Washington, 1995). Unlike formaldehyde, it is not produced in the atmospheric oxidation of methane and isoprene (CARB, 1993).

Given the diversity and abundance of acetaldehyde precursors in urban air, secondary atmospheric formation frequently exceeds direct emissions, especially during photochemical air pollution episodes (Grosjean *et al.*, 1983, 1993, 1994, 1996; Grosjean, 1990a,b; CARB, 1993; Harley and Cass, 1994; Washington, 1995). In California, photochemical oxidation is the largest source of acetaldehyde in the ambient air. It is estimated that it contributes between 41 and 67% of the total atmospheric acetaldehyde (CARB, 1993). Direct emissions of acetaldehyde in Los Angeles were estimated to range from 14 to 18 tonnes per day, compared with 45–180 tonnes per day for secondary formation during smog episodes (CARB, 1993). Harley and Cass (1994) also estimated that photochemical formation was more important than direct emissions in Los Angeles during the summertime days studied; in winter or at night and in the early morning, direct emissions can be more important. This was also observed in Japan, where the concentrations of acetaldehyde in the central mountainous region were not associated directly with motor exhausts but rather were associated with the photochemical oxidation of anthropogenic pollutants occurring there through long-range transport (Satsumabayashi *et al.*, 1995).

2.3 Exposure characterization

2.3.1 Environmental fate

The sections below summarize the available information on the distribution and fate of acetaldehyde released into the environment. More detailed fate information is discussed in Environment Canada (1999).

2.3.1.1 Air

Acetaldehyde emitted to air primarily reacts with photochemically generated hydroxyl (OH) radicals in the troposphere. Minor fate processes include direct photolysis and reactions with nitrate (NO_3^-) radicals, hydroperoxyl (HO_2) radicals and ozone (O_3). Small amounts of acetaldehyde may also transfer into rain, fog and clouds or be removed by dry deposition (Atkinson, 1989; Atkinson *et al.*, 1990, 1993; CARB, 1993).

Photo-oxidation of acetaldehyde occurs in the atmosphere through various mechanisms, such as the reaction with hydroxyl radicals, ozone, hydroperoxyl radicals and nitrate radicals. On the basis of the rate constant for each of the reactions and the concentration of the reactants, the reaction with the hydroxyl radical is considered to be the most important (Atkinson *et al.*, 1990; CARB, 1993). Factors influencing acetaldehyde's atmospheric lifetime, such as time of day, sunlight intensity and temperature, also include those affecting the availability of hydroxyl radicals and nitrate radicals. The atmospheric half-life of acetaldehyde, based on hydroxyl radical reaction rate constants, is calculated to be less than six hours (Darnell *et al.*, 1976).

Products that can be formed from photo-oxidation include peroxyacetyl nitrate, formaldehyde, peroxyacetic acid and acetic acid (Atkinson and Lloyd, 1984; Atkinson, 1989, 1990; Atkinson *et al.*, 1993). Based on data in ambient air (Grosjean, 1982; Grosjean *et al.*, 1983), acetaldehyde is one of the major precursors to peroxyacetyl nitrate formation (Atkinson *et al.*, 1990), although it contributes less than methylglyoxal and other species derived from the oxidation of aromatic compounds in urban atmospheres.

The nighttime destruction of acetaldehyde is expected to occur by the gas-phase reaction with nitrate radicals (U.S. NRC, 1981a); this tends to be more significant in urban areas, where the concentration of the nitrate radical is higher than in rural areas (Altshuller and Cohen, 1964; Gay and Bufalini, 1971; Maldotti *et al.*, 1980). A half-life of 35 days was calculated based on an average atmospheric concentration of nitrate radicals typical of a mildly polluted urban centre

(Atkinson *et al.*, 1990). Nitric acid and acetyl radicals have been identified as products of this reaction. The reaction of the nitrate radical with acetaldehyde is not therefore expected to be a significant loss process under tropospheric conditions.

Photolysis is a minor transformation pathway for acetaldehyde. The estimated half-life for photolysis is 80 hours in the lower troposphere for a zenith angle of 0°. Photolysis of acetaldehyde can take several pathways. One produces methane and carbon monoxide, while the other produces the methyl radical and formyl radical (Horowitz and Calvert, 1982; Meyrahn *et al.*, 1982; CARB, 1993). The methyl radical can react with oxygen to form the methyl peroxyl radical, which reacts with nitric oxide to form formaldehyde (U.S. EPA, 1993).

Overall half-lives for acetaldehyde in air can vary considerably under different conditions. Estimations for atmospheric residence time in several U.S. cities ranged from three hours under conditions typical of clear skies during the day in the summer to 3000 hours (125 days) under conditions typical of winter nights (U.S. EPA, 1993). During the daytime, under clear sky conditions, acetaldehyde's residence time is determined primarily by its reaction with the hydroxyl radical. Photolysis accounted for only 2–5% of the removal.

Given the generally short daytime residence times for acetaldehyde, its net atmospheric lifetimes are short. The overall half-life based on reactivity of acetaldehyde in air was estimated by Mackay *et al.* (1995) as less than 10 hours. There is therefore generally limited potential for long-range transport of this compound.

Because of its high solubility, there may be transfer of acetaldehyde into clouds and precipitation. Washout ratios (concentration in rain/concentration in air) of 28 and 37 were estimated by Atkinson (1989) at 25°C and by Buttery *et al.* (1969), respectively. Gas-phase organic compounds that are efficiently rained out have a washout ratio of greater than 10^5 (CARB, 1993). The washout ratios of acetaldehyde, together with the episodic nature of precipitation events, indicate that the wet deposition (removal of gases and particles by precipitation) of acetaldehyde is expected to be of minor significance as a tropospheric loss process (Atkinson, 1989). Benkelberg *et al.* (1995) estimated that the residence time in the atmosphere due to rain-out is 9.3 years.

2.3.1.2 Water

In water, acetaldehyde can undergo reaction with hydroxyl radicals, oxidation by alkyl or aryl peroxyl radicals, oxidation by singlet oxygen, hydration, biodegradation and volatilization (Howard, 1972; Hendry *et al.*, 1974; Foote, 1976; Mill, 1979; Buxton *et al.*, 1988; Jacob *et al.*, 1989; DMER and AEL, 1996).

Acetaldehyde should biodegrade in several days under optimal conditions (DMER and AEL, 1996). It has been degraded by various mixed cultures obtained from sludges and sewage (Ludzack and Ettinger, 1960; Thom and Agg, 1975; Speece, 1983) and by anaerobic biological treatment with unacclimatized acetate-enriched cultures (Chou and Speece, 1978). Acetaldehyde is readily biodegradable using the biodegradability test (301C) defined in the Organisation for Economic Co-operation and Development guidelines for testing of chemicals (OECD, 1992).

Biodegradation, aquatic oxidation by hydroxyl radicals and volatilization are believed to be significant environmental fate processes in water. However, acetaldehyde's residence time in water depends on the environmental conditions, such as temperature, wind speed, current, ice cover, etc. The overall reactivity-based half-life of acetaldehyde in surface water is estimated to be between 30 and 100 hours (Mackay *et al.*, 1995). No data on the half-life in groundwater were identified.

2.3.1.3 Sediment

Because of its low organic carbon/water partition coefficient (K_{oc}), acetaldehyde is not expected to significantly sorb to suspended solids and sediments in water. Biotic and abiotic degradation are expected to be the significant environmental fate processes in sediment. An overall half-life is estimated by Mackay *et al.* (1995) to be between 100 and 300 hours.

2.3.1.4 Soil

Acetaldehyde is not expected to adsorb to soil particles to a great degree and would be considered mobile in the soil, based on its estimated log K_{oc} value of 0.063. According to Kenaga (1980), compounds with a log K_{oc} of <2 are considered to be moderately mobile. Acetaldehyde can be transported to surface water through runoff and to groundwater as a result of leaching. Parameters other than K_{oc} affecting the leaching to groundwater include the soil type, the amount and frequency of rainfall, the depth of the groundwater and the extent of degradation of acetaldehyde. Acetaldehyde is susceptible to degradation (Ludzack and Ettinger, 1960; Thom and Agg, 1975; Chou and Speece, 1978; Speece, 1983).

2.3.1.5 Biota

Bioconcentration factors of 1.3 and 0.14 were calculated based on a log octanol/water partition coefficient (K_{ow}) of 0.45 (Veith *et al.*, 1980; Mackay, 1982). These values indicate that there would be little uptake or bioconcentration in aquatic organisms. Compounds with a log K_{ow} of 5 or less are generally not expected to have significant food chain build-up. No significant aquatic food chain magnification is predicted from the model calculations and empirical observations of Thomann (1989). Therefore, acetaldehyde is not expected to bioaccumulate or biomagnify.

2.3.1.6 Environmental distribution

Fugacity modelling was conducted to provide an overview of key reaction, intercompartment and advection (movement out of a system) pathways for acetaldehyde and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Assumptions, input parameters and results are presented in Mackay *et al.* (1995) and Environment Canada (1999). This modelling assumed acetaldehyde emissions of 1000 kg/hour to air, water or soil.

Modelling indicates that when acetaldehyde is continuously discharged into a specific medium, most of it can be expected to be found in that medium, as a result of its physical-chemical properties (Mackay *et al.*, 1995; DMER and AEL, 1996; Environment Canada, 1999). More specifically, Level III fugacity modelling predicts that (Mackay *et al.*, 1995):

- when acetaldehyde is released into air, the distribution of mass is 97.1% in air, 2.6% in water, 0.3% in soil and 0.0% in sediment;
- when acetaldehyde is released into water, the distribution of mass is 0.4% in air, 99.5% in water, 0.0% in soil and 0.1% in sediment;
- when acetaldehyde is released into soil, the distribution of mass is 0.8% in air, 5.1% in water, 94.1% in soil and 0.0% in sediment.

Modelling predictions do not purport to reflect actual expected measurements in the environment but rather indicate the broad characteristics of the fate of the substance in the environment and its general distribution between media.

2.3.2 Environmental concentrations

2.3.2.1 Ambient air

Available sampling and analytical methodologies are sufficiently sensitive to detect the presence

of acetaldehyde in most samples of ambient (outdoor) air in Canada. Acetaldehyde was detected (detection limit 0.1 μg/m³) in 2798 (or 99.8%) of 2805 24-hour samples from rural, suburban and urban locations at 14 sites in six provinces surveyed from August 1989 to June 1997. Long-term (one-month to one-year) mean concentrations for these sites ranged from 0.39 to 3.35 μg/m³, with a mean concentration for all samples of 1.9 μg/m³. In urban areas in Canada, mean concentrations of acetaldehyde in 24-hour samples were generally greater than 2 μg/m³; the single highest concentration measured was 16.5 μg/m³ in Windsor, Ontario, in 1991 (Dann, 1998).

In a study in Windsor, Ontario, during 1991 and 1992, acetaldehyde was detected in all 55 samples collected, at concentrations ranging from 0.2 to 9 μg/m³; the overall mean concentration was 2.4 μg/m³ (OMEE, 1994a,b). Acetaldehyde was also detected in all 11 samples of ambient air collected during 1993 from residential and industrial areas of Hamilton, Ontario; the mean concentration was 2.1 μg/m³, with levels ranging from approximately 1.4 to 2.6 μg/m³ (Bell, 1996).

The highest concentrations of acetaldehyde in ambient air in Canada were obtained from daily monitoring data at four monitoring stations at a chemical plant. This facility is the largest reported emitter of acetaldehyde in Canada (Environment Canada, 1996a, 1997b,c). The average monthly concentrations throughout 1996 ranged from below the detection limit of 1.8 μg/m³ at some stations up to a maximum of 1150 μg/m³ at one station in July. The overall mean concentration for all stations was 199 μg/m³, with a median of 94 μg/m³ (Environment Canada, 1997c).

Average concentrations of acetaldehyde at rural Canadian sites in Nova Scotia (Tanner, 1994; Tanner *et al.*, 1994, 1996; Dann, 1998), Quebec (Dann, 1998) and Ontario (Shepson *et al.*, 1991; Dann, 1998) are generally less than or equal to 1 μg/m³. Concentrations of acetaldehyde in urban and rural areas of Canada are similar to those found in the United States and in other countries.

2.3.2.2 Indoor air

In general, concentrations of acetaldehyde in indoor air are greater than outdoor levels, due to the numerous potential indoor sources of this substance (including consumer products, cigarette smoke, combustion appliances, building materials, cooking and infiltration of vehicle exhaust) (CARB, 1996), although available data are inadequate to serve as a basis for characterization of their relative contributions. Acetaldehyde was detected in all 36 indoor air samples collected from homes in Windsor, Ontario, between 1991 and 1992 (OMEE 1994b). The mean indoor concentration (21.5 μg/m³) was considerably higher than the mean outdoor concentration (2.4 μg/m³; n = 55), with individual levels in indoor air ranging from 1.7 to 61.9 μg/m³. Acetaldehyde was detected in 11 samples of indoor air collected in 1993 from homes in residential and commercial areas of Hamilton, Ontario (Bell, 1996). The mean concentration was 15.3 μg/m³, with individual levels ranging from 3.8 to 36.3 μg/m³; the corresponding mean ambient concentration was 2.1 μg/m³ (Bell, 1996). Similar concentrations of acetaldehyde have been measured in residential indoor air studies in the United States (Highsmith *et al.*, 1988; Zhang *et al.*, 1994; Lindstrom *et al.*, 1995).

The concentration of acetaldehyde in the indoor air of office buildings is similar to that of residences. In air quality studies conducted in Canada and the United States between 1989 and 1992, mean concentrations of acetaldehyde in the indoor air of office buildings ranged from 4.1 to 16.1 μg/m³ (NIOSH, 1990; OMEE 1994b; Burt *et al.*, 1996).

Elevated levels of acetaldehyde have been measured in indoor air contaminated with environmental tobacco smoke. In monitoring studies conducted between 1987 and 1995 in Canada, the United States and the United Kingdom, mean concentrations of acetaldehyde

in indoor air contaminated with tobacco smoke ranged from 26.0 to 193.5 µg/m^3 (Lofroth *et al.*, 1989; OMEE 1994b; Williams *et al.*, 1996).

2.3.2.3 Ambient water

Anderson *et al.* (1994) measured concentrations of acetaldehyde in the raw water at three water treatment pilot plants in Ontario. The study included three distinct types of surface waters, covering a range of water parameters and regional influences: a moderately hard waterway with agricultural impacts (Grand River at Brantford), a soft, coloured river (Ottawa River at Ottawa) and a river with moderate values for most parameters, typical of the Great Lakes waterways (Detroit River at Windsor). Acetaldehyde concentrations of 114 µg/L and 1.4 µg/L were measured in samples collected on December 2, 1993, and on February 15, 1994, from the Detroit River. In the Ottawa River, concentrations were below the detection limit (0.9 µg/L) in three profiles taken between April 12 and June 7, 1994. A concentration of 5.9 µg/L was measured on December 9, 1993. No acetaldehyde was detected (0.9 µg/L) on seven sampling dates between May 11 and July 21, 1994, in the Grand River.

Concentrations of acetaldehyde in raw water from the North Saskatchewan River were measured at a drinking water pilot plant in Edmonton, Alberta. Concentrations between March 1989 and January 1990 averaged 8 µg/L, with a peak value of 31 µg/L. These concentrations were influenced by climatological events, as evidenced by an increase in concentrations during spring runoff and major rainfall and a reduction in concentrations (<0.7 µg/L) following river freeze-up (Huck *et al.*, 1990).

Monitoring data for groundwater at the site of the largest known industrial emitter of acetaldehyde in Canada included nine samples in which acetaldehyde concentrations were below the detection limit (50 µg/L) and four samples with measurable concentrations (140, 370, 1200 and 1300 µg/L) (Environment Canada, 1997c).

While no data are available in Canada, concentrations of acetaldehyde in rain, fog, cloud water and snow have been measured in other countries. Concentrations ranged from below detection to 190 µg/L for snow, from 1.3 to 100 µg/L for rain, from 220 to 1100 µg/L for fog water and from below detection to 2400 µg/L (over Los Angeles, California) for cloud water (see Environment Canada, 1999).

2.3.2.4 Drinking water

Data concerning measured levels of acetaldehyde in drinking water in Canada are limited to two investigations conducted at pilot-scale surface water treatment facilities in Alberta and Ontario. In an unspecified number of samples of treated drinking water collected from March 1989 to January 1990 at a treatment plant in Edmonton, Alberta, mean concentrations of acetaldehyde in finished water ranged from 5.5 to 6.3 µg/L (Huck *et al.*, 1990). In a pilot study of Ontario treatment plants located in Ottawa, Brantford and Windsor conducted between 1993 and 1994, reported concentrations of acetaldehyde in finished drinking water ranged from not detected (i.e., <0.9 µg/L) to 20 µg/L (Anderson *et al.*, 1994).

In a study conducted in the United States, acetaldehyde was not detected (i.e., <1.0 µg/L) in six samples of finished drinking water collected at Freemont, California (Wu and White, 1995). Krasner *et al.* (1989) reported median concentrations of acetaldehyde ranging from 2.1 to 6.1 µg/L in 24 samples of treated drinking water collected in 1989 from eight water treatment facilities in the United States. Concentrations of acetaldehyde ranged from not detected (detection limit 1.1 µg/L) to 9.5 µg/L in an unspecified number of samples of finished drinking water collected in July 1988 at one groundwater and one surface water treatment facility in southern California (Glaze *et al.*, 1989). In studies conducted at a surface water treatment facility in Turin, Italy, during 1988, acetaldehyde was detected in 83% of finished drinking water samples at a mean concentration of 0.5 µg/L (Gilli *et al.*, 1989).

2.3.2.5 Sediment and soil

No data on measured concentrations of acetaldehyde in sediments or in soils in Canada were identified.

2.3.2.6 Biota

Data on concentrations of acetaldehyde in Canadian biota were not identified.

2.3.2.7 Food

No data were identified concerning the concentrations of acetaldehyde in foodstuffs consumed in Canada; however, acetaldehyde is a natural component of many foods (Feron *et al.*, 1991) and is generated during the ripening of fruit (Bartley and Schwede, 1989), during cooking and baking (Lorenz and Maga, 1972; Yasuhara and Shibamoto, 1995) and during the storage and maturation of alcoholic beverages (Jones *et al.*, 1986). Acetaldehyde is generally recognized as safe (GRAS) in the United States and is used in Canada and the United States as a synthetic flavouring substance and adjuvant in various foods (including dairy and meat products, fruit juices, baked goods, alcoholic and non-alcoholic beverages, gelatin desserts and candy). Reported concentrations of acetaldehyde in these products have ranged from 3.9 mg/L in beverages to 2000 µg/g in frosting (U.S. FDA, 1982; U.S. NRC, 1985; Burdock, 1995; Feeley, 1996). In a review of the occurrence of acetaldehyde in various foods, Maarse and Visscher (1992) reported concentrations of acetaldehyde ranging from 0.2 to 230 µg/g in fruit and fruit juices (including apples, pears, strawberries, apple juice, orange juice and grapefruit juice), from 0.2 to 400 µg/g in vegetables (cabbage, carrots, celery, cucumber, peas, beans, corn and tomatoes) and from 4.2 to 9.9 µg/g in bread. Reported concentrations of acetaldehyde in dairy products (milk, cheese, cream and yogurt) and fats (butter) have ranged from 0.001 to 76.0 µg/g (Maarse and Visscher, 1992; Miyake and Shibamoto, 1993), while concentrations in seafood, meat, eggs and nuts have ranged from 0.001 to 2.7 µg/g (Halvarson, 1972; Maarse and Visscher, 1992). Measured concentrations of acetaldehyde in non-alcoholic beverages are low, with levels in tea and soft drinks ranging from 0.2 to 0.6 µg/g (Maarse and Visscher, 1992; Miyake and Shibamoto, 1993).

Acetaldehyde is produced as an intermediate during alcoholic fermentation and as an unwanted product during the storage and maturation of alcoholic products, imparting an unpleasant taste (Geiger and Piendl, 1976; Hagemeyer, 1978; Jones *et al.*, 1986). Based on reported concentrations of acetaldehyde in three brands of beer from the United States (Miyake and Shibamoto, 1993), 18 commercial brands of beer purchased in Europe (Delcour *et al.*, 1982) and an unspecified number of samples of beer in the study by Maarse and Visscher (1992), concentrations of acetaldehyde in beer have ranged from 0.6 to 24 µg/g. Based on available data, concentrations of acetaldehyde in wine are highly variable, with measured levels ranging from 0.7 to 290 µg/g (Okamoto *et al.*, 1981; Maarse and Visscher, 1992). Similarly, concentrations of acetaldehyde in other alcoholic products (including rum, whiskey, brandy, gin, cognac and sake) are highly variable, with reported levels ranging from 0.5 to 104 µg/g (Maarse and Visscher, 1992; Miyake and Shibamoto, 1993).

Identified information concerning the concentration of acetaldehyde in breast milk is limited to one study in which this substance was detected (limit of detection not reported) but not quantified in four of 12 samples of breast milk collected from 12 women at four urban locations (Bridgeville, Pennsylvania; Bayonne, New Jersey; Jersey City, New Jersey; and Baton Rouge, Louisiana) in the United States (Pellizzari *et al.*, 1982).

2.4 Effects characterization

2.4.1 Ecotoxicology

There exist several toxicity studies on acetaldehyde due to its wide use in many applications. Below, a brief summary is presented of the most sensitive endpoints found for terrestrial and aquatic organisms. More extensive descriptions of environmental effects are provided in Environment Canada (1999).

2.4.1.1 Terrestrial organisms

While no data on the toxicity of acetaldehyde to terrestrial vertebrate wildlife were identified in the literature, data are available from mammalian toxicology studies (Section 2.4.3). No data were found on avian toxicity.

Acetaldehyde has been shown to be an effective fumigant to control a broad range of bacteria, moulds, yeasts and thrips associated with fruit spoilage (Aharoni and Barkai-Golan, 1973; Aharoni and Stadelbacher, 1973; U.S. NRC, 1981b; Avissar *et al.*, 1990; Yuen *et al.*, 1995). Effect concentrations range from 540 to 357 000 mg/m^3 for 11 species of fungi. The most sensitive response identified was a 95% and 91% reduction in fruit decay by *Penicillium italicum* and *P. digitatum*, respectively, after a five-day exposure to acetaldehyde vapour at 540 mg/m^3 (0.03% v/v) (Yuen *et al.*, 1995).

Invertebrates appear less sensitive than fungi, with reported effect concentrations ranging from 4500 to 36 000 mg/m^3 in air for five species of developing and adult insects and slugs (Burditt *et al.*, 1963; Henderson, 1970; Aharoni *et al.*, 1979; Stewart *et al.*, 1980; Rohitha *et al.*, 1993). The most sensitive species tested was the aphid, *Acythosiphon kondai*, with 100% mortality at all life stages when exposed to 4500 mg acetaldehyde/m^3 (Aharoni *et al.*, 1979).

While toxicity data for terrestrial plants are limited, plants are less sensitive than fungi to acetaldehyde. Acetaldehyde concentrations of 54 000–108 000 mg/m^3 for four hours caused dark-green, water-soaked, necrotic areas on the outer leaves of head lettuce (*Lactuca sativa*). Fumigation with up to 36 000 mg/m^3 did not cause injury to the lettuce (Aharoni *et al.*, 1979; Stewart *et al.*, 1980).

2.4.1.2 Aquatic organisms

Almost all data identified for aquatic organisms were from short-term studies.

The most sensitive aquatic species identified is the fathead minnow (*Pimephales promelas*). A flow-through test was done at 24°C with 30-day-old fish and duplicate exposures. Based on measured concentrations of acetaldehyde, the 96-hour LC_{50} was 30.8 mg/L (95% confidence interval 28.0–34.0 mg/L) (Brooke *et al.*, 1984). Other short-term LC_{50} values for fish, including the guppy (*Poecilia reticulata*), the pinfish (*Lagodon rhomboides*) and the bluegill (*Lepomis macrochirus*), range from 33 to 140 mg/L (Daugherty and Garrett, 1951; Juhnke and Luedemann, 1978; Grahl, 1983; Deneer *et al.*, 1988; Geiger *et al.*, 1990; Nendza and Russom, 1991; Von Burg and Stout, 1991).

Aquatic invertebrates are similarly sensitive to acetaldehyde. The lowest value identified was a 48-hour EC_{50} (immobilization; static conditions) of 42 mg/L reported for the water flea, *Daphnia magna* (Von Burg and Stout, 1991). Other short-term effect concentrations (EC_{50}s, LC_{50}s) range up to 14 221 mg/L for species including the water flea, *Ceriodaphnia dubia*, the common shrimp (*Crangon crangon*) and the pond snail (*Lymnaea stagnalis*) (Portmann and Wilson, 1971; Randall and Knopp, 1980; Takahashi *et al.*, 1987; Mills *et al.*, 1990).

For microorganisms, the most sensitive effect of acetaldehyde reported is for the protozoan, *Chilomonas paramecium*, with a a 48-hour EC_{50} (population growth) of 82 mg/L (Von Burg and Stout, 1991). Five-day LC_{50}s for the diatom, *Nitzchia linearis*, range from 237 to 249 mg/L (Patrick *et al.*, 1968). A 25-minute EC_{50}

of 303 mg/L was reported for *Photobacterium phosphoreum* in a Microtox test (Chou and Que Hee, 1992). Blue-green algae (*Anabaena* sp. and *Nostoc* sp.) have 10- to 14-day EC_{50}s (growth) of 4528–16 244 mg/L (Stratton, 1987).

2.4.2 Abiotic atmospheric effects

The potential for acetaldehyde to contribute to the depletion of stratospheric ozone, to climate change and to formation of ground-level ozone was examined.

Since acetaldehyde is not a halogenated compound, its Ozone Depletion Potential (ODP) is 0, and it will therefore not contribute to the depletion of stratospheric ozone (Bunce, 1996).

Gases involved in climate change strongly absorb infrared radiation of wavelengths between 7 and 13 µm, enabling them to trap and re-radiate the Earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Worst-case calculations were made to determine if acetaldehyde has the potential to contribute to climate change (Bunce, 1996), assuming it has the same infrared absorption strength as the reference compound CFC-11. The Global Warming Potential (GWP) was calculated to be 1.3×10^{-4} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{acetaldehyde}/t_{CFC-11}) \times (M_{CFC-11}/M_{acetaldehyde}) \times (S_{acetaldehyde}/S_{CFC-11})$$

where:

- $t_{acetaldehyde}$ is the lifetime of acetaldehyde (2.4×10^{-3} years),
- t_{CFC-11} is the lifetime of CFC-11 (60 years),
- M_{CFC-11} is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{acetaldehyde}$ is the molecular weight of acetaldehyde (44 g/mol),
- $S_{acetaldehyde}$ is the infrared absorption strength of acetaldehyde (2389/cm^2 per atmosphere, default), and
- S_{CFC-11} is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

Since this estimate for the GWP is much less than 1% of that of the reference compound, acetaldehyde is not considered to be involved in climate change (Bunce, 1996).

The contribution of VOCs to the formation of ground-level ozone and the resulting contribution to smog formation is a complex process and has been studied extensively. The terms reactivity, incremental reactivity and photochemical ozone formation potential denote the ability of an organic compound in the atmosphere to influence the formation of ozone (Paraskevopoulos *et al.*, 1995). Estimates of reactivity of a substance depend on the definition and method of calculation of the reactivity, the VOC/NO_X ratio, the age of the air mass, the chemical mechanisms in the model, the chemical composition of the hydrocarbon mixture into which the VOC is emitted, the geographical and meteorological conditions of the airshed of interest (including temperature and intensity and quality of light), and the extent of dilution (Paraskevopoulos *et al.*, 1995).

The Photochemical Ozone Creation Potential (POCP) is one of the simpler indices of the potential contribution of an organic compound to the formation of ground-level ozone, based on the rate of reaction of the substance with the hydroxyl radical relative to ethene (CEU, 1995). Ethene, a chemical that is considered to be important in ozone formation, has an assigned POCP value of 100. The POCP for acetaldehyde was estimated to be 121 relative to ethene, using the following formula (Bunce, 1996):

$$POCP = (k_{acetaldehyde}/k_{ethene}) \times (M_{ethene}/M_{acetaldehyde}) \times 100$$

where:

- $k_{acetaldehyde}$ is the rate constant for the reaction of acetaldehyde with OH radicals (1.62×10^{-11} cm^3/mol per second),

- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{acetaldehyde}$ is the molecular weight of acetaldehyde (44.1 g/mol).

Various published reactivity values for acetaldehyde and other selected VOCs are presented by Paraskevopoulos *et al.* (1995). The use of a maximum incremental reactivity (MIR) scale has been recommended by Carter (1994) as optimal when applied to the wide variety of conditions where ozone is sensitive to VOCs, being fairly robust to the choices of scenarios used to derive it. Experimental data indicate that for acetaldehyde, direct radical formation from its photolysis is the key factor leading to net contribution to ozone formation under conditions of low reactive organic gas to NO_X ratios (Carter *et al.*, 1995).

Recently, acetaldehyde was one of the VOCs identified in the Canadian 1996 NO_X/VOC Science Assessment as part of the Multi-Stakeholder NO_X/VOC Science Program (Dann and Summers, 1997). Based on air measurements taken at nine urban and suburban sites in Canada from June to August from 1989 to 1993, acetaldehyde was ranked 22nd of the most abundant non-methane hydrocarbon and carbonyl species. Based on these measurements and on a maximum incremental reactivity (MIR) value of 2.56 mol ozone/mol carbon, acetaldehyde represented approximately 3.4% of the total volatile organic carbon reactivity and was ranked 8th when sorted by the total volatile organic carbon reactivities. Total volatile organic carbon reactivity denotes the ability of organic compounds to contribute to the formation of ozone.

Therefore, based on its reactivity and the concentrations encountered in Canada, acetaldehyde is likely to play a role in the photochemical formation of ground-level ozone in urban areas in Canada.

2.4.3 Experimental animals and in vitro

2.4.3.1 Acute toxicity

The acute toxicity of acetaldehyde is low, with LC_{50}s for 30-minute or four-hour inhalation exposures ranging from 24 to 37 g/m^3, and LD_{50}s for oral administration ranging from >600 to 1930 mg/kg-bw. Principal signs of acute toxicity are central nervous system depression, reduced respiratory rate, increased heart rate and blood pressure, pulmonary edema and albuminuria.

2.4.3.2 Irritation and sensitization

No data were identified concerning the potential of acetaldehyde to induce sensitization in experimental animals. Acetaldehyde is irritating to the skin, eyes and upper respiratory tract in inhalation studies and has been shown to induce sensory irritation in rodents (U.S. NRC, 1977; Steinhagen and Barrow, 1984; Babiuk *et al.*, 1985; U.S. EPA, 1987; ITII, 1988; Cassee *et al.*, 1996b).

2.4.3.3 Short-term and subchronic toxicity

2.4.3.3.1 Inhalation

In the study with optimum characterization of concentration–response, Wistar rats exposed to 400, 1000, 2200 or 5000 ppm (720, 1800, 3960 or 9000 mg/m^3) acetaldehyde for six hours per day, five days per week, for four weeks had concentration-related histopathological changes in the nasal olfactory and respiratory epithelium (including thinning and disarrangement of epithelial cells, loss of microvilli and sensory cells, focal hyperplasia, stratified squamous metaplasia and keratinization) (Appelman *et al.*, 1982). [Lowest-Observed-Effect Level (LOEL) = 400 ppm (720 mg/m3)]

In subsequent studies, male SPF Wistar rats were exposed to acetaldehyde for six hours per day, five days per week, for four weeks in three different exposure regimens: as a single daily exposure to 0, 150 or 500 ppm (0, 270 or

900 mg/m^3); as two daily three-hour exposures to 0, 150 or 500 ppm (0, 270 or 900 mg/m^3) with an intervening 1.5-hour resting period; or as two daily three-hour exposures to 0, 110, 150 or 500 ppm (0, 198, 270 or 900 mg/m^3) with a 1.5-hour period of eight five-minute peak exposures to 0, 660 or 3000 ppm (six-hour time-weighted average = 0, 270 or 1050 mg/m^3) (Appelman *et al.*, 1986). Compared with controls, no effects were observed among rats exposed (intermittently or continuously) to 110 or 150 ppm (198 or 270 mg/m^3) acetaldehyde for six hours per day, even when combined with additional (cytotoxic) exposures to 660 or 3000 ppm (six-hour time-weighted average = 270 or 1050 mg/m^3) acetaldehyde. In male rats exposed to 500 ppm (900 mg/m^3) acetaldehyde for six hours per day, five days per week, for four weeks, there were slight histopathological changes (i.e., loss of microvilli and disarrangement of the epithelium) in the olfactory epithelium and a reduction in the phagocytic index of lung macrophages. Variation in the pattern of exposure to include a 1.5-hour resting period did not significantly alter the observed histopathological changes in the nose or the phagocytic index. Intermittent exposure to concentrations up to 3000 ppm (six-hour time-weighted average = 1050 mg/m^3) acetaldehyde for 1.5 hours, in addition to the initial exposure to 500 ppm (900 mg/m^3) acetaldehyde for six hours per day, resulted in significant growth retardation, slight irritation and a further reduction of the phagocytic index, while there was no change in the severity of the histopathological changes observed in the nasal epithelium, compared with rats exposed only to 500 ppm (900 mg/m^3) acetaldehyde for six hours per day (Appelman *et al.*, 1986). [No-Observed-Effect Level (NOEL) = 150 ppm (270 mg/m^3); LOEL = 500 ppm (900 mg/m^3)]

In other short-term inhalation studies, in which only a limited range of endpoints was examined in rats and mice, histopathological changes in the nasal olfactory epithelia and functional changes in the lungs (in rats) were observed at concentrations as low as 243 ppm (437 mg/m^3) acetaldehyde (Watanabe and Aviado, 1974; Saldiva *et al.*, 1985; Cassee *et al.*, 1996a). [Lowest-Observed-Adverse-Effect Level (LOAEL) = 243 ppm (437 mg/m^3)]

In the only subchronic inhalation study identified, Syrian golden hamsters exposed by inhalation to 390, 1340 or 4560 ppm (702, 2412 or 8208 mg/m^3) acetaldehyde for six hours per day, five days per week, for 13 weeks had organ weight changes (ovary and kidney) and concentration-related histopathological changes in the trachea at 1340 ppm (2412 mg/m^3) acetaldehyde and higher (Kruysse *et al.*, 1975). [NOEL = 390 ppm (702 mg/m^3); LOAEL = 1340 ppm (2412 mg/m^3)]

2.4.3.3.2 Ingestion

In short-term studies in which a wide range of endpoints was examined, focal hyperkeratosis of the forestomach, increased relative kidney weights and alterations in clinical chemistry parameters were observed in Wistar rats receiving 675 mg acetaldehyde/kg-bw per day in drinking water for four weeks (Til *et al.*, 1988). [NOEL = 125 mg/kg-bw per day; LOAEL = 675 mg/kg-bw per day]

In the only subchronic investigation identified, in which only overt toxicity, body weight gain and hepatic effects were considered, histopathological effects in the liver (including microvesicular fatty degeneration, fatty accumulation and foci of inflammatory cells) were observed among rats receiving 500 mg acetaldehyde/kg-bw per day in drinking water (Matysiak-Budnik *et al.*, 1996). [NOEL = 120 mg/kg-bw per day; LOAEL = 500 mg/kg-bw per day]

2.4.3.4 Chronic toxicity and carcinogenicity

In the only chronic inhalation study of adequate design, Wistar rats (both sexes) were exposed by inhalation to 750, 1500 or 3000 ppm (1350, 2700 or 5400 mg/m^3) acetaldehyde for six hours per day, five days per week, for up to 28 months (due to early mortality and severe growth retardation, the highest concentration was reduced from 3000 ppm [5400 mg/m^3] in week 20 to

1000 ppm [1800 mg/m^3] in week 52 and beyond) (Woutersen *et al.*, 1984, 1986; Feron *et al.*, 1985; Woutersen and Feron, 1987). Compared with unexposed controls, exposure to acetaldehyde produced histopathological changes (i.e., focal basal cell hyperplasia, aggregates of atypical cells and proliferation) in the nasal olfactory epithelium of both sexes at all levels of exposure. The inclusion of a 26- or 52-week recovery period following exposure to acetaldehyde for 52 weeks resulted in some regeneration of the nasal olfactory epithelium among animals (particularly females) exposed to 750 or 1500 ppm (1350 or 2700 mg/m^3) acetaldehyde, but not among animals exposed to higher concentrations (Woutersen and Feron, 1987). [LOAEL (non-neoplastic histopathological effects in the upper respiratory tract of males and females) = 750 ppm (1350 mg/m^3)]

Compared with controls, there was a significant (concentration-related) increase in the incidence of nasal carcinomas (derived principally from respiratory epithelia) and adenocarcinomas (derived principally from olfactory epithelia) among males and females exposed to acetaldehyde for 52 weeks or 28 months (Woutersen *et al.*, 1984, 1986; Woutersen and Feron, 1987). At 28 months, the incidence of nasal squamous cell carcinomas in male rats exposed to 0, 750, 1500 or 3000/1000 ppm (0, 1350, 2700 or 5400/1800 mg/m^3) acetaldehyde was 1/49, 1/52, 10/53 ($p < 0.05$) and 15/49 ($p < 0.001$), respectively; the incidence in females was 0/50, 0/48, 5/53 and 17/53 ($p < 0.001$), respectively. At 28 months, the incidence of nasal adenocarcinomas in male rats exposed to 0, 750, 1500 or 3000/1000 ppm (0, 1350, 2700 or 5400/1800 mg/m^3) acetaldehyde was 0/49, 16/52 ($p < 0.001$), 31/53 ($p < 0.001$) and 21/49 ($p < 0.001$), respectively; the incidence in females was 0/50, 6/48 ($p < 0.05$), 26/53 ($p < 0.001$) and 21/53 ($p < 0.001$), respectively. The incidence of carcinoma *in situ* in the nasal cavity of rats was not statistically significant. No exposure-related neoplastic lesions were observed in other major tissues and organs examined (Woutersen *et al.*, 1984, 1986; Woutersen and Feron, 1987).

Acetaldehyde did not induce tumours in male Syrian golden hamsters exposed by inhalation (whole body) to a single concentration of 1500 ppm (2700 mg/m^3) acetaldehyde for seven hours per day, five days per week, for 52 weeks (Feron, 1979). However, exposure produced (reversible) non-neoplastic lesions in the dorsal area of the nasal cavity and trachea, a reduction in growth, alterations in hematological and urinary parameters, and increased relative kidney weights, compared with controls (Feron, 1979). [LOAEL for non-neoplastic effects = 1500 ppm (2700 mg/m^3); single exposure level]

In a subsequent study in which Syrian golden hamsters were exposed to a single concentration of 2500 ppm (4500 mg/m^3) acetaldehyde (reduced to 1650 ppm [2970 mg/m^3] due to extensive growth retardation) for seven hours per day, five days per week, for 52 weeks, followed by a 29-week recovery period, exposure produced a reduction in growth and non-neoplastic histopathological lesions in the nasal cavities, larynx and trachea, compared with unexposed controls (Feron *et al.*, 1982). No tumours were observed among surviving animals sacrificed after 52 weeks of exposure, while an increase ($p < 0.05$) in the incidence of laryngeal tumours (including poly/papilloma, carcinoma *in situ*, squamous cell carcinoma and adeno-squamous carcinoma) was observed among animals exposed to acetaldehyde and found dead or moribund; the (combined) incidence of these tumours in males and females was 26% (6/23) and 20% (4/20), respectively, while no tumours were observed among controls. In addition, animals exposed to acetaldehyde and found dead or moribund had tumours in the nasal cavities, including adenomas, adenocarcinomas and anaplastic carcinomas; however, the incidence of these tumours was not statistically significant (Feron *et al.*, 1982). [LOAEL for non-neoplastic effects = 2500/1650 ppm (4500/2970 mg/m^3); single exposure level]

No exposure-related tumours were observed in Syrian golden hamsters (both sexes) administered weekly intratracheal instillations of acetaldehyde (approximately 30 or 60 mg

acetaldehyde/kg-bw per week) for 52 weeks, while exposure produced extensive non-neoplastic changes in the lung of males and females (including peribronchiolar adenomatoid lesions and inflammation of the bronchoalveolar region), compared with saline controls (Feron, 1979; Feron *et al.*, 1982).

Studies concerning the effects of chronic ingestion of acetaldehyde in laboratory animals have not been identified.

2.4.3.5 Genotoxicity

In *in vitro* studies, acetaldehyde was mutagenic in mammalian cells (Wangenheim and Bolcsfoldi, 1986, 1988; He and Lambert, 1990), induced aneuploidy in *Saccharomyces cerevisiae* (Albertini *et al.*, 1993; Ristow *et al.*, 1995), Chinese hamster embryo cells and rat skin fibroblasts, and increased the frequency of micronuclei in rat skin fibroblasts and human lymphocytes (Bird *et al.*, 1982; Dulout and Furnus, 1988; Migliore and Nieri, 1991). Acetaldehyde induced structural chromosomal aberrations in Chinese hamster cells (Au and Badr, 1979; Dulout and Furnus, 1988) and rat skin fibroblasts (Bird *et al.*, 1982), while results have been mixed in human lymphocytes (Badr and Hussain, 1977; Obe *et al.*, 1979). Positive results were observed for sister chromatid exchange in Chinese hamster ovary cells (Obe and Ristow, 1977; Obe and Beek, 1979; DeRaat *et al.*, 1983; Brambilla *et al.*, 1986), human lymphocytes (Ristow and Obe, 1978; Jansson, 1982; Bohlke *et al.*, 1983; He and Lambert, 1985; Knadle, 1985; Norppa *et al.*, 1985; Obe *et al.*, 1986; Lambert and He, 1988; Helander and Lindahl-Kiessling, 1991; Sipi *et al.*, 1992) and pre-implantation mouse embryos (Lau *et al.*, 1991). Acetaldehyde also induced unscheduled DNA synthesis in rat hepatocytes (Stevens *et al.*, 1991) and DNA cross-linking in Chinese hamster ovary cells (Marinari *et al.*, 1984; Olin *et al.*, 1996), *Escherichia coli* plasmid DNA (Kuykendall and Bogdanffy, 1992a,b), calf thymus DNA (Sillanaukee *et al.*, 1991) and homogenates of rat nasal mucosa (Lam *et al.*, 1986; Kuykendall *et al.*, 1993).

In *in vivo* studies (conducted by intraperitoneal injection), acetaldehyde induced sister chromatid exchange in the bone marrow cells of hamsters and mice and increased the frequency of micronuclei in the erythrocytes of mice (Obe *et al.*, 1979; Korte and Obe, 1981; Ma *et al.*, 1985). Acetaldehyde also increased the frequency of chromosomal aberrations in rat embryos exposed by intra-amniotic injection (Barilyak and Kozachuk, 1983) and induced recessive lethal mutations in *Drosophila melanogaster* (Woodruff *et al.*, 1985) and gene mutation in *Caenorhabditis elegans* (Greenwald and Horvitz, 1980).

The results of *in vivo* studies suggest that acetaldehyde can react directly with DNA and proteins to form stable adducts. Acetaldehyde produced a concentration-related reduction in the extractability of DNA (suggestive of increased formation of DNA–protein cross-links) from the respiratory nasal mucosa of Fischer 344 rats exposed (whole body) to 1000 or 3000 ppm (1800 or 5400 mg/m^3) acetaldehyde for six hours or to 1000 ppm (1800 mg/m^3) acetaldehyde for six hours per day for five days. Significant reduction in the extractability of DNA in the nasal olfactory epithelia was observed only following exposure to 1000 ppm (1800 mg/m^3) acetaldehyde for six hours per day for five days (Lam *et al.*, 1986).

2.4.3.6 Reproductive and developmental toxicity

Data concerning the reproductive effects of *in vivo* administration of acetaldehyde (conducted using physiologically relevant routes of exposure) are limited to the results of one subchronic investigation in which an assessment of ovary weights, testicular weights and other testicular parameters was conducted in hamsters exposed by inhalation. Based on the results of this study, reduced gonad weights have been observed at 1340 ppm (2412 mg/m^3) acetaldehyde and higher (Kruysse *et al.*, 1975).

In identified *in vivo* studies concerning the developmental toxicity of acetaldehyde, dose-related embryotoxic, fetotoxic and/or teratogenic effects have been observed (O'Shea and Kaufman, 1979; Sreenathan *et al.*, 1982, 1984a,b; Barilyak and Kozachuk, 1983; Padmanabhan *et al.*, 1983; Webster *et al.*, 1983; Blakely and Scott, 1984; Checiu *et al.*, 1984; Schreiner *et al.*, 1987; Ali and Persaud, 1988; Fadel and Persaud, 1990, 1993). However, in each of these investigations, the dams were exposed by non-physiological routes of administration, primarily because the studies were designed to investigate the effects of acetaldehyde produced as a metabolite of alcohol; moreover, maternal toxicity was not adequately assessed or reported.

2.4.3.7 Neurological effects and effects on the immune system

Although data are limited, results of available toxicity studies conducted (via inhalation) in rodents do not indicate that neurological or immunological effects are critical endpoints associated with exposure to acetaldehyde; i.e., such effects were not observed at concentrations lower than those that induced damage in the respiratory tract (Ortiz *et al.*, 1974; Shiohara *et al.*, 1985; Aranyi *et al.*, 1986; Roumec *et al.*, 1988).

2.4.3.8 Toxicokinetics and mechanism of action

Small amounts of acetaldehyde are produced endogenously during the normal intermediary catabolism of deoxyribose phosphate and various amino acids (Nicholls *et al.*, 1992; Jones, 1995). Consumption of alcoholic beverages is also an important source of acetaldehyde in the body, formed through the metabolism of ethanol by alcohol dehydrogenase.

Consistent with effects being observed primarily at the initial site of exposure following inhalation (i.e., in the respiratory tract), available data indicate that the greatest proportion of inhaled acetaldehyde is retained at the site of contact, becoming rapidly and irreversibly bound to free protein and non-protein sulphydryl groups (notably, cysteine and glutathione). The results of pharmacokinetic studies conducted in humans (Dalhamn *et al.*, 1968; Egle, 1970) and rodents (David and Heck, 1983; Morris, 1997) indicate that the absorption of acetaldehyde into the systemic circulation is likely not extensive following inhalation. Based on the high degree of retention of acetaldehyde in the respiratory tract following inhalation in humans, it is likely that the predominant pathway for the metabolism of acetaldehyde involves conjugation to thiols (i.e., cysteine and glutathione) at the site of exposure, subsequent formation of hemimercaptal or thiazolidine intermediates, and elimination of thioethers and disulphides in the urine (Sprince *et al.*, 1974; Cederbaum and Rubin, 1976; Hemminiki, 1982; Brien and Loomis, 1983; Nicholls *et al.*, 1992). Inhaled acetaldehyde is also rapidly oxidized (to acetate) by aldehyde dehydrogenase in human nasal and lung epithelia (Bogdanffy *et al.*, 1986; Yin *et al.*, 1992; Morris *et al.*, 1996).

Many of the toxicological effects of acetaldehyde may be due to the saturation of protective cellular mechanisms at the initial site of exposure. As with formaldehyde, the potential for acetaldehyde to react with epithelial DNA (and other cellular components) in the upper respiratory tract may be dependent upon the levels of intracellular thiols (notably glutathione and cysteine), which prevent binding of acetaldehyde with critical sulphydryl groups in proteins, peptides and DNA (Cederbaum and Rubin, 1976; U.S. EPA, 1987; von Wartburg, 1987). In addition, regional deficiencies in aldehyde dehydrogenase activity in rats correlate with the distribution of nasal lesions in another strain of rats exposed to acetaldehyde in inhalation studies (Bogdanffy *et al.*, 1986). Observed decreases in uptake of acetaldehyde at high concentrations (>100 ppm [>180 mg/m^3]) in a range of species may be a function of exceedance of the metabolic capacity of nasal aldehyde dehydrogenase (Morris, 1997).

The pattern of observed irritancy of acetaldehyde at the site of contact and the results of studies indicating that it can react directly

with DNA and proteins to form stable adducts is similar to that for other aldehydes (such as formaldehyde) that have been carcinogenic to the respiratory system in sensitive inhalation bioassays. Although the exact mechanism is unknown, induction of tumours by these aldehydes is considered to be a function of both regenerative proliferative response and DNA–protein cross-linking at the site of contact.

Similarly, it has been proposed that the genotoxicity of acetaldehyde is based principally upon its ability to interact with single-stranded DNA during cell division (Feron *et al.*, 1982, 1984; Woutersen *et al.*, 1986; Roe and Wood, 1992; DECOS, 1993). Thus, a crucial determinant in the carcinogenicity of acetaldehyde in the nasal passages may be the cytotoxicity of this substance at high concentrations (Feron *et al.*, 1982, 1984; Woutersen *et al.*, 1986; Roe and Wood, 1992); cytotoxic concentrations of acetaldehyde cause recurrent tissue damage (and the presence of single-stranded DNA) and possess significant initiating activity. Moreover, the increased cell turnover may strongly enhance the fixation of relevant DNA damage and subsequently increase the progression of pre-cancer (initiated) cells to cancer.

However, the limited available data indicate that the pattern of DNA–protein cross-linking and proliferative response induced by acetaldehyde varies from that of other aldehydes, such as formaldehyde. For acetaldehyde, at concentrations at which tumours are observed (750 ppm [1350 mg/m^3]), there are increases in DNA–protein cross-links in the respiratory and olfactory mucosa of rats but no increase in proliferation (Cassee *et al.*, 1996a).[1] For formaldehyde, at the lower concentrations at which tumours are observed (6 ppm [7.2 mg/m^3]), there are increases in DNA–protein cross-links and proliferation in the nasal respiratory (but not olfactory) epithelium (Casanova *et al.*, 1994).

While acetaldehyde is genotoxic *in vitro* and *in vivo*, information concerning the potential roles of cytotoxicity, cell proliferation and DNA–protein cross-links in tumour formation is lacking.

2.4.4 Humans

Acetaldehyde is an upper respiratory tract and eye irritant in humans. The threshold concentration for the perception of acetaldehyde vapour may be as low as 0.2 µg/m^3 (Ruth, 1986). Ocular irritation has been observed at concentrations as low as 25 ppm (45 mg/m^3) acetaldehyde (Silverman *et al.*, 1946), while nasal and/or throat (sensory) irritation has been observed following exposure to concentrations just less than 200 ppm (360 mg/m^3) (Sim and Pattle, 1957).

Effects including headache, narcosis, decelerated heart rate and respiration, irritation of the eyes, skin, respiratory tract and throat, bronchitis, pulmonary edema, paralysis and death have been observed in individuals accidentally exposed to elevated levels of acetaldehyde (U.S. NRC, 1981a; ACGIH, 1991).

In patch tests, dermal irritation (i.e., cutaneous erythema) was observed in 12/12 volunteers exposed to a 75% aqueous solution of acetaldehyde (Wilkin and Fortner, 1985).

The only identified epidemiological study (Bittersohl, 1975) is considered inadequate to assess the carcinogenicity of acetaldehyde in humans, since it entailed only rather qualitative observations; there was no quantitative analysis by tumour site with a comparison population, standardizing for age and sex. Moreover, workers were exposed concomitantly to several other compounds.

[1] No increase in cell proliferation was observed in the nasal olfactory or respiratory epithelia of Wistar rats following repeated exposure (by inhalation) to concentrations up to 1500 ppm (2700 mg/m^3) acetaldehyde (concentrations similar to those that induced tumours in carcinogenesis bioassays in this strain) (Cassee *et al.*, 1996a).

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are the basis for selection of environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

Acetaldehyde enters the Canadian environment mainly from natural and anthropogenic combustion sources, notably vehicle emissions, from industrial on-site releases and through secondary formation as a result of the oxidation of anthropogenic and natural organic compounds in air. Almost all environmental formation and releases of acetaldehyde are to air, with small amounts released to water.

Given its physical-chemical properties, acetaldehyde undergoes various degradation processes in air, with very small amounts transferring into water. When released to water or soil, acetaldehyde is expected to remain primarily in the original compartment to which it was released, where it undergoes various biological and physical degradation processes. Acetaldehyde is not bioaccumulative or persistent in any compartment of the environment.

Based on the sources and fate of acetaldehyde in the ambient environment, biota are expected to be exposed to acetaldehyde primarily in air and, to a lesser extent, in water. Little exposure of soil or benthic organisms is expected. While acetaldehyde occurs naturally in plants and animals, it is readily metabolized and does not bioaccumulate in organisms. Therefore, the focus of the environmental risk characterization will be on terrestrial and aquatic organisms exposed directly to ambient acetaldehyde in air and water.

3.1.1.1 Terrestrial

Data on terrestrial toxicity are available for a variety of bacteria, fungi, plants and invertebrates (Section 2.4.1.1), as well as from mammalian toxicology studies (Section 2.4.3). Identified sensitive endpoints include the inhibition of growth of fungi (Yuen *et al.*, 1995), necrosis of plant leaves (Stewart *et al.*, 1980), mortality of insects (Aharoni *et al.*, 1979) and histopathological changes in nasal olfactory epithelium in rats (Appelman *et al.*, 1986).

Fungi are ubiquitous in terrestrial ecosystems and, as saprophytes, are essential for nutrient cycling. Terrestrial plants are primary producers, provide food and cover for animals and provide soil cover to reduce erosion and moisture loss. Invertebrates are an important component of the terrestrial ecosystem, both consuming plant

and animal matter and serving as forage for other animals. Vertebrate wildlife species are key consumers in most terrestrial ecosystems.

Therefore, although limited, the available toxicity studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to terrestrial biota. The single most sensitive response for all of these endpoints will be used as the CTV for the risk characterization for terrestrial effects.

3.1.1.2 Aquatic

Data on aquatic toxicity are available for a variety of microorganisms, algae, invertebrates and fish (Section 2.4.1.2). Identified sensitive endpoints include population growth of protozoans (Von Burg and Stout, 1991), the reduction of growth of algae (Stratton, 1987), immobilization of crustaceans (Von Burg and Stout, 1991) and mortality in fish (Brooke *et al.*, 1984).

Algae are primary producers in aquatic systems, forming the base of the aquatic food chain, while zooplankton, including protozoans and crustaceans, are key consumers and are themselves consumed by many species of invertebrates and vertebrates. Fish are consumers in aquatic communities and are themselves eaten by piscivorous fish, birds and mammals.

Therefore, although limited, the available studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to aquatic biota. The single most sensitive response for all of these endpoints is considered as the CTV for the risk characterization for aquatic effects.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial organisms

Environmental exposure to acetaldehyde in air is expected to be greatest near sites of continuous release or formation of acetaldehyde, namely in urban centres and near industrial facilities releasing acetaldehyde. Extensive recent data for concentrations in air are available for urban, suburban and rural sites in Canada, and data covering a full year are available for the single largest industrial emitter of acetaldehyde.

The highest reported concentration of acetaldehyde in air in Canada is a monthly average concentration of 1150 µg/m^3, obtained at one sampling station at an industrial site in July 1996 (Environment Canada, 1997c). The overall mean concentration for all stations at the industrial site was 199 µg/m^3 over the year, with a median of 94 µg/m^3. By comparison, the single highest 24-hour concentration for urban air was 16.5 µg/m^3, while the highest one-month to one-year mean in a city was 3.35 µg/m^3 (Dann, 1998). The concentration of 1150 µg/m^3 will be used as the EEV in the hyperconservative analysis for terrestrial organisms.

For the exposure of terrestrial organisms to acetaldehyde in air, the CTV is 540 mg/m^3, based on a five-day exposure concentration causing a 95% reduction in fruit decay by the fungus *Penicillium italicum* (Yuen *et al.*, 1995). This LOEL was the most sensitive effect value retained from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial bacteria, fungi, plants, invertebrates and mammals. While a slightly lower LOEL of 437 mg/m^3 was identified for histopathological changes in the nasal epithelium of rats (see Section 2.4.3.3.1), the studies retained for the dose–response analyses for inhalation by mammals had a slightly higher LOEL of 720 mg/m^3 (see Section 3.3.3.1 and Table 3).

The five-day exposure for *Penicillium* can be considered as chronic exposure (covering a significant portion of the life span of the organism). However, CTVs are preferably identified for lower levels of effects, and an application factor can account for the high level of effect (95% reduction in fruit decay) associated with the LOEL in this study. Thus, for the hyperconservative analysis, the ENEV for

terrestrial organisms is derived by dividing the CTV by a factor of 100. This factor accounts for the high level of effect associated with the LOEL and uncertainty surrounding the conversion of the chronic LOEL to a chronic no-effect value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 5.4 mg/m^3 (5400 µg/m^3).

The hyperconservative quotient is calculated by dividing the EEV of 1150 µg/m^3 by the ENEV for *P. italicum*, as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{1150\ \mu g/m^3}{5400\ \mu g/m^3}$$

$$= 0.21$$

Since the hyperconservative quotient is less than one, it is unlikely that acetaldehyde causes adverse effects on populations of terrestrial organisms in Canada.

3.1.2.2 Aquatic organisms

Environmental exposure to acetaldehyde in water is expected to be greatest near areas of high atmospheric concentrations (where some acetaldehyde can partition from air into water) and near spills or other potential point sources. Data for ambient surface water are available only for limited sampling at four drinking water treatment plants in urban areas in Ontario and Alberta and for groundwater at the site of the largest industrial emitter.

The highest concentration of acetaldehyde reported in surface water is 114 µg/L, obtained for a sample collected from the Detroit River near the Windsor pilot plant in December 1993 (Anderson *et al.*, 1994). While no data are available for concentrations in surface water near point sources, acetaldehyde was measured in groundwater at concentrations greater than the detection limit at four of 13 sampling stations at the industrial site; the highest concentration was 1300 µg/L (Environment Canada, 1997c). This value will be used as the EEV in the hyperconservative analysis for aquatic organisms, based on the conservative assumption that the groundwater could recharge directly to surface water at its full concentration.

For exposure of aquatic biota to acetaldehyde in water, the CTV is 30.8 mg/L, based on a 96-hour LC_{50} for the fathead minnow (Brooke *et al.*, 1984). This was the most sensitive value identified from a moderate data set composed of acute toxicity studies conducted on at least 12 species of aquatic microorganisms, algae, invertebrates and fish.

For a hyperconservative analysis, the ENEV is derived by dividing this CTV by a factor of 100. This factor accounts for the uncertainty surrounding the extrapolation from an acute LC_{50} to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. The resulting ENEV is 0.308 mg/L (308 µg/L).

The hyperconservative quotient is calculated by dividing the EEV of 1300 µg/L by the ENEV, as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{1300\ \mu g/L}{308\ \mu g/L}$$

$$= 4.22$$

Since the hyperconservative quotient is more than one, it is necessary to consider further the likelihood of biota being exposed to such concentrations in Canada.

It is highly unlikely that the groundwater at a single sampling station would recharge directly to surface water. A more realistic

representation of groundwater quality at the industrial site could be achieved using the median or mean concentration in groundwater at the 13 sampling stations. The median would be <50 µg/L (detection limit), while the mean could be calculated as being between 232 µg/L and 266 µg/L (assigning values of 0 µg/L or 50 µg/L, respectively, to samples reported as being below the detection limit). The highest of these values is 266 µg/L and can be used as a conservative estimate of possible concentrations in the event of surface recharge.

The conservative quotient is calculated by dividing the EEV of 266 µg/L by the ENEV, as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{266\ \mu g/L}{308\ \mu g/L}$$

$$= 0.86$$

Alternatively, a conservative quotient can be calculated using the single highest concentration measured in ambient water (114 µg/L obtained from the Detroit River). The conservative quotient calculated by dividing the EEV of 114 µg/L by the ENEV is:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{114\ \mu g/L}{308\ \mu g/L}$$

$$= 0.37$$

Since these two conservative quotients are less than one, it is unlikely that acetaldehyde causes chronic adverse effects on populations of aquatic organisms in Canada.

A summary of the critical values for the environmental risk analysis of acetaldehyde is presented in Table 2.

3.1.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment. Regarding effects of acetaldehyde on terrestrial and aquatic organisms, there is uncertainty concerning the extrapolation from available toxicity data to potential ecosystem effects. While the toxicity data set included studies on organisms from a variety of ecological niches and taxa, there are relatively few good chronic studies available. To account for these uncertainties, application factors were used in the environmental risk analysis to derive ENEVs.

Regarding environmental exposure, there could be concentrations of acetaldehyde in Canada that are higher than those identified and used in this assessment.

Few data are available for concentrations of acetaldehyde in air near point sources. However, the measurements used in this assessment are considered acceptable because they were selected from an extensive set of recent air monitoring data of urban and other sites and from data at the industrial facility with the highest reported import, production, use and release of acetaldehyde in Canada. These sites can also be associated with high concentrations of volatile organic compounds associated with secondary formation of acetaldehyde. Thus, available data on atmospheric concentrations are considered representative of the highest concentrations likely to be encountered in air in Canada.

Only limited data are available for concentrations of acetaldehyde in water, although concentrations are expected to be low because of the limited releases to this medium that have been identified and the limited partitioning of acetaldehyde from air into water. The available data on concentrations in groundwater are from the site of the largest emitter of acetaldehyde, and it can reasonably be expected that concentrations are the highest likely to occur in Canada. Since data are not available regarding surface recharge of the contaminated groundwater, the assessment

TABLE 2 Summary of the hyperconservative and conservative environmental risk analysis

Exposure scenario	EEV	CTV	Application factor	ENEV	Quotient (EEV/ENEV)
Terrestrial organisms: highest concentration in air at industrial site	1150 µg/m^3	540 000 µg/m^3	100	5400 µg/m^3	0.21
Aquatic organisms: highest concentration in groundwater at industrial site	1300 µg/L	30 800 µg/L	100	308 µg/L	4.22
Aquatic organisms: mean concentration in groundwater at industrial site	266 µg/L	30 800 µg/L	100	308 µg/L	0.86
Aquatic organisms: highest concentration in surface water	114 µg/L	30 800 µg/L	100	308 µg/L	0.37

very conservatively assumed that recharge occurred at concentrations equivalent to those measured in the groundwater.

Despite some data gaps regarding the environmental effects and exposure of acetaldehyde, the data available at this time are considered adequate for making a conclusion on the environmental risk of acetaldehyde in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

Acetaldehyde does not deplete stratospheric ozone and its potential for climate change is negligible. The photolysis of acetaldehyde leads to the direct formation of radicals that are active in the formation of ground-level ozone (Carter *et al.*, 1995). It is more reactive (POCP of 121) than compounds such as ethene that are recognized as important in the formation of ground-level ozone. Given its reactivity and concentrations measured in air in Canada, acetaldehyde represented approximately 3.4% of the total volatile organic carbon reactivity, ranking it 8th among non-methane hydrocarbons and carbonyl compounds contributing to the formation of ground-level ozone (Dann and Summers, 1997). Acetaldehyde, along with other reactive volatile organic chemicals, may therefore be important in the photochemical formation of ground-level ozone in urban areas. It is therefore concluded that acetaldehyde is considered "toxic" as defined in CEPA Paragraph 64(b).

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Point estimates of total daily intakes of acetaldehyde by six age groups of the general population of Canada were developed primarily to determine the relative contributions from various media. These estimates indicate that the daily intake of acetaldehyde via inhalation is consistently less than that by ingestion, although it should be noted that no data on concentrations of acetaldehyde in foodstuffs in Canada were identified. Also, though intermediary metabolism and ingestion of alcoholic beverages contribute to levels of acetaldehyde in the body, critical effects of exposure to exogenous acetaldehyde, based on studies in animals, occur at the site of first contact

(i.e., the respiratory tract following inhalation and the gastrointestinal tract following ingestion). For this reason, effects of exposure by different routes are addressed separately. However, available toxicological data are inadequate to serve as a basis for development of a measure of dose–response for critical site of contact effects following ingestion. Probabilistic estimates of 24-hour time-weighted concentrations of acetaldehyde in the air to which Canadians are exposed have been developed, therefore, for comparison with the Tolerable Concentration (TC) in this medium. This approach is also supported on the basis that anthropogenic emissions of acetaldehyde are released principally to air, where it degrades, with little movement into other media.

In this exposure scenario, the general population is considered to be exposed to acetaldehyde in air for a full 24 hours per day. The exposure is assumed to occur by inhalation of ambient (outdoor) air and indoor air. When indoors, it is assumed that the general population is exposed to acetaldehyde concentrations similar to those in the indoor air of their homes, as there are insufficient data concerning concentrations in other indoor environments.

This exposure scenario requires consideration of the proportion of the 24-hour day that is spent indoors versus the proportion spent outdoors. A mean time spent outdoors of three hours is assumed based on point estimates of time spent indoors and outdoors (Environmental Health Directorate, 1997). The distribution of the time spent outdoors is arbitrarily assumed to be normal in shape with an arithmetic standard deviation of one hour. The time spent indoors is calculated as 24 hours minus the time spent outdoors.

To represent the concentrations of acetaldehyde in ambient air, the distribution of the 24-hour concentrations from the National Air Pollution Surveillance (NAPS) Program (Dann, 1998) was selected, in which individual data were available for 2805 samples of ambient air collected (between 1989 and 1997) at 14 rural, urban and suburban locations in six provinces (New Brunswick, Nova Scotia, Quebec, Ontario, Manitoba and British Columbia). Acetaldehyde was detected in 99.8% of samples (detection limit 0.1 μg/m^3) in this data set.

For concentrations of acetaldehyde in indoor air, the (limited) results of the only identified relevant investigation in Canada, the Windsor Air Quality Study (Bell *et al.*, 1993; OMEE, 1994a,b; Bell, 1995, 1996, 1997), were selected. The concentrations of acetaldehyde in 47 samples of indoor air from homes in Windsor and Hamilton, Ontario, were measured between 1991 and 1993. Acetaldehyde was detected in all of the samples (detection limit 0.1 μg/m^3) in this data set.

Estimates of the distribution of time-weighted 24-hour concentrations of acetaldehyde to which the general population is exposed were developed using simple random sampling with Crystal Ball™ Version 4.0 (Decisioneering, Inc., 1996) and simulations of 10 000 trials. This process was repeated for a total of five simulations to assess the reproducibility of the estimates.

Based on the assumptions underlying this scenario, one person in every two would be exposed to a 24-hour average concentration of acetaldehyde of 14 μg/m^3 (i.e., median concentration) or greater, and one in 20 persons (i.e., 95th percentile) would be exposed to a 24-hour average concentration of at least 52 μg acetaldehyde/m^3.

In addition, as described in Section 2.3.2.1, there are data on concentrations of acetaldehyde in the vicinity of industrial sources in Canada. While there is no indication of the proximity of monitoring sites to residential areas, the average monthly concentrations at four monitoring stations at a chemical plant in Edmonton, Alberta, considered to be the largest emitter in Canada throughout 1996, ranged from below the detection limit of 1.8 μg/m^3 at some stations up to a maximum of 1150 μg/m^3 at one station in July. The overall mean concentration

for all stations was 199 µg/m^3, with a median of 94 µg/m^3 (Environment Canada, 1996a, 1997b,c).

3.3.2 Hazard characterization

3.3.2.1 Effects in humans

Data relevant to the assessment of the potential adverse effects of exposure to acetaldehyde in humans are limited primarily to irritation. Based on early clinical studies of small numbers of volunteers exposed for short periods, ocular and nasal/throat irritation have been observed at concentrations as low as 25 ppm (45 mg/m^3) and just less than 200 ppm (360 mg/m^3), respectively (Silverman *et al.*, 1946; Sim and Pattle, 1957). The only identified epidemiological study (Bittersolh, 1975) is inadequate to serve as a basis for assessment of the carcinogenicity of acetaldehyde.

Due to the limited nature of the human data, hazard characterization and dose–response analysis for acetaldehyde are based primarily on studies in animals.

3.3.2.2 Effects in experimental animals

Acetaldehyde has low acute toxicity, is irritating to the skin, eyes and upper respiratory tract, and induces sensory irritation in rodents.

The effects of acetaldehyde have been most extensively investigated following exposure by inhalation. In short- and long-term inhalation studies in rats and hamsters, the target tissue has consistently been the site of entry, with non-neoplastic and neoplastic effects occurring principally in the upper respiratory tract at lowest concentrations, without appreciable effects in other organ systems. (Systemic effects in repeated-exposure studies, generally observed at concentrations considerably higher than the lowest concentrations that induce effects in the respiratory tract, have been confined to effects on body and some organ weights, hematological parameters and some liver enzymes.) This is consistent with observations in toxicokinetic studies in rats and humans, in which the highest proportion of inhaled acetaldehyde is retained at the site of contact.

In repeated-exposure inhalation studies, species-related differences in sensitivity to acetaldehyde have been observed. Available data indicate that hamsters are less sensitive than rats, with adverse effects in the respiratory tract appearing at higher vapour concentrations. Moreover, inhalation of acetaldehyde in hamsters results in lesions in more distal airways (i.e., larynx, trachea), whereas effects in rats at the lowest exposure concentrations are confined primarily to the proximal airways (i.e., nasal cavity). At lowest concentrations, degenerative changes have been observed in the olfactory epithelium in rats and the trachea in hamsters. At higher concentrations, degenerative changes in the respiratory epithelium and larynx have been noted in both species. The proximal to distal pattern of lesions with increasing concentration observed in the inhalation studies is consistent with the reactivity and solubility of acetaldehyde.

In long-term inhalation studies, an increased incidence of tumours has been observed in rats and hamsters at concentrations that induce damage in the respiratory tract. In rats, there were concentration-related increases in adenocarcinomas of the olfactory epithelium and squamous cell carcinomas of the respiratory epithelium, with the latter being predominant and occurring at lowest concentrations (Woutersen *et al.*, 1986). In hamsters, significant increases in laryngeal carcinomas and non-significant increases in nasal carcinomas (site not specified) have been reported (Feron *et al.*, 1982).

Data for ingestion are limited to one short-term study conducted in rats in which a wide range of endpoints was examined (Til *et al.*, 1988) and one subchronic investigation in which only overt toxicity, body weight gain and hepatic effects were examined in rats (Matysiak-Budnik *et al.*, 1996), both following ingestion in drinking water. Consistent with observations for inhalation, effects were observed at the portal of entry, with

hyperkeratosis of the forestomach observed in rats (Til *et al.*, 1988).

Available data are inadequate to serve as a basis for assessment of the carcinogenicity of acetaldehyde following ingestion. Tumours were not observed in the only long-term ingestion study identified (Matysiak-Budnik *et al.*, 1996). However, this investigation was limited by small group sizes and the very limited range of endpoints examined (i.e., only histopathology in the liver examined).

Available data are inadequate to assess the potential reproductive, developmental, neurological or immunological effects of direct exposure to acetaldehyde. Based on the limited number of investigations conducted to date, however, reproductive, developmental, neurological and immunological effects have not been observed at concentrations below those that induce damage in the upper respiratory tract (Ortiz *et al.*, 1974; Kruysse *et al.*, 1975; Shiohara *et al.*, 1985; Aranyi *et al.*, 1986; Roumec *et al.*, 1988).

Acetaldehyde has induced a broad spectrum of mutagenic, clastogenic and aneugenic effects *in vitro*. Although the number of relevant studies is limited, there is also evidence that acetaldehyde is genotoxic *in vivo*.

3.3.3 Dose–response analyses

3.3.3.1 Inhalation

In inhalation studies conducted in rodents, the respiratory tract has consistently been affected at lowest concentrations, with similar effects noted in the critical studies, although with some species variation in sensitivity and principal site. In identified short-term investigations, degenerative changes (including inflammation, hyperplasia, thinning and disarrangement of epithelial cells, and loss of microvilli and sensory cells) and associated functional effects were observed in the nasal olfactory epithelium in rats exposed (by inhalation) to ≥243 ppm (≥437 mg/m^3) acetaldehyde, while degenerative changes in the nasal respiratory epithelium, larynx, trachea and lungs were observed at higher concentrations (i.e., ≥1000 ppm [≥1800 mg/m^3]) (Appelman *et al.*, 1982, 1986; Saldiva *et al.*, 1985; Cassee *et al.*, 1996a). In the only subchronic inhalation study identified, in which hamsters were exposed to acetaldehyde for 13 weeks (Kruysse *et al.*, 1975), non-neoplastic lesions in the tracheal epithelium (including stratification, keratinization, inflammation, metaplasia and granulation) were observed at ≥1340 ppm (≥2412 mg/m^3) acetaldehyde (considered to be the LOAEL), while histopathological lesions in the nasal cavities, larynx, bronchi and lungs were observed only at 4560 ppm (8208 mg/m^3) acetaldehyde; the NOEL in this study was considered to be 390 ppm (702 mg/m^3) acetaldehyde (Kruysse *et al.*, 1975). In chronic inhalation studies in which rats were exposed to acetaldehyde for up to 28 months, focal basal cell hyperplasia of the nasal olfactory epithelium was observed at ≥750 ppm (≥1350 mg/m^3) acetaldehyde (considered to be the LOAEL), while non-neoplastic lesions in the nasal respiratory epithelium (squamous metaplasia, papillomatous hyperplasia, and focal or pseudoepitheliomatous hyperplasia) and larynx (squamous metaplasia and hyperplasia) were observed at concentrations ≥1500 ppm (≥2700 mg/m^3) acetaldehyde (Woutersen *et al.*, 1984, 1986; Feron *et al.*, 1985; Woutersen and Feron, 1987). Similarly, non-neoplastic lesions in the nasal epithelia, larynx and trachea have been observed in hamsters exposed by inhalation to ≥1500 ppm (≥2700 mg/m^3) acetaldehyde for 52 weeks (Feron, 1979; Feron *et al.*, 1982).

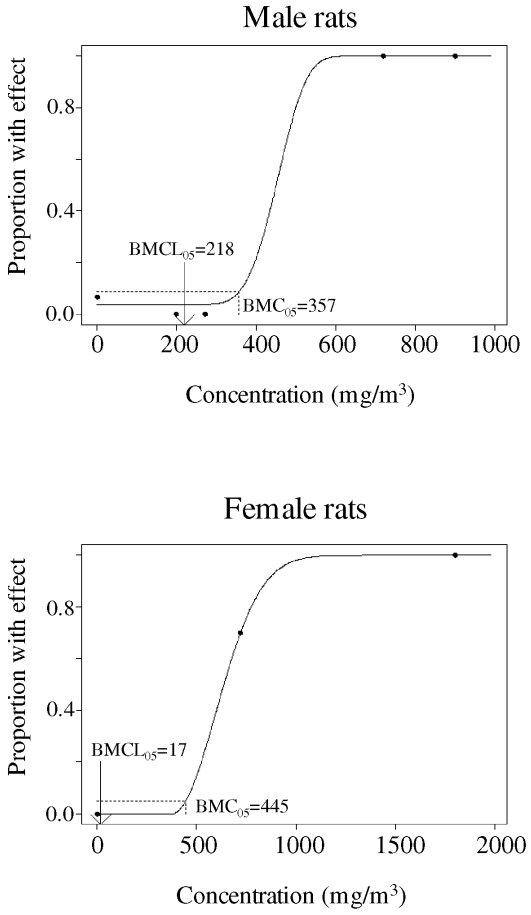
A tolerable concentration (TC) for acetaldehyde has been derived on the basis of a benchmark concentration (BMC) for non-neoplastic effects in the respiratory tract of rats, the most sensitive species, divided by an uncertainty factor. This BMC is compared with Tumorigenic Concentrations (TC_{05}s, the concentrations associated with a 5% increase in the incidence of relevant tumours) in rats. Despite differences in the anatomy and physiology of the respiratory tract in rats and humans, respiratory tract defence mechanisms are similar. Thus, it is reasonable to assume that the response of the human respiratory

tract mucosa to acetaldehyde will be qualitatively similar to that of experimental species, although the likely site of development of lesions may vary due to oro-nasal breathing patterns in humans, which result in greater potential to deliver acetaldehyde to the lower respiratory tract.

The studies that provide best characterization of concentration–response for the critical effects in the most sensitive species (i.e., rats) are the short-term studies of Appelman *et al.* (1982, 1986). Therefore, a TC has been developed on the basis of BMCs for degeneration in the nasal olfactory epithelium of Wistar rats exposed to acetaldehyde (by inhalation) for four weeks, using combined data from the critical studies for characterization of concentration–response mentioned above (Appelman *et al.*, 1982, 1986). The value is also compared with that which might be derived based on the NOEL in rats (Appelman *et al.*, 1986).

For many types of effects, studies of short duration are not preferred as the basis for development of a TC. Although the data were derived from short-term studies, the incidence of degenerative changes in the olfactory epithelium was not dissimilar to that observed in the same strain of rats in the long-term carcinogenesis bioassay at similar concentrations, conducted by Woutersen *et al.* (1986). Although group sizes were larger in the long-term bioassay, concentration–response for these lesions was not well characterized because of the small number of dose groups exposed to higher concentrations compared with the short-term study and early mortality among animals at the highest concentration. Indeed, data in the Woutersen *et al.* (1986) study are insufficient to serve as a basis for development of a meaningful BMC for acetaldehyde, even simply for purposes of comparison. Therefore, BMCs for non-neoplastic effects have been calculated for degeneration in the nasal olfactory epithelium of Wistar rats exposed (by inhalation) to acetaldehyde for four weeks, based on data from the critical studies by Appelman *et al.* (1982, 1986). The critical data are presented in Table 3. Using the THRESH program (Howe, 1995), the BMC_{05} (the concentration associated with a 5% increase in the incidence of nasal olfactory epithelial lesions) for male Wistar rats is 357 mg/m^3; the lower 95% confidence limit for this value ($BMCL_{05}$) is 218 mg/m^3. For female Wistar rats, the BMC_{05} and $BMCL_{05}$ are 445 mg/m^3 and 17 mg/m^3,

FIGURE 1 $BMCL_{05}$s for effects in the nasal olfactory epithelium (without correction for continuous exposure)



respectively (Figure 1). A TC has been developed on the basis of the $BMCL_{05}$ for non-neoplastic lesions in the nasal olfactory epithelium of rats as follows:

$$TC = \frac{218\ mg/m^3}{100} \times \frac{6}{24} \times \frac{5}{7}$$

$$= 390\ \mu g/m^3$$

TABLE 3 Benchmark concentrations (BMC_{05}s and $BMCL_{05}$s) for acetaldehyde based on the incidence of degenerative changes in the nasal olfactory epithelium of Wistar rats (Appelman *et al.*, 1982, 1986)

Concentration, mg/m³ (ppm)	Incidence of degenerative changes	Benchmark concentration (without adjustment for continuous exposure)	Parameter estimates
Males			
0	2/30		
198 (110)	0/10	5% concentration: 357 mg/m³	Chi-square goodness of fit: 1.3×10^{-8}
270 (150)	0/10		
720 (400)	9/10	95% confidence limit: 218 mg/m³	Degrees of freedom: 0
900 (500)	10/10		
1800 (1000)	10/10		p-value: 1.00
3960 (2200)	9/9		
9000 (5000)	10/10		
Females			
0	0/10		
198 (110)	NA[1]	5% concentration: 445 mg/m³	Chi-square goodness of fit: 1.3×10^{-8}
270 (150)	NA		
720 (400)	7/10	95% confidence limit: 17 mg/m³	Degrees of freedom: 0
900 (500)	NA		
1800 (1000)	10/10		p-value: 1.00
3960 (2200)	10/10		
9000 (5000)	10/10		

[1] NA = not available.

where:

- 218 mg/m³ is the 95% lower confidence limit of the concentration estimated to be associated with a 5% increase in non-neoplastic lesions in the nasal olfactory epithelium of male Wistar rats (the most sensitive sex and that for which the data set is most robust) exposed by inhalation to acetaldehyde for four weeks (Appelman *et al.*, 1982, 1986);
- 6/24 and 5/7 are the adjustments of intermittent (six hours per day for five days per week) to continuous exposure. There are no data that provide direct evidence and few related data to serve as a basis for whether or not such an adjustment is appropriate for acetaldehyde. In short-term studies in the same strain of rats, effects seemed slightly more severe following exposure for eight hours per day (Saldiva *et al.*, 1985) versus six hours per day for four weeks (Appelman *et al.*, 1986). Interruption of daily exposure by 1.5-hour exposure-free periods or by the superimposition of eight five-minute peak exposure periods did not appreciably influence the cytotoxic potency of acetaldehyde in short-term studies in rats compared with uninterrupted exposure to a fixed concentration (Appelman *et al.*, 1986); and,
- 100 is the uncertainty factor (×10 for interspecies variation, ×10 for intraspecies variation). Available data are inadequate to further address toxicokinetic and toxicodynamic aspects of components of uncertainty with data-derived values.

The value for interspecies variation is considered to be conservative since, due to greater penetration of inhaled gases into the lower airways of rodents versus humans, the compound is distributed over a larger surface area for the latter; available data are inadequate, however, to quantitatively account for this variation. No additional quantitative element has been included to address limitations of the database such as lack of adequate developmental or reproductive studies by a relevant route of exposure, due to the fact that a TC that is based on critical effects at the site of entry is likely to be protective for systemic effects. Also, in view of the fact that there is no indication that severity of the critical effects increases with duration of exposure, an additional quantitative element to address the use of a shorter-term study as the basis for the TC is considered inappropriate.

This TC is similar to that derived from the NOEL for irritation in the most sensitive species (Wistar rats), identified in the short-term study of Appelman *et al.* (1986). Based on the NOEL of 270 mg/m^3 (150 ppm), with adjustment for intermittent to continuous exposure ($6/24 \times 5/7$) and an uncertainty factor of 100 ($\times$10 for interspecies variation, $\times$10 for intraspecies variation), the resulting value is 490 µg/m^3.

On the basis of limited available data in human studies, the TCs derived above (390 and 490 µg/m^3) are two orders of magnitude lower than the threshold for sensory irritation (i.e., 45 mg/m^3 [25 ppm]) (Silverman *et al.*, 1946).

In view of the genotoxicity of acetaldehyde and relative lack of information concerning the mechanism of induction of tumours for this substance, an estimate of the carcinogenic potency (TC_{05}) has also been derived, based on the increased incidence of nasal tumours (squamous cell carcinoma, adenocarcinoma and carcinoma *in situ*) in male and female Wistar rats exposed (by inhalation) to acetaldehyde for up to 28 months (Woutersen *et al.*, 1986). This was the only study in which carcinogenicity was investigated in the most sensitive species (i.e., rats). It was also considered the most appropriate for quantitative assessment of the TC_{05} of acetaldehyde, owing to the larger size of the study group (n = 55 compared with 18–35 in hamsters), the longer duration of the exposure period (28 months versus 12 months in hamsters) and the larger number of exposure concentrations (three concentrations and controls).

The critical data upon which the TC_{05}s are based are presented in Table 4. The highest concentration group was not included in the derivation, since exposure levels were decreased gradually from 5400 to 1800 mg/m^3 due to high mortality. The TC_{05}s and lower 95% confidence limits (TCL_{05}s) (presented in Table 4, Figures 2 and 3) were calculated using a multistage model, with adjustment for intermittent to continuous exposure ($6/24 \times 5/7$). Inclusion of an f^2 term to account for the fact that tumours occur more frequently later in life (where f is the length of the experiment divided by the standard lifetime) was unnecessary, since animals in the critical study were exposed for up to 28 months and killed at weeks 120–122. Values have not been adjusted by the ratio of inhalation to body weight, since tumours were restricted to the site of exposure. With adjustment for intermittent to continuous exposure, the resultant TC_{05} for nasal adenocarcinomas and squamous cell carcinomas in the most sensitive sex (males) is 86 mg/m^3, while the TCL_{05} is 28 mg/m^3. These values are approximately twofold higher than and the same as the TC_{05} and TCL_{05}, respectively, for adenocarcinomas alone and three- and sixfold less than the TC_{05} and TCL_{05}, respectively, for squamous cell carcinomas alone.

3.3.3.2 Ingestion

Available data are inadequate to provide quantitative guidance concerning the potential risks associated with ingestion of acetaldehyde. Data are limited to one short-term study in rats in which a wide range of endpoints was examined (Til *et al.*, 1988) and one subchronic investigation

TABLE 4 Tumorigenic concentrations (TC_{05}s and TCL_{05}s) for acetaldehyde based on the incidence of tumours in the nasal cavity of Wistar rats (Woutersen *et al.*, 1986)

Tumour type	Concentration, mg/m³ (ppm) [1]	Tumour incidence [2,3]	TC_{05} (TCL_{05}) (without correction for continuous exposure)	TC_{05} (TCL_{05}) (with correction for continuous exposure) [4]	Parameter estimates
Males					
Squamous cell carcinoma	0	1/49	1508 (906)	271 (163)	Chi-square = 1.62
	1350 (750)	1/52			Degrees of freedom = 1
	2700 (1500)	10/53*			p-value = 0.20
	5400/1800 (3000/1000)	15/49***			
Adenocarcinoma	0	0/49	225 (135)	41 (24)	Chi-square = 0.00
	1350 (750)	16/52***			Degrees of freedom = 1
	2700 (1500)	31/53***			p-value = 1.00
	5400/1800 (3000/1000)	21/49***			
Carcinoma *in situ* [5]	0	0/49	– (–)	– (–)	
	1350 (750)	0/52			
	2700 (1500)	0/53			
	5400/1800 (3000/1000)	1/49			
Combined	0	1/49	478 (157)	86 (28)	Chi-square = 0.00
	1350 (750)	17/52			Degrees of freedom = 0
	2700 (1500)	41/53			p-value = –
	5400/1800 (3000/1000)	–			
Females					
Squamous cell carcinoma	0	0/50	2161 (1374)	389 (247)	Chi-square = 1.20
	1350 (750)	0/48			Degrees of freedom = 2
	2700 (1500)	5/53			p-value = 0.55
	5400/1800 (3000/1000)	17/53***			
Adenocarcinoma	0	0/50	731 (365)	132 (66)	Chi-square = 0.58
	1350 (750)	6/48*			Degrees of freedom = 2
	2700 (1500)	28/53***			p-value = 0.75
	5400/1800 (3000/1000)	21/53***			
Carcinoma *in situ*	0	0/50	2813 (2700)	506 (486)	Chi-square = 0.70
	1350 (750)	0/48			Degrees of freedom = 2
	2700 (1500)	3/53			p-value = 0.70
	5400/1800 (3000/1000)	5/53			
Combined	0	0/50	621 (400)	112 (72)	Chi-square = 3.09
	1350 (750)	6/48			Degrees of freedom = 2
	2700 (1500)	36/53			p-value = 0.21
	5400/1800 (3000/1000)	–			

[1] The highest concentration was gradually reduced from 5400 mg/m³ during the first 20 weeks to 1800 mg/m³ in week 52; the time-weighted average concentration for 28 months of exposure was calculated by the Task Group to be 2760 mg/m³.

[2] Total number of tumour-bearing animals not specified.

[3] Significance: Fisher Exact Test, * $p < 0.05$, *** $p < 0.001$.

[4] The TC_{05}s were multiplied by (6 hours per day/24 hours per day) × (5 days per week/7 days per week) to adjust for intermittent to continuous exposure.

[5] The Tumorigenic Concentration for carcinoma *in situ* in male rats cannot be calculated since the highest concentration group was eliminated and all three remaining groups had zero response.

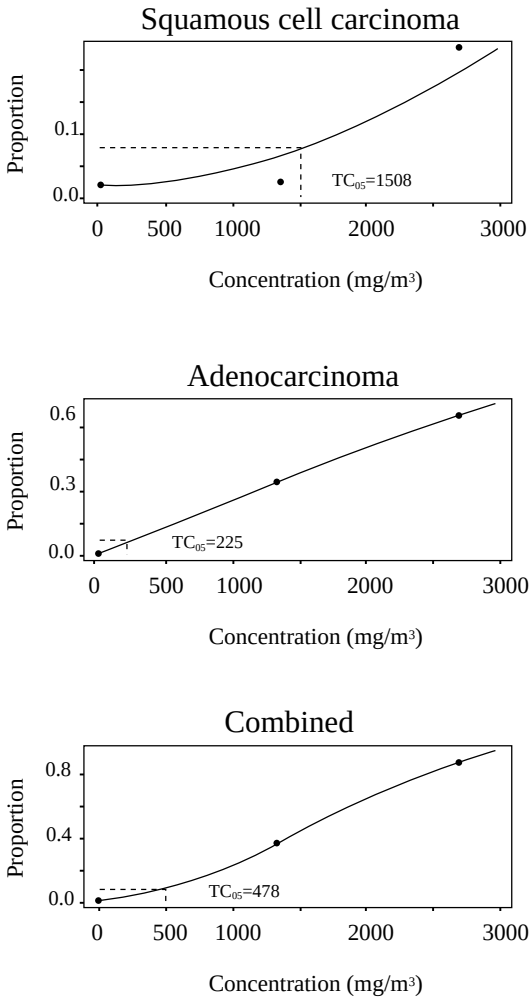
in which only a very limited range of endpoints was considered (Matysiak-Budnik *et al.*, 1996), both via ingestion in drinking water. In the latter study, non-neoplastic changes in the liver (microvesicular fatty degeneration, fatty accumulation and foci of inflammatory cells) were observed at 500 mg acetaldehyde/kg-bw per day (considered to be the LOAEL), while no effects were observed at 120 mg acetaldehyde/kg-bw per day (considered to be the NOEL). Effect levels were similar in the short-term study conducted in the same strain of rats, in which the LOAEL and NOEL were 675 and 125 mg acetaldehyde/kg-bw per day, respectively, based on focal hyperkeratosis of the forestomach and increased renal weight (Til *et al.*, 1988). Interestingly, results of the short-term study contrast somewhat with those of the longer-term study of Matysiak-Budnik *et al.* (1996), since hepatic effects were not observed at 675 mg/kg-bw per day in the former.

3.3.4 Human health risk characterization

While the cytotoxicity of acetaldehyde along with the induction of DNA–protein cross-links are likely crucial determinants in the carcinogenicity of this compound at high concentrations, there is a relative lack of information concerning their potential roles in tumour induction. Indeed, available data are inadequate to quantitatively take both of these likely endpoints into account in development of measures of dose–response relevant to the general population. Moreover, based on limited available data, the pattern of DNA–protein cross-linking, cytotoxicity and proliferative response induced by acetaldehyde varies from that of other aldehydes such as formaldehyde.

For compounds such as acetaldehyde, where data are insufficient to quantitatively adequately assimilate the information on likely intermediate endpoints in development of measures of dose–response, and in view of the genotoxicity of the compound both *in vitro* and *in vivo*, estimates of exposure are compared with quantitative estimates of cancer potency (Exposure Potency Index)

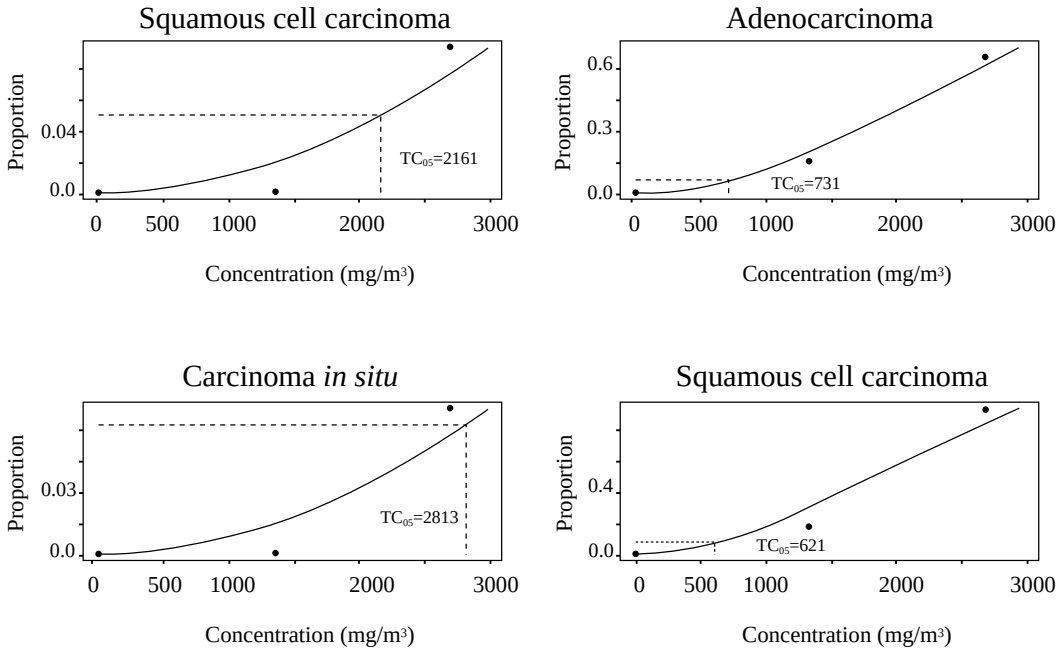
FIGURE 2 TC_{05}s for male Wistar rats (without correction for continuous exposure)



to characterize risk and provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) under CEPA.

However, in view of the likely critical role of cytotoxicity as well as genotoxicity in the carcinogenicity of this compound, measures of cancer potency are compared with those for non-cancer effects. Exposure of the general population is also compared with the TC for non-neoplastic effects.

FIGURE 3 TC_{05}s for female Wistar rats (without correction for continuous exposure)



The lowest TC_{05} was 86 mg/m³ for nasal adenocarcinomas and squamous cell carcinomas in the male rat; the lower 95% confidence limit was 28 mg/m³. Based upon probabilistic estimates of 24-hour time-weighted concentrations of acetaldehyde in air in Canada, median and and 95th percentiles are estimated to be 13.5 and 51.7 µg/m³, respectively. These estimated concentrations are three orders of magnitude less than the TC_{05} and TCL_{05}.[2] On this basis, priority for investigation of options to reduce exposure is considered moderate.

It is of some interest that the measure of carcinogenic potency (TC_{05} of 86 mg/m³) is similar to but slightly less than a comparable value for non-cancer effects (i.e., $BMCL_{05}$ of 218 mg/m³).

The median and 95th percentile estimates of the 24-hour time-weighted concentrations of acetaldehyde in air in Canada discussed above are one order of magnitude less than the TC for acetaldehyde for non-neoplastic effects.

While there is no indication of the proximity of monitoring sites to residential areas, average monthly concentrations at four monitoring stations at a chemical plant in Edmonton, Alberta, considered to be the largest emitter in Canada, are 1–4 orders of magnitude less than the TC_{05} and TCL_{05}. Based upon the median concentration of acetaldehyde (i.e., 94 µg/m³) determined at these monitoring stations, concentrations of acetaldehyde in ambient air near industrial point sources are three orders of magnitude less than the TC_{05} and TCL_{05}.[3] On this basis, priority for investigation of options to reduce exposure is considered to be high. In addition, these values approach and exceed the TC based on non-neoplastic effects.

[2] For comparison with Exposure Potency Indexes for PSL 1 compounds where exposure was expressed as a proportion of potency, the relevant value is 1.5×10^{-4}.

[3] For comparison with Exposure Potency Indexes for PSL 1 compounds where exposure was expressed as a proportion of potency, the relevant value is 1.1×10^{-3}.

3.3.5 Uncertainties and degree of confidence in human health risk characterization

There are a number of uncertainties associated with the human health risk characterization of acetaldehyde.

Uncertainty associated with data on concentrations of acetaldehyde in outdoor air from the 14 NAPS sites is judged to be low, since the analytical and sampling methodologies are among the best available for determining low concentrations of acetaldehyde in air. Moreover, all of the samples were analysed by a single specialized laboratory, the effects of diurnal variations were minimized by the 24-hour sampling duration, the data set is large (n = 2805) and reasonably current (i.e., 1989 to early 1997), acetaldehyde was present in concentrations greater than the limit of detection (i.e., 0.1 mg/m^3) in a high proportion of the samples (i.e., >99%) and the concentrations of acetaldehyde measured are consistent with concentrations reported for outdoor air in other Canadian and international studies. However, some uncertainty is expected, since the locations of the 14 NAPS sites were not determined by a random sampling scheme, and, at some sites, the air is sampled at elevations higher than the breathing zone. The greatest source of uncertainty in the estimates of exposure in air is attributable to lack of information concerning geographical population distribution in relation to the NAPS monitoring sites. However, samples from Canada's three major urban centres (i.e., Montréal, Quebec; Toronto, Ontario; Vancouver, B.C.) account for 49% of the NAPS samples, and samples from three other cities (i.e., Saint John, New Brunswick; Ottawa, Ontario; Windsor, Ontario) account for another 39%.

Uncertainty associated with data on concentrations of acetaldehyde in indoor air from two studies in Canada was judged to be moderate. The analytical and sampling methodologies are among the best available for determining low concentrations of acetaldehyde in air, all of the samples were analysed by a single specialized laboratory, the sampling and analytical methodologies were the same as those employed for measuring the outdoor (ambient) concentrations in the NAPS data set, the effects of diurnal variations are minimized by the 24-hour sampling duration, the studies are reasonably current (i.e., 1991–1993), acetaldehyde was detected in all of the 47 samples, and the concentrations of acetaldehyde measured are consistent with limited data reported for residential indoor air in other studies, especially those that are more recent. However, some uncertainty is introduced because this is a very small data set, the homes sampled were not selected by a random sampling scheme and often involved volunteers, homes in Windsor and Hamilton may not be representative of all homes in Canada, and indoor locations other than home (e.g., work sites, public places, vehicle cabins) are not included. Additional uncertainty is introduced in the probabilistic assessment of intakes, since the actual distribution of concentrations in indoor air is represented by an assumed lognormal distribution; however, this is expected to make a minor contribution to the overall uncertainty associated with estimates of intake of acetaldehyde by the inhalation route.

Uncertainty concerning the time spent indoors by Canadians is judged to be low, since the estimate is based on the most current Canadian data, a random sampling scheme was used to obtain the time–activity data, and analysis of the data involved population weighting; however, the same mean time spent outdoors is assumed for Canadians of all age groups and in all regions of the country, a normal distribution is assumed for the hours per day spent outdoors, and the variance of the assumed normal distribution is also assumed (i.e., standard deviation of one).

There is a high degree of uncertainty concerning the content of acetaldehyde in food currently consumed by Canadians. Data on concentrations in this medium are restricted to a very small number of food samples collected in other countries, and details concerning the numbers of samples analysed and the locations and dates of sample acquisition are lacking. Based

on the known widespread natural occurrence of acetaldehyde in a variety of foods, estimates based on the limited reported data are likely less than the true intake. However, acetaldehyde is not expected to partition into the fatty compartments of foods, and fugacity modelling does not predict significant bioconcentration.

There is a moderate degree of certainty that consumption of drinking water does not contribute significantly to the daily intake of acetaldehyde by Canadians, based on sensitive measurements of Canadian water from a small number of treatment plants in Alberta and Ontario. However, these data are lacking in terms of numbers of samples collected and the frequency of detection of acetaldehyde. Nevertheless, the data are consistent with the limited data on concentrations of acetaldehyde in drinking water in other countries.

Although there are data on concentrations of acetaldehyde in the vicinity of the largest industrial emitter in Canada, similar information is not available for other industrial sources, nor is the proximity of measured values to residential areas for the largest emitter known.

The degree of confidence in the database on toxicity that serves as the basis for the development of the tolerable concentration (TC) for inhalation is moderate, although there is a relatively high degree of confidence that critical effects occur at the initial site of exposure. Available data are considered inadequate to characterize dose–response for adverse effects following ingestion, and further study in this area is desirable. Studies in humans are extremely limited and, for inhalation, are restricted primarily to early investigations of subjective sensory irritation; there are no studies in which histopathological effects in the upper respiratory tract of humans exposed to acetaldehyde have been examined for comparison with the results of investigations in animals.

By far the greatest source of uncertainty in the health assessment, however, is the relative lack of information concerning the potential roles of cytotoxicity, proliferation and induction of DNA–protein cross-links in the carcinogenicity of this compound at high concentrations and the resulting inability to take both the genetic and tissue damage endpoints quantitatively into account in development of measures of dose–response relevant to the general population. Additional investigation in this area is warranted. However, it seems unlikely that this additional work will impact significantly on the priority for investigation of options to reduce exposure indicated here, which is only moderate.

The TC_{05} and TCL_{05} for the combined incidence of adenocarcinomas and squamous cell carcinomas developed in this assessment are approximately twofold higher than and the same as the TC_{05} and TCL_{05}, respectively, for adenocarcinomas alone and three- and sixfold less than the TC_{05} and TCL_{05}, respectively, for squamous cell carcinomas alone.

The measure of carcinogenic potency (TC_{05}) developed in this assessment was approximately 2.5 times less than a comparable value ($BMCL_{05}$) for non-cancer effects. While the midpoint estimate for a BMC for non-neoplastic effects developed on the basis of the less robust data in female rats was greater than that in males (basis of the BMC_{05} in this assessment), the lower 95% confidence limit was 13-fold less than the corresponding value for males. The lower 95% confidence limits for both the carcinogenic potency (TC_{05}) and measure of dose–response for non-cancer effects (BMC_{05}) developed in this assessment were at most threefold less than the midpoint estimates.

3.4 Conclusions

CEPA 1999 64(a): Based on available data, it has been concluded that acetaldehyde is not entering the environment in a quantity or concentration or under conditions that have or may

have an immediate or long-term harmful effect on the environment or its biological diversity. Therefore, acetaldehyde is not considered to be "toxic" as defined in Paragraph 64(a) of CEPA 1999.

CEPA 1999 64(b): Based on available data, it has been concluded that acetaldehyde is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, acetaldehyde is considered to be "toxic" as defined in Paragraph 64(b) of CEPA 1999.

CEPA 1999 64(c): Although other factors may also play a role, there is a genetic component of the induction of tumours by inhalation of acetaldehyde. On this basis, acetaldehyde is considered to be "toxic" as defined in Paragraph 64(c) of CEPA 1999. For compounds where induction of cancer through direct interaction with genetic material cannot be ruled out, this approach is consistent with the objective that exposure be reduced wherever possible and obviates the need to establish an arbitrary "*de minimis*" level of risk for the determination of "toxic" under CEPA 1999. However, based on this approach and estimates of population exposure, the priority for investigation of options to reduce exposure for the general population in the ambient environment is considered to be moderate only, but high in the vicinity of an industrial point source.

Overall conclusion: Based on critical assessment of relevant information, acetaldehyde is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Acetaldehyde may be important in the photochemical formation of ground-level ozone along with other reactive volatile organic chemicals. It is recommended that key sources of acetaldehyde be addressed, therefore, as part of management plans for volatile organic chemicals that contribute to the formation of ground-level ozone.

Based on the adopted approach to the assessment of the carcinogenicity of acetaldehyde and estimates of population exposure, the priority for investigation of options to reduce exposure in the general population in the ambient environment is considered to be moderate only. In general, therefore, investigation of options to reduce exposure in the context of CEPA is not considered a high priority and should be undertaken only if deemed appropriate in the context of other likely (higher) priorities for other PSL compounds, although additional work in the vicinity of industrial sources and on indoor air may be warranted.

Additional monitoring in residential areas in the vicinity of industrial sources is recommended, based on data collected in the vicinity of the largest emitter in Canada, which indicates that the priority for options to reduce exposure based on carcinogenic potency is high and the tolerable concentration for non-neoplastic effects is exceeded.

Concentrations of acetaldehyde in indoor air are consistently higher (by a factor of approximately 10-fold) than levels in ambient air. Available data are inadequate to determine the relative contribution of identified sources, such as consumer products, cigarette smoke, combustion appliances, building materials, cooking and infiltration of vehicle exhaust, although cigarette smoke appears to be important in this context. Identification of sources may be an area that deserves prioritization for further investigation.

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APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether acetaldehyde is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches conducted between January and May 1996 of the following databases: Aqualine (Water Research Centre, Buckinghamshire; 1990–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio; 1990–1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1990–1992, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996).

A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997d). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data on acetaldehyde that were available to them if they met the trigger quantity of 1000 kg acetaldehyde per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of acetaldehyde. Data obtained after January 1999 were not considered in this assessment unless they were critical data received during the 60-day public review of the report (August 14 to October 13, 1999).

Health assessment

Data relevant to the assessment of the potential risks of acetaldehyde to human health were identified through evaluation of existing review documents of the U.S. Environmental Protection Agency, Environmental Criteria Assessment Office (U.S. EPA, 1987), the International Programme on Chemical Safety (IPCS, 1995), the International Agency for Research on Cancer (IARC, 1985, 1987) and the Dutch Expert

Committee on Occupational Standards (DECOS, 1993), as well as a review prepared under contract for Health Canada (1996). A survey of Canadian industries was conducted under Section 16 of CEPA, in which companies were required to supply information concerning the use, release, environmental levels and toxicological effects of acetaldehyde (Environment Canada, 1997d). To identify additional relevant exposure and toxicological data, literature searches on acetaldehyde were conducted using the strategy of searching by its name or CAS registry number in the following databases: Canadian Research Index, CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), Dialog, EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory), GENE-TOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health). Its name, registry number and major synonyms were searched in the Toxline (U.S. National Library of Medicine; 1985–1998) and Medline (U.S. National Library of Medicine; 1989–1998) databases. The CAS registry number was searched in the Toxnet (1985–1997) database. The EMBASE database (on-line version of Excerpta Medica, Elsevier Science), from 1985 to 1997, was searched using the name, registry number and major synonyms. Only relevant toxicity data acquired prior to February 1998 and exposure data acquired prior to April 1998 were considered in the determination of whether acetaldehyde is “toxic” to human health.

Health Council of the Netherlands

Acetaldehyde

Re-evaluation of the carcinogenicity and genotoxicity

2014/28

Health Council of the Netherlands

Acetaldehyde

Re-evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Acetaldehyde*
Uw kenmerk : DGV/BMO/U-932542
Ons kenmerk : U-8234/JR/cn/246-W19
Bijlagen : 1
Datum : 13 november 2014

Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan aceetaldehyde.

Dit advies is een herevaluatie van een eerder door de Gezondheidsraad uitgebracht advies voor een classificatie als kankerverwekkende stof. De raad is gevraagd om deze herevaluatie omdat de voorgestelde classificatie uit het eerdere advies afwijkt van de classificatie die op dit moment in de Europese Unie wordt gehanteerd. Tevens is de raad gevraagd de stof te classificeren voor mutageniteit. De classificaties in het voorliggende advies zijn gebaseerd op het Europese classificatiesysteem.

De conclusie van het advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad. De subcommissie heeft daarbij gebruik gemaakt van commentaren die zijn ontvangen op een openbaar concept van dit advies en van de oordelen die intern zijn ingewonnen bij de Beraadsgroep Gezondheid en omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. J.L Severens,
vicevoorzitter

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Acetaldehyde

Re-evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of the
Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2014/28, The Hague, Noverber 13, 2014

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

This report can be downloaded from www.healthcouncil.nl.

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Contents

Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de Subcommissie Classificatie van carcinogene stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de Gezondheidsraad, hierna kortweg aangeduid als de commissie. Verder heeft het ministerie aan de Gezondheidsraad gevraagd om een aantal stoffen te herevalueren en daarbij ook een voorstel voor classificatie voor mutageniteit in geslachtscellen te doen. In het voorliggende advies herevalueert de commissie aceetaldehyde. Aceetaldehyde wordt vooral gebruikt als intermediair bij de synthese van diverse producten, waaronder de synthese van azijnzuur. Het wordt verder onder meer gebruikt als oplosmiddel bij de productie van diverse chemische stoffen en als conserveringsmiddel voor bijvoorbeeld vis en fruit.

De commissie concludeert dat aceetaldehyde beschouwd moet worden als kankerverwekkend voor de mens, en beveelt aan de stof in categorie 1B te classificeren.* Op basis van de beschikbare gegevens beveelt de commissie aan om aceetaldehyde te classificeren als mutageen voor geslachtscellen in categorie 1B (stof die beschouwd moet worden als een stof die erfelijke mutaties

* Zie bijlage F (carcinogeniteit) en G (mutageniteit) voor classificatiesysteem.

veroorzaakt in de geslachtscellen van mensen).* Aceetaldehyde heeft een stochastisch genotoxisch werkingsmechanisme.

* Zie Annex F (carcinogeniteit) en G (mutageniteit) voor classificatiesysteem.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on Classifying carcinogenic substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the committee. In addition, the ministry asked the Health Council to re-evaluate a series of substances, and to include in the re-evaluation a proposal for classification on germ cell mutagenicity. In this report, such a re-evaluation was made for acetaldehyde. Acetaldehyde is mainly used as intermediate, for instance in the production of acetic acid. It, furthermore, is used for instance as a solvent in the production of various chemical substances, and as a fish and fruit preservative.

The committee concludes that acetaldehyde is presumed to be carcinogenic to man, and recommends classifying the substance in category 1B.* Based on the available data, the committee furthermore recommends classifying acetaldehyde as a germ cell mutagen in category 1B (substance to be regarded as if it induces heritable mutations in the germ cells of humans).* The substance acts by a stochastic genotoxic mechanism.

* See Annex F (carcinogenicity) and G (mutagenicity) for the classification system.

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex F). In addition to classifying substances on carcinogenicity, the Health Council also assesses the genotoxic properties of the substance in question.

Recently, with reference to the EU Regulation 1272/2008 on classification, labelling and packaging of substances, the ministry of Social Affairs and Employment asked the Health Council to update the evaluations and classification on carcinogenicity of a series of substances, and to propose for these substances a classification on germ cell mutagenicity as well.

In this report, such an update was performed for acetaldehyde. An earlier evaluation of this substance was published in 2012.[1] The re-evaluation now includes a proposal for classification on germ cell mutagenicity.

The Committee is aware that acetaldehyde is an intermediate substance in the metabolism of ethanol, and that it has been suggested that acetaldehyde accounts for a great part of the toxic effects of ethanol. However, the Committee

emphasizes that this report focuses on acetaldehyde alone and does not consider combined exposure with ethanol and ethanol-related adverse health effects.

1.2 Committee and procedures

The re-evaluation is performed by the Subcommittee on Classifying carcinogenic substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the Minister can be found in Annex C.

In 2014 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report. The received comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Data

The evaluation and recommendation of the Committee is standardly based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of acetaldehyde, such an IARC-monograph is available, of which the summary and conclusion of IARC (1999) is inserted in Annex E.

Furthermore, relevant data from the European Chemicals Agency (ECHA) were retrieved and included in this advisory report.

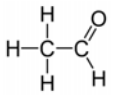
Additional data were obtained from the online databases Toxline, Medline and Chemical Abstracts, covering the period up to September 2014, using acetaldehyde and CAS no 75-07-0 as key words in combination with key words representative for carcinogenesis and mutagenesis.

Chapter 2

Identity of the substance

2.1 Name and other identifiers of the substance

Table 1 Substance identity.

EC number	:	200-836-8
EC name	:	Acetaldehyde, ethanal
CAS number (EC inventory)	:	75-07-0
CAS number	:	75-07-0
CAS name	:	Acetaldehyde
IUPAC name	:	Acetaldehyde
CLP Annex VI Index number	:	605-003-00-6
Molecular formula	:	C_2H_4O
Molecular weight range	:	44.05 g/mol
Structural formula	:	

2.2 Composition of the substance

Not applicable.

2.3 Physico-chemical properties

Table 2 Summary of physico-chemical properties.

Properties	Value	Reference	Comment
State of the substance	: Liquid at 20 °C and 101.3 kPa	IUCLID 2000	
Melting/freezing point	: -123.5 °C	SCCNFP 2004[2]	
Boiling point	: 20.4 °C	SCCNFP 2004[2]	
Relative density	: 0.78 g/cm^3 at 20 °C	IUCLID 2000	
Vapour pressure	: 98 kPa at 20 °C	SCCNFP 2004[2]	
Surface tension	: -	IUCLID 2000	
Water solubility	: Miscible at 20 °C	IUCLID 2000	
Partition coefficient n-octanol/water	: log *P*, 0.43	IARC 1999[3]	
Flash point	: -40 °C (open cup), -38 °C (closed cup)	IARC 1999[3]	
Flammability	: Extremely flammable	IUCLID 2000	
Explosive properties	: -	IUCLID 2000	
Self-ignition temperature	: -		
Oxidising properties	: -		
Granulometry	: -		
Stability in organic solvents	: - (and identity of relevant degradation products)		
Dissociation constant (pK$_a$)	: 13.6 at 25 °C	NTP 2010	
Viscosity	: 0.2456 mPa x sec at 15 °C	SCCS 2012	

2.4 International classifications

2.4.1 European Commission

Acetaldehyde is classified for carcinogenicity in Annex VI of regulation (EC) No 1272/2008 as follows: Carc 2 (suspected human carcinogen; H351: suspected of causing cancer). The substance is not classified for mutagenic activity. The classification by the European Commission dates from 1991.

2.4.2 IARC

In 1999, IARC concluded that there was inadequate evidence in humans for the carcinogenicity of acetaldehyde, and that there was sufficient evidence in experimental animals (see Annex E).[3] Therefore, IARC classified the substance in Group 2B (‘possibly carcinogenic to humans’).

In 2010, IARC evaluated the risk of cancer due to alcohol consumption, including acetaldehyde. It confirmed that there was sufficient evidence in animal experiments for the carcinogenicity of acetaldehyde.[4] Moreover, in 2012 IARC

concluded that ‘acetal-dehyde associated with alcohol consumption’ is carcinogenic to humans (Group 1).[5]

Chapter 3

Manufacture and uses

3.1 Manufacture

Not relevant for classification.

3.2 Identified uses

Acetaldehyde is an aldehyde, occurring widely in nature. For instance, it occurs naturally in coffee, bread, and ripe fruit, and is produced by plants as part of their normal metabolism. Acetaldehyde is also formed endogenously in humans in small amounts, for instance during the breakdown of ethanol in the body. It is, furthermore, present in tobacco smoke.

Acetaldehyde is produced on a large industrial scale for many purposes and uses.[6] For instance, it is used as an intermediate in the production of acetic acid; in the production of cellulose acetate, pyridine derivates, perfumes, paints (aniline dyes), plastics and synthetic rubber; in leather tanning and silvering mirrors; as a denaturant for alcohol; in fuel mixtures; as a hardener for gelatine fibres; in glue and casein products; as a preservative for fish and fruit; in the paper industry; and, as a flavouring agent.

Chapter 4

Summary of toxicokinetics

The data presented below is a summary from evaluations and reviews by others, such as IARC,[3-5] IPCS,[7] DFG,[8] and SCCNFP.[2]

4.1 Absorption, distribution and elimination

In human volunteers, a significant uptake (45-70%) by the respiratory tract of inhaled acetaldehyde was observed after a very short exposure duration of 45 to 75 seconds. In various tissues of rats, acetaldehyde was found to be increased after a single exposure by inhalation, compared to unexposed control animals. Limited data obtained from animal experiments suggest that acetaldehyde (administered by intraperitoneal injection) may be partially transferred from maternal to foetal blood. It is also found in foetal liver. In a few studies acetaldehyde was detected in the blood and brain of animals, which were given the substance by intragastric administration or intraperitoneal injections. No data are available on dermal or percutaneous absorption.

Data on elimination are very limited. In one study using dogs, a single administration of acetaldehyde via a stomach tube revealed the presence of the substance in urine in minor quantities, but in most dogs no urinary acetaldehyde could be detected at all. Most likely this is due to the rapid metabolism of the substance in the liver.

4.2 Metabolism

Quantitative data on metabolism of acetaldehyde are based on animal experiments. Acetaldehyde is rapidly oxidized into acetate by NAD+-dependent acetaldehyde dehydrogenases. These enzymes are located in the cells of most tissues, including the liver, mucosal tissue of the respiratory tract, and the testes of mice. Acetaldehyde dehydrogenases show genetic polymorphism that gives rise to differences in vulnerability in humans concerning toxicity. To a minor part, the substance is probably oxidized by cytochrome P450 2E1, and by different aldehyde oxidases. Acetate is further metabolised into carbon dioxide and water by the citric acid cycle. There is no reason to believe that metabolism of acetaldehyde in rodents is significantly different from that of humans.

In general, data indicate a highly effective metabolism, in that half-time values in the blood for acetaldehyde were found to be three minutes in rats (after repeated exposure by inhalation) and mice (single intraperitoneal injection). For humans, no reliable data on half-times are available.

Acetaldehyde is a highly reactive electrophile, which reacts with nucleophilic groups of cellular macromolecules, such as proteins and DNA, to form adducts.

Chapter 5

Genotoxicity

Numerous studies have been performed on the genotoxic properties of acetaldehyde (see Tables 3 through 11).

5.1 Non-human information

5.1.1 In vitro data

Data on in vitro mutagenicity testing are presented in Table 3.

Table 3 Summary of in vitro mutagenicity studies.

Method	Cell type	Concentration Range[a]	Results - negative + positive	Klimisch[9] score[b]	References
Micro-organisms					
Reverse mutation; multi-substance study	*S. typhimurium* TA98, TA100, TA1535, TA1537	0 - 10,000 µg/plate	- (tested in two laboratories)	2	Mortelmans et al. 1986[10]
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.005, 0.01, 0.1, 1.0, 5.0, and 10 µg/plate: + and - S9	-	2	ECHA registration data, vitro.001, study report 1979 (echa.europe.eu;)
Reverse mutation	*S. typhimurium* TA100, TA102, TA104	0.1 - 1.0 ml/chamber, vapour; - and + S9	-	2	Dillon et al. 1998[11]

Reverse mutation	*S. typhimurium* TA104	Max. non-toxic dose: 2,515 µg/ml; -S9	-	3; only one strain tested	Marnett et al. 1985[12]
Reverse mutation	*S. typhimurium* TA102	0 - 3 µg/plate; cytotoxic over 5,000 µg/plate	-	3; only one strain tested, no positive control	Chang et al. 1997[13]
Reverse mutation	*S. typhimurium* TA1535, TA1537	10 µg/plate (exact dose not given)	-	3; one dose tested only	Rosenkranz 1977[14]
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	0.5% in air (highest dose; - and + S9)	-	4; from secondary source	JETOC 1997[15]
Reverse mutation	*S. typhimurium* TA98 and TA100	No exposure concentration given; +/- S9	-	4; abstract only	Sasaki and Endo 1978[16]
Reverse mutation	*E. coli WP2 uvrA*	Six different concentrations in the range of 0.02 to 10 mM for 18 hours (-S9)	- (also alkylation rate did not increase)	2	Hemminki et al. 1980[17]
Reverse mutation	*E. coli WP2 uvrA*	0.5% in air (highest dose; - and + S9)	-	4; from secondary source	JETOC 1997[15]
Reverse mutation	*E. coli WP2 uvrA*	0.1%	+	4; abstract only; no data on controls; no data on viability	Igali and Gaszó 1980[18]
Chromosomal aberration	*Aspergillus nidulans*	Up to 300 µg/ml; -S9	+ (chromosomal malsegregation); percentage survivors decreases from 100 µg/ml onwards	3	Crebelli et al. 1989[19]
Mammalian cells					
Gene mutation	Human TK6 cells; mutants determined at the *hprt* and *tk* locus	0.001, 0.005, 0.01, 0.05, 0.25, 0.5, 1.0, 2 and 4 mM for 24 hours	- *hprt* locus; + *tk* locus (dose-dependent increase)	1	Budinsky et al. 2013[20]
Gene mutation	Human lymphocytes, *hprt* locus	0 - 2.4 mM (24 hr-treatment, 0-0.6 mM (48-hr treatment); doses selected were based on low-cytotoxicity); -S9	+ (dose-related increase in number of mutants)	2	He and Lambert 1990[21]
Gene mutation spectrum	Human lymphocytes, *hprt* locus	2.4 mM for 22 hours; cloning efficiency was 50% at 1.2 mM compared to control	+ (mutation spectrum of acetaldehyde induced mutations was different from control)	2	Noori and Hou 2001[22]
Gene mutation	Human lymphocytes from donors, *hprt* locus	1.2 to 2.4 mM for 24 hours; 0.2 to 0.6 mM for 48 hours	+ (dose-dependent increase in number of mutants); large genomic deletions; most lesions are likely point mutations	3; no positive control; no data on cytotoxicity	Lambert et al. 1994[23]

Gene mutation; multi-substance study	Mouse lymphoma L5178T cells, *tk* locus	176 - 352 µg/ml; -S9	+; growth reduces with increasing exposure	2	Wangenheim and Bolcsfoldi 1988[24]
Gene mutation	Human fibroblast cell line with shuttle vector plasmid containing *supF* suppressor tRNA gene	0, 0.25, 0.5, 1.0 and 2.0 M	+ (after replication). Mutations were specified as tandem based substitutions (GG→TT); single-strand and double strand DNA mutations increased with increasing dose	2	Matsuda et al. 1998[25]
Gene mutation (6-TG resistant mutations)	Normal human fibroblasts	Concentrations up to 10 mM for 5 hours; positive and negative control included; cell viability tests performed	+ (bell-shaped dose-response relationship); survival at 5 mM was 50%; cells treated with 8 and 10 mM showed delayed recovery of the growth rate.	2	Grafström et al. 1994[26]
Chromosome aberrations	Different DNA-repair deficient Chinese hamster ovary cells	0.3, 0.6, 1.0, 1.8, 2.5 and 3.6 mM for 2 hours; 100 metaphases scored/ group	CA: + (concentration-related increase)	2; no positive control	Mechilli et al. 2008[27]
Chromosome aberration	Primary rat skin fibroblasts	0.1 - 10 mM for 12 and 24 hours; 50 metaphases analysed/ dose	12 hours: - 24 hours: + ($p<0.05$), except lowest dose, concentration-related increase in aneuploidy	3; no positive controls; no data on cytotoxicity	Bird et al. 1982[28]
Chromosome aberration	Chinese hamster embryonic diploid fibroblasts	0, 20, 40 and 60 µg/ ml; -S9	+	3; no data on cytotoxicity; no positive control	Dulout and Furnus 1988[29]
Chromosome aberration	Human peripheral lymphocytes (from 3 healthy volunteers)	0, 0.001 and 0.002 % (v/v); 100 or 200 mitoses scored/ sample	-	3; no positive control; no data on cytotoxicity	Obe et al. 1979[30]
Chromosome aberration	Human peripheral blood lymphocytes	0.02 and 0.04 mg/mL culture medium; no positive control	+	4; abstract only	Badr and Hussain 1977[31]
Micronuclei	Human lymphoblastoid TK6 cells	0.005, 0.01, 0.05, 0.25, 0.5, 1.0, and 2 mM; plates sealed due to volatility substances	+ (dose-related increase); with increasing exposure also the number of apoptotic cells increased	1	Budinsky et al. 2013[20]

Micronuclei	Human lymphoblastoid TK6 cells	8 different concentrations tested, between 0.005 and 4 mM; negative and positive controls included; only data analysed when cytotoxicity was below 55%	+ (0.25, 0.5 and 1.0 mM)	2	ECHA registration data, vitro.002, study report 1979 (echa.europe.eu)
Micronuclei; multi-substance study	Human lympho-cytes isolated from peripheral blood from one healthy non-smoking donor	0, 0.6, 0.8 and 1.0 mM	+ (dose-related increase, $p<0.05$); - (after hybridization with a centromeric DNA probe)	2; optimal doses were assessed determining degree of decrease in bi-/ mononucleated ratio	Migliore et al. 1996[32]
Micronuclei; multi-substance study	HepG2 and Hep3B cells	0, 0.9 and 9 mM for 24 hours; per experimental point 1,500 cells evaluated.	+ (concentrations-related increase)	2; no data on cytotoxicity	Majer et al. 2004[33]
Micronuclei	MCL-5 human lymphoblastoid cell line	0 - 2 % (v/v; a range of 6 differrent concentrations) for 22 hours; > 4,000 cells per dose examined	+ (from 0.4 % onwards, $p<0.05$), dose-dependent increase -: aneuploidy	2; no positive control included	Kayani and Parry 2010[34]
Micronuclei	Primary rat skin fibroblasts	0.1 - 10 mM for 12, 24 or 48 hours; > 1,000 cells analysed/ dose	+ ($p<0.05$; except lowest dose tested)	3; no positive controls; no data on cytotoxicity	Bird et al. 1982[28]
Micronuclei	V79 Chinese hamster cells	0.5 - 10 mM (MN);	+ (dose-dependent increase)	2; No positive control	Speit et al. 2008[35]

[a] + or - S9, with or without metabolic activation system.

[b] Klimisch score is expressed in reliability levels (cited from original publication):

- Reliability 1 (reliably without restriction). For example, guideline study (OECD, etc.); comparable to guideline study; test procedure according to national standards (DIN, etc.).
- Reliability 2 (reliable with restrictions). For example, acceptable, well-documented publication/study report which meets basic scientific principles; basic data given: comparable to guidelines/standards; comparable to guideline study with acceptable restrictions.
- Reliability 3 (not reliable). For example, method not validated; documentation insufficient for assessment; does not meet important criteria of today standard methods; relevant methodological deficiencies; unsuitable test system.
- Reliability 4 (not assignable). For example, only short abstract available; only secondary literature (review, tables, books, etc.).

5.1.2 In vivo data

A summary on the in vivo mutagenicity of acetaldehyde is shown in Table 4.

Table 4 Summary of in vivo mutagenicity studies (animal studies).

Method	Animal	Exposure conditions	Results	Klimisch[9] score[a]	References
Somatic cell mutagencicity					
Gene mutation and micronuclei	Wildtype and knock-out mice with inactive ALDH2[b] gene; micronuclei determined in reticulocytes; mutations were determined by T-cell receptor (TCR) gene mutation assay	Inhalation, 125 and 500 ppm vapour, continuously for two weeks; negative control was inhalation of clean air	*Micronuclei*: + in knock-out mice ($p<0.05$); - in wild-type mice. *Mutation* (TCR mutant frequency): + in knock-out mice ($p<0.05$); - in wild-type mice.	2	Kunugita et al. 2008[36]
Gene mutation and micronuclei	Wildtype and knock-out mice with inactive ALDH2 gene; micronuclei determined in reticulocytes; mutations were determined by TCR gene mutation assay	Oral administration, 0 and 100 mg/kg bw, daily, once a day for two weeks; 5 - 10 animals/ group	*Micronuclei*: + in knock-out mice ($p<0.05$); - in wild-type mice. *Mutation* (TCR mutant frequency): + in knock-out mice ($p<0.05$); - in wild-type mice	2	Kunugita et al. 2008[36]
Micronuclei; multi-substance study	Male SD and F344 rats, bone marrow erythrocytes and peripheral blood erythrocytes	Highest dose tested was maximum tolerated dose; at least four animals/group	+ (250 mg/kg bw, intraperitoneal injection, both cell types)	2; only highest dose tested	Wakata et al. 1998[37]
Micronuclei	5 male CD-1 mice	0 - 400 mg/kg bw, Intraperitoneal injection, three dose levels; tests on acute toxicity performed	+ (dose-related increase)	2	Morita et al. 1997[38]
Micronuclei	Male Han rats, 5 animals/group	Single intraperitoneal injection of 125 or 250 mg/kg bw; blood samples collected after 0, 24, 48 and 72 hours	+ (at 24 and 48 hours), dose-related increase; no data at 72 hours due to toxicity	2	Hynes et al. 2002[39]
Chromosomal aberrations	Rat embryos	Single intra-amniotic injection of 7,800 mg/kg bw	+	4; original publication available in Russian only	Bariliak and Kozachuk 1983[40]
Germ cell mutagenicity					
Meiotic micronuclei in spermatids	C57BL/6J x C3H/He mouse early spermatids	125, 250, 375 and 500 mg/kg bw per day, single dose, intraperitoneal injection; 4 animals/ group	- ; survival rate was significantly decreased in highest exposure group	2	Lähdetie 1988[41]

Sex-linked recessive lethal mutations; multi-substance study	*Drosophila melanogaster*	1) Single injection of 22,500 ppm; 2) 25,000 ppm in feed; data presented on mortality and sterility	+ (injection) - (feed)	2	Woodruff et al. 1985[42]

[a] See footnote in Table 3 for explanation of the Klimisch-scores.
[b] ALDH2, aldehyde dehydrogenase 2 family (mitochondrial), converts acetaldehyde into acetate.

Germ cells

Lähdetie (1988) studied the induction of meiotic micronuclei in spermatids of mice.[41] Mice (4 animals per group) were given a single intraperitoneal injection of acetaldehyde at a concentration of 0 (control vehicle), 125, 250, 375 and 500 mg/kg bw. A group of mice served as positive control (cyclophosphamide injection). Thirteen days after treatment the mice were killed to examine the presence of meiotic micronuclei in early spermatids (1,000 spermatids scored per mouse). Compared to the vehicle control, the number of spermatids with micronuclei did not increase after acetaldehyde treatment, whereas in the positive control it did. The author reported that at a dose of 500 mg/kg bw all animals died due to acute toxicity, whereas all survived at lower doses. In a separate experiment, the author also investigated the sperm morphology in mice treated with acetaldehyde for a short period (up to 250 mg/kg bw; 5-day exposure regimen). However, acetaldehyde did not decrease sperm count, testis weight or seminal vesicle weight, nor did it induce abnormal sperm at the doses. The highest administered dose was lethal to half of the animals in the group.

The Committee noted that in a sex-linked recessive lethal mutation assay, acetaldehyde was positive after injection (Woodruff et al. 1985).[42] This shows that the substance induces mutations in germ lines of the insect.

Somatic cells

Kunugita et al. (2008) studied the induction of gene mutations and micronuclei in knock-out mice having an inactive acetaldehyde dehydrogenase (Aldh2, converts acetaldehyde into acetate) gene.[36] Both wildtype and the knockout mice inhaled acetaldehyde at concentrations of 0, 225 or 900 mg/m^3, continuously for two weeks. In addition, groups of mice (5-10 animals per group) were given acetaldehyde orally at doses of 0 or 100 mg/kg bw, once a day for two weeks. Two weeks after the last exposure, all animals were killed and the number of reticulocytes with micronuclei was determined. Also the mutations in the *TCR* gene of T-lymphocytes was measured. Irrespective the route of exposure, in

knockout mice, the number of micronuclei positive cells, and the frequency of *TCR* gene mutations in lymphocytes was statistically significantly increased compared to the respective controls. In wildtype animals, acetaldehyde did not cause any effects on these endpoints. See Table 5 for a summary of the results.

In a well-performed study, Wakata et al. (1998) showed that in bone marrow polychromatic and peripheral blood erythrocytes of SD and F344 rats, micronuclei were induced after exposure to acetaldehyde by a single intraperitoneal injection of 250 mg/kg bw.[37] Bone marrow and blood cells were harvested 24 hours after the treatment. The study included concurrent negative (solvent/vehicle) and positive (cyclophosphamide) controls.

In addition, Morita et al. (1997) reported on acetaldehyde-induced micronuclei in bone marrow polychromatic erythrocytes of male CD-1 mice.[38] Five/six mice received the substance by a single intraperitoneal injection. Dose levels were based on acute toxicity test results. Two different lots were used, because the experiment was performed in two different laboratories. Twenty four hours after injections, bone marrow cells were harvested for the micronucleus assay. In Table 6 a summary of the results is shown.

Table 5 Induction of micronuclei and TCR gene mutations in knockout mice (Kunugita et al 2008).[36]

Exposure route	Exposure level	Micronuclei in reticulocytes	Mutant frequency in T-cell receptor gene
Knock-out mice (Aldh2 -/-)			
Inhalation	0 (control)	-	-
	225 mg/m^3	+ [a]	Not determined
	900 mg/m^3	+ [b/c]	+[b]
Oral administration	0 (control)	-	-
	100 mg/kg bw	+ [b/c]	+ [b/c]
Wildtype mice (Aldh2 +/+)			
Inhalation	0 (control)	-	-
	225 mg/m^3	-	-
	900 mg/m^3	-	-
Oral administration	0 (control)	-	-
	100 mg/kg bw	-	-

[a] Compared to Aldh2 +/+ control mice (p<0.05).
[b] Compared to Aldh2 +/+ control mice (p<0.01).
[c] Compared to Aldh2 -/- control mice (p<0.05).

Table 6 Induction of micronuclei in male CD mice (Morita et al. 1997).[38]

Manufact. lot	LD_{50}	Dose	Percentage of micronuclei in bone marrow cells		
	mg/kg bw	mg/kg bw	mean	SD	*p*-value[a]
Wako	470	0	0.12	0.08	-
		95	0.22	0.15	0.132
		190	0.33	0.10	0.010
		380	0.85	0.21	0.000
Merck	338	0	0.12	0.08	-
		100	0.10	0.07	0.726
		200	0.44	0.11	0.002
		300	0.62	0.16	0.000
		400	1.10	0.25	0.000

[a] *P*-value of pairwise comparisons.

Table 7 Induction of micronuclei in blood cells of rats treated with acetaldehyde (Hynes et al. 2002).[39]

Dose (mg/kg bw)	Time (h)	Laboratory[a]	Mean RET[b] ± SD	Mean MNRET[b] per 20,000 RET ± SD	Mean MNNCE[b] ± SD
0	0	GW	1.29 ± 0.29	0.13 ± 0.06	0.01 ± 0.00
		LL	1.47	0.14	0.01
125	24	GW	0.80 ± 0.12	0.21 ± 0.07	0.01 ± 0.00
		LL	0.91	0.19	0.01
	48	GW	1.32 ± 0.21	0.30 ± 0.09	0.01 ± 0.00
		LL	1.37	0.19	0.01
	72	GW	1.82 ± 0.18	0.14 ± 0.05	0.01 ± 0.00
		LL	1.65	0.18	0.01
250	24	GW	1.00 ± 0.42	0.28 ± 0.07	0.02 ± 0.01
		LL	0.99	0.32	0.01
	48	GW	1.31 ± 0.25	0.33 ± 0.11	0.02 ± 0.01
		LL	1.14	0.39	0.01
	72	GW	1.90 ± 0.42	0.14 ± 0.05	0.01 ± 0.01
		LL	1.42	0.16	0.01

[a] GW, GlaxoWellcome; LL, Litron Laboratories.

[b] RET, reticulocytes; MNRET, micronucleated reticulocytes; MNNCE, micronucleated monochromatic erythrocytes. No data on statistical significance presented.

Hynes et al. (2002) exposed male Wistar Han rats (5 animals per group) to acetaldehyde by a single intraperitoneal injection of 125 or 250 mg/kg bw.[39] For micronuclei testing, peripheral blood cells were harvested 0, 24, 48 and 72 hours after the injection. Micronuclei were scored by flow cytometric analysis. The study included negative (vehicle) and positive (cyclophosphamide) controls. Acetaldehyde at a dose of 250 mg/kg bw induced micronuclei, with maximum increases at 48 hours (see Table 7).

5.2 Human information

Table 8 summarizes a few studies performed on humans, in which effects were related to acetaldehyde. All volunteers were alcohol abusers or smokers.

Table 8 Summary of human studies.

Method	Population	Cells	Results and remarks	Quality and/or reliability of study	References
DNA-adducts (^{32}P-postlabelling)	Alcohol abusers (n=24) and controls (n=12)	Peripheral white blood cells (granulocytes and lymphocytes)	+ in alcohol abusers compared to controls ($p<0.001$). Average adduct levels (adducts /10^7 nucleotides): - abusers: 3.4 ± 3.8 - controls: 2.1 ± 0.8	Reliability low in that subjects in the alcoholic group were heavy smokers; in control group one moderate smoker.	Fang and Vaca 1997[43]
DNA-adducts	Cancer-free male Japanese alcoholic patients with different acetaldehyde dehydrogenase (ALDH) genotypes	Peripheral white blood cells	+, adduct level was significantly higher in alcoholics with ALDH2*1*2 genotype compared to alcoholics with ALDH2*1*1 genotype.	Past exposure to ethanol; no non-alcoholic healthy controls included	Matsuda et al. 2006[44]
Acetaldehyde specific DNA-adducts (N^2-ethylidene-deoxiguanosine)	Smokers, before and after smoking cessation	Leucocytes	Decrease in number of adducts after cessation. Note: cigarette smoke contains acetalde-hyde, but also other potential carcinogens.	Reliability low, because of smoking history participants and co-exposure	Chen et al. 2007[45]

5.3 Other relevant information

In the Tables 9 and 10 data are shown on the DNA damaging and genotoxic (other than mutagenicity) properties of acetaldehyde.

Table 9 Summary of other information on DNA damage.

Method	Cell type	Concentration	Results	Klimisch[9] score[a]	References
In vivo studies					
DNA-protein crosslinks	Male Fischer-344 rats; DNA-protein cross-links studied in nasal respiratory mucosa and olfactory cells	1) Inhalation; 100, 300, 1,000 and 3,000 ppm; single 6-hour exposure 2) inhalation; 1,000 ppm; 6-hours/day, daily, 5-days samples of three rats were combined	1) + (respiratory mucosa; dose-dependent increase, $p<0.05$); - (olfactory mucosa) 2) + (respiratory mucosa); + (olfactory mucosa, $p<0.05$)	2	Lam et al. 1986[46]

In vitro tests using human cells

DNA single and double strand breaks	Human lymphocytes from two healthy donors	0, 1.56, 6.25, 25 and 100 mM for one hour; for each dose 50 cells were analysed from each subject	+ (single strand breaks at all exposures) + (double strand breaks at 100mM only) Authors reported that > 80% of cells were not viable after exposure to 100 mM for 2 hours	2; no positive control	Singh and Khan 1995[47]
Comet assay[b]	Human peripheral blood lymphocytes	3, 10, 30 and 100 mM for one hour; doses were based on cytotoxicity data	+ (dose-dependent)	2	Blasiak et al. 1999[48]
Comet assay[a]	Human lymphocytes, gastric and colonic mucosa cells	3 mM (lympho-cytes), 100 mM (gastric and colonic mucosa cells)	+ No differences were noted among the different cell types; viability was over 70% at the tested doses	2; one dose tested only	Blasiak et al. 2000[49]
Comet assay[a]	Human bronchial epithelial cells	Exposure to 3, 10, 30 and 100 mM for 1 hour in thiol free medium	+, dose-dependent effects - for single strand breaks	2	Grafström et al. 1994[26]
DNA-adducts	DNA form primary human liver cells, samples from normal liver	Incubation of cells with 5.7 mM [$^{13}C_2$]acetaldehyde; 12 liver samples analysed	+ (N^2-ethyl-deoxiguanosine adducts)	3	Wang et al. 2006[50]
Alkaline elution assay[a]	Human lymphocytes	10 - 20 mM for 4 hours	+, DNA cross-links - ,DNA strand-breaks	3; No data on cytotoxicity; no positive controls	Lambert et al. 1985[51]
Alkaline elution assay[a]; multi-substance study	Normal human bronchial epithelial cells and humane leucocytes	1 mM for 1 hour	- (without metabolic activation); at 1 mM no significant growth reduction noted	3; only one concentratio n used	Saladino et al. 1985[52]
Alkaline elution assay[a]	Human bronchial epithelial cells	10 mM for 1 hour	-	3; only one dose tested; no data on con-trols; 10 mM acetaldehyd e induced 50% cytotoxicity	Grafström et al. 1986[53]
DNA-protein crosslinks	EBV-transformed human Burkitt's lymphoma cells (EBV, Epstein Barr virus)	0.035, 0.175, 0.875, 3.5 and 17.5 mM for 2 hours; Maximum tolerated dose was 17.5 mM	+ (> 5 mM, $p<0.05$)	2	Costa et al. 1997[54]
DNA-adducts	normal epithelial cells, and SV40T antigen-immortalized human buccal epithelial cells	1-100 mM for one hour; ^{32}P-postlabeling assay	+ (N^2-ethyl-3'-dG-monophosphate adducts, dose-dependent	2	Vaca et al. 1998[55]

In vitro tests using rodent cells					
Comet assay[a]	V79 Chinese hamster cells	0.2 - 20 mM	-; authors reported more than 50% reduction of cell viability at 20 mM	2; no positive control	Speit et al. 2008[35]
Alkaline elution assay[a]	Chinese hamster ovary cells (K1 cells)	0.5, 1.5 and 4.5 mM for 90 minutes	- (strand breaks); + (crosslinks); cell viability > 80%	2; no positive control	Marinari et al. 1984[56]
Alkaline elution assay[a]; multi-substance study	Primary rat hepatocytes	0.03, 0.3 and 3 mM for 3 hours; cytotoxicity < 55%	-	3	Sina et al. 1983[57]
Other test systems					
DNA-adducts	Calf thymus DNA	1 M for 30 minutes at 37 °C; negative control included	+ (without metabolic activation)	3; only one concentration tested	Ristow and Obe 1978[58]
DNA-adducts	Calf thymus DNA	0.01-40 mM for 20 to 96 hours	+ (mainly N^2-ethylidene-deoxi-guanosine DNA-adducts, but also (< 10%) 1,N-propano-deoxi-guanosine, N^2-dimethyldioxane-deoxiguanosine, and a cross-link adduct detected).	2	Wang et al. 2000[59]
DNA-adducts	Calf thymus DNA	1.8 mM for 92 hours; ^{32}P-postlabeling assay	+ (N^2-ethyl-3'-dG-monophosphate adducts)	3	Fang and Vaca 1995[60]
DNA-adducts	Calf thymus DNA in 2'-deoxy-guanosine-3'-monophosphate	Up to 79,000 µg/ml	+	3	Fang and Vaca 1997[43]
DNA-protein crosslinks	Calf thymus DNA in 2'-deoxy-guanosine-3'-monophosphate	100, 300 and 1,000 mM for one hour	+	3	Lam et al. 1986[46]
Alkaline elution assay[a]	*Saccharomyces cerevisiae* (yeast)	0.85 M for 2 or 4 hours	+	3; no positive control; no data on statistical analysis	Ristow et al. 1995[61]
DNA repair host-mediated assay, in vivo; multi-substance study	repair-deficient *E.coli* K-12 *uvrB/recA*; tests performed in mice	Highest tested concentration 370 mM/L; - and + S9	- (- and + S9)	3; method not validated	Hellmer and Bolcsfoldi 1992[62]

[a] See footnote in Table 3 for explanation of the Klimisch-scores.
[b] Comet assay and alkaline elution assay: DNA single and double strand breaks, DNA cross-links.

Table 10 Summary of genotoxicity studies.

Method	Cell type	Concentration	Results and remarks	Klimisch[9] Score[a]	References
Mammalian cells (in vitro tests)					
Sister chromatid exchange	Different DNA-repair deficient Chinese hamster ovary cells	0.3, 0.6, 1.0, 1.8, 2.5 and 3.6 mM for 2 hours; 250 metaphases scored/ group	+	2; no positive control	Mechilli et al. 2008[27]
Sister chromatid exchange	Chinese hamster ovary cells	0, 30, 100 and 300 µM; -S9	+ (dose-dependent increase	2	Brambilla et al. 1986[63]
Sister chromatid exchange	V79 Chinese hamster cells	0.2 - 5 mM	+ (dose-dependent increase)	2; No positive control	Speit et al. 2008[35]
Sister chromatid exchange	Chinese hamster ovary cells	0, 0.8, 2, 4, 7.8, 39.4 and 78 µg/ml; + and - S9; 20 metaphases/sample scored	+, dose-related response	3; no data on cytotoxicity; no positive control	de Raat et al. 1983[64]
Sister chromatid exchange	Chinese hamster ovary cells	$0.25x10^{-3}$, $0.5x10^{-3}$, $1x10^{-3}$, and $1.5x10^{-3}$ % (v/v); - S9; 100 mitoses scored/ sample	+	3; no positive controls, no data on cytotoxicity	Obe et al. 1979[65]
Sister chromatid exchange	Human peripheral lymphocytes	0 - 1,080 µM; -S9; reduction of cell growth noted above 720 µM	+, dose-related response	2; no positive controls	Böhlke et al. 1983[66]
Sister chromatid exchange	Human peripheral lymphocytes	1 - 100 µM	+	2; no positive controls	Knadle 1985[67]
Sister chromatid exchange	Human lymphocytes and fibroblast of normal subjects	40, 400 and 800 µM;	+	3; limited information on test protocol	Véghelyi and Osztovics 1978[68]
Sister chromatid exchange	Human lymphocytes	0, 63, 125, 250 500 and 2,000 µM; -S9	+ (dose-dependent increase)	3; no positive controls; no data on cytotoxicity	Norppa et al. 1985[69]
Sister chromatid exchange	Human lymphocytes	0, 0.0005, 0.001, and 0.002 % (v/v); -S9	+, dose-related response	3; no positive controls; no data on cytotoxicity	Ristow and Obe 1978[58]
Sister chromatid exchange	Human lymphocytes	0 - 500 µM; - S9	+, dose-related response	3; no data on cytotoxicity; no positive controls	Sipi et al. 1992[70]
Sister chromatid exchange	Human peripheral lymphocytes	100 - 400 µM; - S9; exposure performed in capped bottles	+ (dose-dependent increase)	3; no positive controls; no data on cytotoxicity	Helander and Lindahl-Kiessling 1991[71]
Sister chromatid exchange	Human peripheral lymphocytes	$2x10^{-3}$ % (v/v); + or - acetaldehyde metabolizing enzyme ALDH	+	3; no positive controls, no data on cytotoxicity	Obe et al. 1986[72]
Sister chromatid exchange	Human lymphocytes	100 - 2,400 µM; - S9	+ (dose-dependent increase	3; no positive controls used, no data on cytotoxicity	He and Lambert 1985[73]

Sister chromatid exchange	Human peripheral lymphocytes	0 - 0.001% (v/v); -S9	+ (dose-dependent increase)	3; limited information on test protocol	Jansson 1982[74]
Rodents (in vivo somatic cell tests)					
Sister chromatid exchange	Bone-marrow cells of Chinese hamsters (strain not specified)	Single intra-peritoneal injection of 0.01, 0.1 and 0.5 mg/kg bw; 6-7 animals/ dose; negative and positive control included	+ at the highest exposure level only; at this level signs of intoxica-tion were noted; no signs of intoxication at 0.1 and 0.01 mg/kg bw	2	Korte et al. 1981[75]
Sister chromatid exchange	Male mouse (NIH) bone marrow cells	0.4, 4.0, 40 and 400 mg/ kg bw, single intraperitoneal injection	+ (40 and 400 mg/kg bw, $p<0.05$) Mitotic index and average generation time did not differ from control	3; number of mice per group not given; no positive control	Torres-Bezauri et al. 2002[76]
Sister chromatid exchange	Male CBA mouse	Single intraperi-toneal injection of 1 or 0.5 mL of a 10^{-4} % (v/v) solution; one animal/ dose	+	3; low number of animals in study, no positive controls	Obe et al. 1979[30]
Rodents (in vivo germ cell tests)					
Sister chromatid exchange	Mouse spermatogonial cells	Single intraperitoneal injection; 0.4, 4.0, 40 and 400 mg/kg bw; 4 - 5 animals/concentration; cells were isolated, 53 h after injection.	+ (all doses applied, $p<0.05$); no clear exposure-response relationship observed	2; authors did test for intoxication; concentrations used were considered non-toxic/-lethal	Madrigal-Bujaidar et al. 2002[77]

[a] See footnote in Table 3 for explanation of the Klimisch-scores.

Germ cells

Madrigal-Bujaidar et al. (2002) injected NIH mice (4-5 mice per group) with acetaldehyde at concentrations of 0 (vehicle control), 0.4, 4, 40 and 400 mg/kg bw (single treatment), or cyclophosphamide (positive control).[77] Fifty-three hours later, the animals were killed, and the tunica albuginea was removed from each testes to obtain spermatogonial cells in the seminiferous tubules. A statistically significant increase in the number of cells with sister chromatid exchange was reported (30 metaphases per mouse scored; see Table 11). The authors determined a LD_{50}-dose of 560 mg/kg bw.

Somatic cells

Lam et al. (1986) reported on the formation of DNA-protein crosslinks in the nose tissue of male Fischer-344 rats after inhalation exposure.[46] The animals

were exposed to acetaldehyde at concentrations of 0,180, 540, 1,800 and 5,400 mg/m^3 for a single six hours, or to 5,400 mg/m^3, 6 hours a day for 5 consecutive days. Immediately after the final exposure the animals were killed, and nasal respiratory mucosa was obtained for further examination. After a single inhalation, a dose dependent increase in DNA-protein crosslinks was observed in the respiratory mucosa, but not in the olfactory mucosa. Short-term repeated inhalation induced DNA-protein crosslinks in the respiratory and the olfactory mucosa.

In bone marrow cells of Chinese hamsters (6-7 animals per group), a single intraperitoneal injection of acetaldehyde increased the number of sister chromatid exchanges at the two highest doses applied (0.1 and 0.5 mg/kg bw; Korte et al., 1981).[75] The authors reported that exposure to concentrations of 0.6 mg/kg bw and higher was lethal.

Table 11 Sister chromatid exchanges in spermatogonial cells of mice treated with acetaldehyde (Madrigal-Bujaidar et al. 2002).[77]

Dose (mg/kg bw)	SCE/cell ± SD[a]	SCE increase
0	1.9 ± 0.16	
0.4	2.9 ± 0.33[b]	1.1
4	4.1 ± 0.34[b]	2.2
40	4.6 ± 0.51[b]	2.7
400	5.1 ± 0.8[b]	3.2
50 (cyclophosphamide)	6.0 ± 0.1[b]	4.1

[a] SCE, sister chromatid exchange.
[b] Statistically significant different compared to control, $p < 0.05$.

5.4 Summary and discussion of mutagenicity

Below, only data are summarized of reliable (with or without restrictions) experimental design (according to the Klimisch criteria (1997)).[9]

Germ cell genotoxicity

The Committee found two animal studies on germ cell genotoxicity by acetaldehyde. The first is the study by Lähdetie et al. (1988), in which a single intraperitoneal injection of acetaldehyde did not induce meiotic micronuclei in early spermatids nor sperm abnormalities.[41] The second study is published by Mardigal-Bujaidar et al. (2002), and considers the induction of sister chromatid exchanges in mouse spermatogonial cells.[77] Although no clear dose-response

relationship could be assessed, the authors reported that acetaldehyde induced sister chromatid exchanges (see Table 11). However, based on this endpoint alone, the Committee cannot conclude that acetaldehyde is genotoxic in germ cells.

Mutagenicity in bacteria and mammalian cells

Numerous data have been presented on the mutagenic properties of acetaldehyde in bacteria, mammalian cells (other than germ cells) and rodents (see Tables 3 and 4). Overall, negative outcomes were found in bacteria using the reverse mutation assay, whereas positive outcomes (gene mutations, chromosome aberrations) were reported in mammalian cells in vitro, and in rodents in vivo (gene mutation and micronuclei in blood cells). In part of these positive studies also a dose-related response was found. Based on these findings, the Committee concludes that acetaldehyde has mutagenic properties in at least somatic mammalian cells in vitro and in vivo.

DNA damage and cytogenicity

In addition to mutagenicity testing, various studies have been performed showing that acetaldehyde induced DNA damage (DNA-crosslinks, DNA-adducts, and DNA strand breaks) (see Table 9) in vivo and in vitro. Together with data on mutagenicity, these data indicate that acetaldehyde may damage DNA directly. Therefore, the Committee is of the opinion that acetaldehyde acts by a stochastic genotoxic mechanism. Data on human volunteers are limited, since factors like alcohol (ab)use and smoking may have influenced the outcomes (see Table 8).

Numerous data have been presented on the induction of sister chromatid exchanges by acetaldehyde using in vitro, and to a lesser extent, in vivo test systems. In most of these studies acetaldehyde scored positive, and in some of these studies also a dose-related response was found. Based on these findings, the Committee concludes that acetaldehyde induces cytogenetic effects.

5.5 Comparison with criteria

According to the criteria in Annex VI of the European regulation No. 1272/2008 (see Annex G), classification as a mutagen in category 1 is warranted when positive evidence for *in vivo heritable germ cell* mutagenicity in humans (1A) or mammals (1B) has been reported. No data have been presented on human germ cell mutagenicity, and the only animal germ cell mutagenicity study did not show

mutagenic activity (Lähdetie et al., 1988).[41] Overall, due to a lack of data the Committee concludes that there is no positive direct evidence for in vivo heritable germ cell mutagenicity of acetaldehyde.

In addition, substances may be categorized in 1B if there are

positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells.

The latter may be based on a)

supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo

or b)

by demonstrating the ability of the substance or its metabolites to interact with the genetic material of germ cells

(see Annex G). Sufficient evidence has been found for in vivo mutagenicity testing in somatic cells of mammals. Regarding the second part of the criterion, there is limited evidence that acetaldehyde is genotoxic (sister chromatid exchanges) in germ cells of mice (Madrigal-Bujaidar et al. 2002), when the substance was given by intraperitoneal injection.[77] These findings indicate that acetaldehyde is able to reach the germ cells, and interacts with the genetic material, which would be in line with the findings on absorption and distribution kinetics (see Chapter 4). However, in another animal study no abnormal sperm cells, and no meiotic micronuclei in spermatids were observed at dose levels inducing acute toxicity (Lähdetie et al. 1988).[41]

Overall, the Committee is of the opinion that some evidence exists that acetaldehyde has potential to cause mutations in germ cells. Therefore, it recommends classifying the substance in category 1B.

5.6 Conclusions on classification and labelling

Based on the available data, the Committee recommends classifying acetaldehyde as a germ cell mutagen in category 1B (substance to be regarded as if they induce heritable mutations in the germ cells of humans).

The Committee is furthermore of the opinion that acetaldehyde acts by a stochastic genotoxic mechanism.

Chapter 6

Carcinogenicity

6.1 Non-human information

Data on animal carcinogenicity studies are summarized in Table 12.

Table 12 Summary of animal carcinogenicity studies on acetaldehyde exposure.

Species	Design	Exposure levels	Observations and remark	References
Oral administration				
Rats, Sprague Dawley	50 animals/sex/group; animals kept in observation until spontaneous death (last animal died in week 161); gross necroscopy and histopathological examinations.	0 - 50 - 250 - 500 - 1,500 - 2,500 mg acetaldehyde/ L drinking water (*ad libitum*; dose in kg/kg bw not given).	*Klimisch-score*: 2. *General*: No difference between control and exposed animals on consumption, body weight and survival. *Lesions*: Number of malignant tumour-bearing animals did not differ significantly from controls; Number of tumours per 100 animals was statistically significantly increased at 50 (females only), and at 2,500 mg/L (males – female – both sexes, $*p<0.05$): - 0 mg/L: 34% - 46% - 40% - 50 mg/L: 52% - 82%* - 67% - 2,500 mg/L: 66%*- 78%*- 72%. *Remark*: The EFSA noted that the animals may have been infected with *mycoplasma pulmonis*. Therefore, DECOS considers the study of questionable relevance.	Soffritti et al., 2002[78]

Rats, Wistar	10 male animals/ group; study duration 8 months; immuno-histochemistry and histopathological examination of the tongue, epiglottis, and forestomach; no other tissue examined.	0 or 120 mM in drinking water (*ad libitum*; dose in kg/kg bw not given).	*Klimisch-score*: 3 (only one dose used, short exposure period, limited examination of tissues). *General*: No difference between control and exposed animals on consumption, body weight and survival. *Lesions*: No cancerous or dysplastic lesions observed. Microscopic examination revealed hyperplasia in basal layers of squamous epithelia in the examined tissues of exposed animals.	Homann et al., 1997[79]
Inhalation				
Rats, Wistar	105 animals/sex/ group; six hours/day, five days/ week for 28 months; gross necroscopy and histopathological examination.	0 - 1,350 - 2,700 - 5,400 mg/m^3; due to toxicity, the highest exposure level was reduced to 1,800 mg/m^3 over a period of 11 months.	*Klimisch-score*: 2. *General*: lower survival and body weights were observed in exposed animals compared to controls. *Lesions*: exposure induced malignant tumour in the respiratory tract. See main text and Table 13. *Note*: only the respiratory tract was examined for the presence of abnormalities.	Woutersen et al., 1986[80]
Hamster, Syrian golden	36 animals/sex/group; seven hours/day, five days/week for 52 weeks, week 53-81, post-exposure period; gross necroscopy and histopathological examination; 6 animals/ sex were killed for interim examination.	4,500 mg/m^3 (week 1-9), 4,050 mg/m^3 (week 10-20), 3,600 mg/m^3 (week 21-29), 3,240 mg/m^3 (week 30-44) and 2,970 mg/m^3 (week 45-52); due to considerable growth retardation and to avoid early death, exposures were reduced gradually during experiment.	*Klimisch-score*: 2 (no standard procedure of doses applied). *General*: from week 4 onwards, exposed animals showed significant reduced body weight compared to controls; reduction diminished partly in the post-exposure period. *Lesions*: exposure induced rhinitis, hyperplasia and metaplasia in the nasal, laryngeal and tracheal epithelium. Also laryngeal and nasal carcinomas and polyps were observed; respiratory tract tumours: 0/30 - 8/29 (male, control-exposed) 0/28 - 5/29 (female, control-exposed)	Feron et al., 1982[81]
Hamster, Syrian golden	35 animals/group (males only); 7 hours/day, five days/week for 52 weeks, animals killed after 78 weeks; at week 52, 5 animals were killed for interim examination; gross necroscopy and histopathological examination.	0 or 2,700 mg/m^3	*Klimisch-score*: 2 (only one sex used, only one dose applied). *General*: in exposed animals, body weights were slightly lower than in controls. In the last part of the exposure period mortality increased more rapidly in exposed animals than in controls. *Lesions*: no substance-related tumours found. Acetaldehyde induced hyperplastic, metaplastic and inflammatory changes. *Note*: exposure level may have been too low to induce adverse health effects.	Feron et al., 1979[82]

Dermal exposure				
Rats	14 to 20 animals; subcutaneous injection.	(Total) dose not known; repeated injections.	*Klimisch-score*: 4 (data from secondary source; original study in Japanese; no abstract available)) *General*: no data. *Lesions*: spindle-cell sarcomas at site of injections (in four animals that survived the period up to 554 days).	Watanabe and Sugimoto 1956[83]
Intratracheal installation				
Hamsters, Syrian golden	35 animals/sex/group; weekly installations for 52 weeks, experiment was terminated at week 104.	0 or 2% acetaldehyde (installation volume, 0.2 mL).	*Klimisch-score*: 3 (only one dose applied; experiment not performed according to today's standard methods). *General*: no clear effects on body weight or mortality. *Lesions*: No substance-related tumours found. Hyperplastic and inflammatory changes observed in the bronchioalveolar region of exposed animals.	Feron et al., 1979[82]

6.1.1 Carcinogenicity: oral administration

Male and female Sprague-Dawley rats (50 animals/sex/group) were exposed to 0, 50, 250, 500, 1,500 and 2,500 mg/L acetaldehyde in drinking water (dose in kg bw not given), beginning at six weeks of age (Soffritti et al., 2002).[78] Animals were kept under observation until spontaneous death. In various organs and tissues neoplastic lesions were observed. However, no clear increase in number of tumour-bearing animals was found in any of the exposed groups compared to the control group. The investigators reported a significantly increased total number of tumours (per 100 animals) in groups exposed to 50 mg/L (females only), and 2,500 mg/L (males; females). The Committee noted the lack of statistical analysis, and the limited examination of non-neoplastic end-points. Furthermore, the European Food Safety Authority (EFSA) has evaluated the studies performed by the European Ramazzi Foundation of Oncology and Environmental Sciences, who performed this study, and noted that the animals used by this foundation, may have been infected with Mycoplasma pulmonis. This may have resulted in chronic inflammatory changes.[84] For these reasons, the Committee considers the findings of the study of questionable relevance.

Homann et al. (1997) have given male Wistar rats (N=10/group) either water containing acetaldehyde (120 mM) or tap water to drink for eight months.[79] Animals were then sacrificed, and of each animal tissue samples were taken from the tongue, epiglottis, and forestomach. No tumours were observed. However, in these organs, microscopic examination revealed statistically significant

hyperplasia of the basal layers of squamous epithelia in rats receiving acetaldehyde (compared to controls). Furthermore, in the three organs of the treated animals, cell proliferation was significantly increased, and the epithelia were significantly more hyperplastic, than in control animals.

6.1.2 *Carcinogenicity: inhalation*

In a carcinogenicity study by Woutersen et al. (1986), Wistar rats (105 animals/sex/group) inhaled acetaldehyde at a concentration of 0, 750, 1,500 or 3,000 ppm (0, 1,350, 2,700 or 5,400 mg/m^3) for six hours a day, five days per week for a maximum of 28 months.[80] The highest exposure level was reduced progressively over a period of eleven months to 1,000 ppm (1,800 mg/m^3) due to toxicity. The study focussed on lesions in the respiratory tract.

In general, animals exposed to acetaldehyde showed lower survival rates and body weights compared to controls. This was most pronounced in males exposed to the highest concentration of acetaldehyde. Gross examination at autopsy did not reveal acetaldehyde-related lesions, except for decolourisation of the fur and nasal swellings in all exposed groups. Microscopic examination revealed several non-neoplastic lesions in the respiratory tract of males and females, such as: hyperplasia in the respiratory nasal and olfactory epithelium; squamous metaplasia in the respiratory nasal epithelium; and, squamous metaplasia/hyperplasia in the larynx. These lesions were mainly noted in the mid and/or high exposure groups, and were statistically significantly increased compared to controls. No lesions were found in the lungs.

In the nose, also exposure-related neoplastic lesions were observed (see Table 13). It concerned squamous cell carcinoma in the respiratory epithelium of the nose, and adenocarcinomas in the olfactory epithelium. The relative lower tumour incidences in the high exposure groups were explained by the investigators by early mortality due to other causes than cancer. According to the authors, the observations support the hypothesis that nasal tumours arise from degeneration of the nasal epithelium. The same research group reported earlier on degeneration of the olfactory epithelium in rats inhaling acetaldehyde for four weeks, under comparable experimental conditions (Appelman et al., 1986).[85]

In a separate publication, the same authors reported on the interim results obtained in the first 15 month of the study (Woutersen et al. 1984).[86] In short, nasal lesion were reported in exposed animals, indicating chronic and permanent inflammation.

In a study by Feron et al. (1982), Syrian golden hamsters (n=36/sex/group) inhaled decreasing concentrations of acetaldehyde (from 2,500 ppm to 1,650

ppm (equal to 4,500 to 2,970 mg/m^3)) or clean room air, for seven hours a day, five days per week for 52 weeks.[81] The concentrations were reduced during the study because of considerable growth retardation and to avoid early death. Acetaldehyde induced rhinitis, hyperplasia and metaplasia of the nasal, laryngeal and tracheal epithelium. The exposed animals also developed laryngeal carcinomas with a few laryngeal polyps, and nasal polyps and carcinomas. The incidences of respiratory tract tumours were 0/30 (males, control), 8/29 (males, exposed), 0/28 (females, control) and 5/29 (females, exposed) (see Table 14). According to the Committee, the study by Feron et al. supports the findings of the carcinogenicity study by Woutersen et al. (1986) with rats.

Male Syrian golden hamsters (n=35/group) were exposed to 1,500 ppm (2,700 mg/m^3) acetaldehyde combined with weekly intratracheal instillations of benzo[a]pyrene (0.0625, 0.125, 0.25, 0.5 or 1 mg/kg bw) (Feron et al., 1979).[82] The exposure was for seven hours a day, five days per week for 52 weeks. No tumours were found in hamsters exposed to acetaldehyde alone, whereas in animals treated with benzo[a]pyrene alone, or with a combination of acetaldehyde and benzo[a]pyrene, a dose-related increase in respiratory-tract tumours were found.

Table 13 Respiratory tract tumour incidences in rats, which were exposed by inhalation to acetaldehyde for 28 months.[80]

Exposure level (ppm)	0	750	1,500	3,000-1,000
Male animals				
Nose:				
Papilloma	0/49	0/52	0/53	0/49
Squamous cell carcinoma	1/49	1/52	10/53[a]	15/49[b]
Carcinoma in situ	0/49	0/52	0/53	1/49
Adenocarcinoma	0/49	16/52[b]	31/53[b]	21/49[b]
Larynx: carcinoma in situ	0/50	0/50	0/51	0/47
Lungs: poorly differentiated adenocarcinoma	0/55	0/54	0/55	0/52
Female animals				
Nose:				
Papilloma	0/50	1/48	0/53	0/53
Squamous cell carcinoma	0/50	0/48	5/53	17/53[b]
Carcinoma in situ	0/50	0/48	3/53	5/53
Adenocarcinoma	0/50	6/48[a]	26/53[b]	21/53[b]
Larynx: carcinoma in situ	0/51	0/46	1/47	0/49
Lungs: poorly differentiated adenocarcinoma	0/53	1/52	0/54	0/54

[a] Fischer exact test: $p<0.05$.
[b] Fischer exact test: $p<0.001$.

Table 14 Respiratory tract tumour incidences in hamsters, which were exposed by inhalation to acetaldehyde for 52 weeks (Feron et al., 1982).[81]

	Incidence of tumours: males		Incidence of tumours: females	
	Control	Acetaldehyde	Control	Acetaldehyde
Nose				
Adenoma	0/24	1/27	0/23	0/26
Adenocarcinoma	0/24	0/27	0/23	1/26
Anaplastic carcinoma	0/24	1/27	-	-
Larynx				
Polyp/papilloma	0/20	1/23	0/22	1/20
Carcinoma in situ	0/20	3/23	0/22	0/20
Squamous cell carcinoma	0/20	2/23	0/22	1/20
Adeno-squamous cell carcinoma	-	-	0/22	2/20
Total	0/30	8/29[a]	0/28	5/29

[a] Statistical significance (Fisher's exacttest).

6.1.3 *Carcinogenicity: dermal exposure*

Watanabe et al. (1956) reported on the induction of sarcomas in rats given acetaldehyde by subcutaneous injections.[83] The Committee noted the limited study design, such as the small number of animals and the lack of a control group.

6.1.4 *Carcinogenicity: other routes of exposure*

No tumours were found in Syrian golden hamsters (n=35/sex/dose), which were given acetaldehyde by intratracheal installations, weekly or biweekly, for 52 weeks, followed by a recovery period for another 52 weeks (Feron et al., 1979).[82] Doses applied were 0.2 mL of 2% or 4% solutions. In positive controls, which were given benzo[a]pyrene and N-nitrosodiethylamine, a variety of tumours in the respiratory tract were found.

6.2 Human information

No human studies addressing the carcinogenicity of acetaldehyde alone have been retrieved from public literature.

In East-Germany, nine cancer cases were found in a factory where the main process was dimerization of acetaldehyde, and where the main exposures were to acetaldol, acetaldehyde, butyraldehyde, crotonaldehyde and other higher, condensed aldehydes, as well as to traces of acrolein.[87,88] Of these 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 observed in the population of East-Germany. A matched control group was not included. The Committee noted the combined exposure with other potential carcinogenic substances, the small number of cases, and the poorly defined exposed population.

6.3 Other relevant information

6.3.1 Alcohol consumption

Regarding the general population, some investigators suggest a role for acetaldehyde in cancer development (and other disorders) in humans after alcohol consumption, in particular in people with a genetic predisposition of one of the enzymes that are involved in ethanol metabolism.[3,4,89-95] Acetaldehyde is the major metabolite of ethanol (ethyl alcohol).[3,92,96-98] First, ethanol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, and subsequently acetaldehyde is converted by aldehyde dehydrogenase (ALDH2) to acetate. Both enzymes show genetic polymorphisms. This means that depending on the genotype, the enzymes may lead to a faster breakdown of ethanol to acetaldehyde, and/or to a slower breakdown of acetaldehyde to acetate. Thus, people having unfavourable genotypes of these enzymes are likely to be exposed internally to higher levels of acetaldehyde after alcohol consumption than would be the case when not having one of these isoenzymes. This would increase the susceptibility to cancer development after alcohol consumption, since it is suggested that acetaldehyde possesses carcinogenic properties.

Several studies reported on the association between genetic polymorphism and ethanol-related cancer development, all suggesting a role for acetaldehyde. As a result, a few meta-analyses have been performed to get more clarity. For instance, Chang et al. (2012) performed a meta-analysis to study the association between ADH1B* and ADH1C genotypes in head and neck cancer risk.[99] The analysis included twenty-nine studies. According to the authors, having at least one of the fast alleles ADH1B*2 or ADH1C*1 reduced the risk for head and neck cancer (odds ratios: 0.50 (95% confidence interval (CI), 0.37-0.68) for ADH1B*2; 0.87 (95%CI, 0.76-0.99).

Wang et al. (2012) performed a meta-analysis to derive a more precise estimate of the relationship between ADH1C genotypes, and breast cancer risk.[100] Twelve case-control studies were included in the analysis, covering 6,159 cases and 5,732 controls (all Caucasians). The investigators did not find any significantly increased breast cancer risk that could be related to any ADH1C genotype.

Boccia et al. (2009) reported on a meta-analysis to study the relationship between ALDH2 homozygous and heterozygous genotypes, alcohol consumption, and head and neck cancer.[101] The analysis included six case-control studies, covering 945 Japanese cases and 2,917 controls. For the analysis, the investigators used a Mendelian randomization approach. The homozygous genotype ALDH2*2*2 (unable to metabolize acetaldehyde) reduced the risk of head and neck cancer, whereas the heterozygous genotype ALDH2*1*2 (partly able to metabolize acetaldehyde) did significantly increase the risk compared to the homozygous ALDH2*1*1 genotype (able to metabolize acetaldehyde). According to the authors, the reduction of cancer risk in ALDH2*2*2 was most likely explained by the fact that people having this genotype consumed markedly lower levels of alcohol compared to the other genotypes, probably due to discomfort. Therefore, the authors conclude that their study supports the hypothesis that alcohol increases head and neck cancer risk through the carcinogenic action of acetaldehyde.

The same results were obtained by Fang et al. (2011), who carried out a meta-analysis of ALDH2 genotypes and esophageal cancer development.[102] Data from sixteen studies (hospital- or population-based, one multicenter study) were analysed, covering 2,697 Asian cases and 6,344 controls. The analysis showed that the heterozygous ALDH2*1*2 genotype increased the risk of esophageal cancer, whereas the homozygous ALDH2*2*2 genotype reduced the risk.

Yokoyama and Omori (2005) reviewed a number of case-control studies (including those performed by themselves) on the relationship of genetic polymorphism of ADH1B, ADH1C and ALDH2 genotypes and esophageal, and head and neck cancer risk.[103] They found positive associations between the less-active ADH1B*1 genotype and inactive heterozygous ALDH2*1*2 genotype,

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* ADH has seven isoenzymes, which are divided into five classes. Most relevant for alcohol metabolism in the liver of adults are the class one isoenzymes ADH1B and ADH1C (formerly known as ADH2 and ADH3 isoenzymes).[99] For each isoenzyme two or three different alleles are known, leading to different genotypes and thus to functional polymorphism. The genotypes of the isoenzyme ADH1B are expressed as ADH1B*1, ADH1B*2 and ADH1B*3; those for the isoenzyme ADH1C are expressed as ADH1C*1 and ADH1C*2. The metabolic speed is highest for homozygote genotypes ADH1B*2, ADH1B*3 and ADH1C*1. ADH1B*1 and ADH1C*2 are considered slow metabolisers.

and the risk for esophageal cancer in East Asian heavy drinkers. Light-to-moderate drinkers showed a higher vulnerability. According to the authors, some studies suggest similar associations for the risk for head and neck cancer in moderate-to-heavy-drinking Japanese. Data on ADH1C genotype were controversial.

The Committee emphasizes that in none of the studies on genetic polymorphism and alcohol-related cancer risk, a direct association was found between acetaldehyde and cancer, although the indirect data are suggestive for this.

6.3.2 *Cell transformation tests*

Koivisto and Salaspuro (1998) reported on a transformation test in which human colon adenocarcinoma cell line Caco-2 were used to study changes in cell proliferation, cell differentiation, and adhesion due to exposure to acetaldehyde.[104] In the absence of cell cytotoxicity, on acute exposure (for 72 hours), acetaldehyde (0.5 or 1 mM) inhibited the cell proliferation rate, but on chronic exposure (for five weeks) it stimulated cell proliferation. Furthermore, acetaldehyde clearly disturbed the cell differentiation (concentration applied was 1 mM for 7, 14 or 21 days); and, a clear decrease of adhesion of Caco-2 cells to collagens was observed when acetaldehyde was applied to the cells at a concentration of 0.5 or 1 mM for four days. According to the authors, the increased proliferation rate, disturbed differentiation, and reduced adhesion, would *in vivo* predict more aggressive and invasive tumour behaviour.

Eker and Sanner (1986) used a rat kidney cell line in a two-stage cell transformation assay.[105] Acetaldehyde (up to 3 mM) did not affect cytotoxicity nor did it induce colony formation of the cells. When acetaldehyde treatment (3 mM) was followed by a tumour promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), the ability of the cells to form colonies was increased.

In a poorly reported study by Abernathy et al. (1982), acetaldehyde (10-100 µl/ml (LC_{50}, 25 µg/ml)) induced cell transformation in C3H/10T½ cells, in the presence of TPA.[106] Treatment with acetaldehyde alone did induce transformed foci.

The Committee emphasizes that the value of transformation test in assessing carcinogenic potential is under debate. Therefore, it attaches little value to the outcomes of these tests.

6.4 Summary and discussion of carcinogenicity

Epidemiological studies are not available. In the literature, it is suggested that acetaldehyde may play a role in cancer development in humans after alcohol consumption, in particular in combination with a genetic predisposition for enzymes that convert ethanol in acetaldehyde, and for enzymes that convert acetaldehyde in acetate. The Committee emphasizes that in none of the studies on genetic polymorphism and alcohol-related cancer risk, a direct association was found between acetaldehyde and cancer, although the indirect data are suggestive for this.

Regarding animal carcinogenicity studies, chronic inhalation of acetaldehyde induced squamous cell carcinomas and adenocarcinomas in the nose of male and female rats. In hamsters, inhaling the substance, one study showed the presence of laryngeal and nasal tumours, whereas in another study – using a lower exposure concentration – no tumours were observed at all.

6.5 Comparison with criteria

For epidemiological data there is little or no data to support statements concerning an association between exposure to acetaldehyde and cancer. Therefore, the Committee is of the opinion that human data are insufficient to make a final conclusion on the carcinogenic potential of acetaldehyde in humans. For animal data, the Committee found sufficient evidence of carcinogenicity, since a causal relationship was established between malignant tumours in animals and chronic inhalation to acetaldehyde in two studies (Woutersen et al., 1986, Feron et al., 1982), the main route of exposure in an occupational environment.[80,81] According to the CLP classification criteria, acetaldehyde should, therefore, be classified as “presumed to have carcinogenic potential for humans”, which corresponds to classification in category 1B. Supporting evidence for its carcinogenic potential is that the substance has mutagenic properties, and acts by a stochastic genotoxic mechanism.

The Committee noticed that in 1991, the European Commission classified the substance as a carcinogen in category 2 (according to the current CLP-system). The classification was based on the same carcinogenicity studies as described in the present report. Most likely the difference in outcome is explained by differences in criteria used presently (criteria laid down in Regulation No. 1272/2008) and used in the late eighties of the twentieth century (criteria laid down in Annex VI of Directive 67/548/EEC).

6.6 Conclusions on classification and labelling

The Committee concludes that acetaldehyde is *presumed to be carcinogenic to man*, and recommends classifying the substance in category 1B*.

* See for classification system Annex F.

Chapter 7

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A	Request for advice
B	The Committee
C	The submission letter (in English)
D	Comments on the public review draft
E	IARC evaluation and conclusion
F	Classification on carcinogenicity
G	Classification on mutagenicity

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Quality of Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. Van Benthem
  Genetic Toxicologist, National Health Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Maastricht University, Maastricht
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

With respect to the data presentation and interpretation, the Committee consulted an additional expert, Mr. A. Muller, Toxicologist from Bureau REACH, National Health Institute for Public health and the Environment, Bilthoven.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter (in English)

Subject : Submission of the advisory report *Acetaldehyde*
Your Reference: DGV/MBO/U-932342
Our reference : U-8234/JR/cn/246-W19
Enclosed : 1
Date : November 13, 2014

Dear State Secretary,

I hereby submit the advisory report on the effects of occupational exposure to acetaldehyde.

This advisory report is a re-evaluation of an advisory report on the classification as a carcinogenic substance that has earlier been published by the Health Council. The Council is asked for a re-evaluation because the proposed classification differs from the classification that applies in the European Union. In addition, the Council is asked to also propose a classification for mutagenicity. The classifications are based on the European classification system.

The conclusions in the advisory report were drawn by a subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The subcommittee has taken comments into account from a public review, and included the opinions by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)
Professor J.L. Severens,
Vice President

Annex **D**

Comments on the public review draft

A draft of the present report was released in 2014 for public review. The following organisations and persons have commented on the draft document:

- D. Coggon, University of Southampton, UK
- T.J. Lentz and Q. Ma, National Institute for Occupational Safety and Health (NIOSH), Cincinnati OH, USA.

Annex **E**

IARC evaluation and conclusion

Acetaldehyde (Group 2B), Volume 71 (1999) (p. 319)

Summary of Data Reported and Evaluation

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.

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 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.

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.

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.

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).

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987).

Synonyms: Acetic aldehyde; ‘Aldehyde’; Ethanal; Ethylaldehyde.

Annex **F**

Classification on carcinogenicity

The Committee expresses its conclusions in the form of standard phrases*:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category[a]	
		67/548/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be as carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

[a] See Section 3.6 (Carcinogenicity) of Regulation No. 1272/2008 of the European Parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances.

* Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[107]

Annex **G**

Classification on mutagenicity

Source: Section 3.5 (Germ cell mutagenicity) of Regulation No. 1272/2008 of the European Parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances.

3.5.1 Definitions and general considerations

3.5.1.1 A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

3.5.1.2 The more general terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

3.5.2 Classification criteria for substances

3.5.2.1 This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from

mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

3.5.2.2 For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

3.5.2.3 Specific considerations for classification of substances as germ cell mutagens

3.5.2.3.1 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in in vitro tests shall also be considered.

3.5.2.3.2 The system is hazard based, classifying substances on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of substances.

Table 3.5.1 Hazard categories for germ cell mutagens.

Categories	Criteria
CATEGORY 1:	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
Category 1A:	The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.
Category 1B:	The classification in Category 1B is based on: • positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or • positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/ genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or • positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2:	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: • positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: • somatic cell mutagenicity tests in vivo, in mammals; or • other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. *Note*: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

3.5.2.3.3 Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in Regulation (EC) No 440/2008 adopted in accordance with Article 13(3) of Regulation (EC) No 1907/2006 ('Test Method Regulation') such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.4 In vivo heritable germ cell mutagenicity tests, such as:

- rodent dominant lethal mutation test;
- mouse heritable translocation assay.

3.5.2.3.5 In vivo somatic cell mutagenicity tests, such as:

- mammalian bone marrow chromosome aberration test;
- mouse spot test;
- mammalian erythrocyte micronucleus test.

3.5.2.3.6 Mutagenicity/genotoxicity tests in germ cells, such as:

(a) mutagenicity tests:

- mammalian spermatogonial chromosome aberration test;
- spermatid micronucleus assay;

(b) Genotoxicity tests:

- sister chromatid exchange analysis in spermatogonia;
- unscheduled DNA synthesis test (UDS) in testicular cells.

3.5.2.3.7 Genotoxicity tests in somatic cells such as:

- liver Unscheduled synthesis test (UDS) in vivo;
- mammalian bone marrow Sister Chromatid Exchanges (SCE);

3.5.2.3.8 In vitro mutagenicity tests such as:

- in vitro mammalian chromosome aberration test;
- in vitro mammalian cell gene mutation test;
- bacterial reverse mutation tests.

3.5.2.3.9 The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the substance compared to the route of human exposure shall also be taken into account.

3.5.3 Classification criteria for mixtures

3.5.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.5.3.1.1 The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2 Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.

Ingredient classified as:	Concentration limits triggering classification of a mixture as:		
	Category 1A mutagen	Category 1B mutagen	Category 2 mutagen
Category 1A mutagen	≥ 0,1 %	-	-
Category 1B mutagen	-	≥ 0,1 %	-
Category 2 mutagen	-	-	≥ 1,0 %

Note. The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.3.2 Classification of mixtures when data are available for the complete mixture

3.5.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.5.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

3.5.3.3.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.4 Hazard communication

3.5.4.1 Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.3 Label elements of germ cell mutagenicity.

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201, P202, P281	P201, P202, P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

3.5.5 Additional classification considerations

It is increasingly accepted that the process of chemical-induced tumorigenesis in humans and animals involves genetic changes for example in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of substances in somatic and/or germ cells of mammals in vivo may have implications for the potential classification of these substances as carcinogens (see also Carcinogenicity, section 3.6, paragraph 3.6.2.2.6).

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory reports that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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ACETALDEHYDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 319)

CAS No.: 75-07-0
Chem. Abstr. Name: 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 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)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)

Synonyms

- Acetic aldehyde
- ‘Aldehyde’
- Ethanal
- Ethylaldehyde

Last updated: 12 April 1999

Acetaldehyde

Supplement 2008	
MAK value (1982)	**50 ml/m³ (ppm) ≙ 91 mg/m³**
Peak limitation (2000)	**Category I, excursion factor 1**
momentary value 100 ml/m³	
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2007)	**Carcinogen Category 5**
Prenatal toxicity (2007)	**Pregnancy Risk Group C**
Germ cell mutagenicity (2007)	**Germ Cell Mutagen Category 5**
BAT value	**–**
Synonyms	ethanal
	ethyl aldehyde
Chemical name (CAS)	acetaldehyde
CAS number	75-07-0

The 1986 supplemental documentation (documentation "Acetaldehyde" 1992) confirmed the classification of acetaldehyde in Carcinogen Category 3B and the provisional MAK value of 50 ml/m³. In analogy to formaldehyde, it was assumed that chronic local tissue damage is a precondition for the development of tumours also in the case of acetaldehyde. Observance of the MAK value of 50 ml/m³, at which no irritation and no local tissue damage in the nasal mucosa were observed in animal studies, should thus also protect against the formation of tumours. In the light of new data, this supplement re-evaluates classification of the substance in Carcinogen Category 3B and the MAK value of 50 ml/m³.

The MAK-Collection Part I, MAK Value Documentations 2013
DFG, Deutsche Forschungsgemeinschaft

1 Toxic Effects and Mode of Action

After long-term inhalation exposure to concentrations of 750 ml/m³ and above, acetaldehyde produces adenocarcinomas in the olfactory epithelium of rats, while concentrations of 1500 ml/m³ and above cause squamous cell carcinomas in the respiratory epithelium of the nasal mucosa in rats, and tumours in the nose and larynx in hamsters. Acetaldehyde is genotoxic *in vitro* and *in vivo*. SCE (sister chromatid exchange), DNA adducts, DNA crosslinks and mutations were observed in mammalian cells *in vitro* without metabolic activation. Acetaldehyde was found also to be clastogenic *in vivo*. In mice, acetaldehyde induces micronuclei in the bone marrow; systemic availability is therefore to be assumed. In *Drosophila melanogaster*, acetaldehyde causes the induction of lethal mutations.

The target organ after repeated inhalation exposure is the upper respiratory tract. The olfactory epithelium reacts more sensitively than the respiratory epithelium. After exposure to concentrations as low as 243 ml/m³ for 5 weeks, degeneration of the olfactory epithelium was described in rats. Inflammatory changes with hyperplasia and metaplasia were found in the trachea of hamsters after inhalation exposure to concentrations of 1340 ml/m³ and above for 90 days. At higher concentrations, similar findings were obtained for the bronchi, larynx and nasal epithelium.

In humans, acetaldehyde does not cause contact sensitization. Respiratory sensitization has not been investigated to date. Findings from animal studies, which, however, were not performed according to test guidelines, indicate contact-sensitizing potential, but provide no clear evidence.

There are no valid fertility studies available.

Acetaldehyde, the primary metabolite of ethanol, has been suggested as a cause of developmental toxicity in the children of alcoholic mothers. After oral administration of acetaldehyde to rats, no developmental toxicity was found at the highest dose tested of 400 mg/kg body weight and day. Embryotoxic effects were found in mice and rats after intraperitoneal and intravenous doses of 31 and 50 mg/kg body weight and day, and above, respectively.

2 Mechanism of Action

The tumours caused by acetaldehyde can be attributed to genotoxic and tissue-damaging effects.

Cytotoxic effects

After nose-only inhalation exposure to 750 ml/m³ for a mere 3 days, an increase in the incidence of single cell necrosis was observed in the olfactory epithelium of rats (Cassee et al. 1996), which confirms the pronounced cytotoxic effect of acetaldehyde. In carcinogenicity studies at tumorigenic concentrations, also cytotoxic effects were found in rats. In the olfactory epithelium, degeneration (flattening, cell

necrosis) with hyperplasia, metaplasia and basal cell hyperplasia occurred at concentrations of 750 ml/m³ and above. At 1500 ml/m³ and above, hyperplasia and metaplasia of the nasal respiratory epithelium occurred, frequently accompanied by keratinization and, occasionally, by cellular and nuclear atypia. According to the authors, acetaldehyde is probably not a complete carcinogen at non-cytotoxic concentrations, but only a weak initiator. The authors assume that the cytotoxic effects with repeated tissue damage and repair can contribute greatly to tumour formation in the nose (Woutersen et al. 1985). After 4-week inhalation exposure of rats to acetaldehyde, a NOAEC (no observed adverse effect concentration) of 150 ml/m³ was obtained for damage to the olfactory epithelium, whereas 500 ml/m³ produced morphological changes (see Table 2; Appelman et al. 1985 in documentation "Acetaldehyde" 1992).

Genotoxicity

– Crosslinks *in vitro*

Like formaldehyde, acetaldehyde induces the formation of DNA–protein crosslinks (DPX) *in vitro* (Costa et al. 1997; Kuykendall and Bogdanffy 1992 a, b, 1994; Olin et al. 1996; Stanek and Morris 1999; WHO 1995). Also DNA–DNA crosslinks were found in human cells, CHO cells (a cell line derived from Chinese hamster ovary) and synthetic oligonucleotides treated with acetaldehyde (Cho et al. 2006; Grafström et al. 1994; Lao and Hecht 2005; Lambert et al. 1985; Marinari et al. 1984; Matsuda et al. 1998; Stein et al. 2006; WHO 1995). In the case of DPX formation and the formation of DNA–DNA crosslinks, acetaldehyde was found to be less effective on a molar basis than formaldehyde. Thus, the amount of crosslinked DNA was higher than that in control cells by a factor of 1.8 with 2.5 mM acetaldehyde and by a factor of 4.3 with 2.0 mM formaldehyde (Olin et al. 1996). After incubation with histone and a DNA plasmid, a 100 000-fold higher concentration of acetaldehyde is necessary *in vitro* in order to form as many DNA–protein crosslinks as those formed by formaldehyde (Kuykendall and Bogdanffy 1992 a), and the link with acetaldehyde is less stable at 37°C (Kuykendall and Bogdanffy 1992 b). Increased DPX formation was observed in human lymphoma cells at 17.5 mM and above; this concentration was also cytotoxic for the cells (Costa et al. 1997). Increased DPX levels were found in human bronchial epithelial cells at concentrations of 10 mM and above; the concentration that produced 50% inhibition was 25 mM (Grafström et al. 1994). In *in vitro* investigations with homogenates of nasal tissue from F344 rats, an increased percentage of DPX was found after acetaldehyde concentrations of 500 mM, but not after 100 mM (Stanek and Morris 1999).

The lowest concentrations at which *in vitro* crosslinks were observed were 3 mM (DNA–DNA crosslinks: interstrand crosslinks) in human bronchial epithelial cells (Grafström et al. 1994) and 1.5 mM in CHO cells (Marinari et al. 1984).

– Crosslinks *in vivo*

In F344 rats exposed to acetaldehyde concentrations of 100, 300, 1000 or 3000 ml/m³ for 6 hours, a statistically significant increase in the number of DPX

in the respiratory epithelium was found after concentrations of 1000 ml/m³ and above. The DPX level was not significantly increased at 300 ml/m³. No increase in DPX was found in the olfactory epithelium up to and including 3000 ml/m³. There was, however, a statistically significant increase in DPX in the olfactory epithelium after 5-day inhalation exposure to 1000 ml/m³ (6 hours/day). In contrast, the DPX from the respiratory epithelium after 5 days exposure to 1000 ml/m³ acetaldehyde was not further increased compared with that after only a single day of exposure (Lam et al. 1986). As concentrations lower than 1000 ml/m³ were not investigated in the 5-day exposure study, it is not possible to give a NOEC (no observed effect concentration).

In another study, there was no statistically significant increase in the number of DPX in the respiratory epithelium in rats exposed for 6 hours to 1500 ml/m³ by nose-only inhalation. DPX formation was not determined in the olfactory epithelium (Stanek and Morris 1999). The analytical method used to determine DPX was not a chloroform-isoamyal alcohol-phenol extraction as in Lam et al. (1986), but a KCl-SDS precipitation method. However, an increase in DPX after incubation with 500 mM acetaldehyde could be demonstrated *in vitro*. The authors gave no explanation for the different results; the precipitation method is possibly less sensitive than the extraction method.

– DNA adducts – isolated DNA

Figure 1 shows the formation of DNA adducts with acetaldehyde after reaction with isolated DNA.

The main DNA adduct of acetaldehyde is N^2-ethylidene deoxyguanosine (Hecht et al. 2001 a, b; Inagaki et al. 2003; Vaca et al. 1995; Wang et al. 2000), which is a Schiff's base. Acetaldehyde reacts with the exocyclic amino group of guanine to form the corresponding, relatively instable, imine (Fang and Vaca 1995). N^2-ethylidene deoxyguanosine is instable as a nucleoside, but stable in DNA (Hecht et al. 2001 a). In addition, three diastereomers of N^2-aldoxane deoxyguanosine are produced after the addition of aldol, formation of the imine on the exocyclic amino group of the guanine and subsequent cyclization with a third acetaldehyde molecule.

N^2-Propano-deoxyguanosine (*(R)* and *(S)* configuration due to a chiral α-C atom of the methyl group (Cho et al. 2006) can be formed from *N^2*-ethylidene-deoxyguanosine by reaction with another acetaldehyde molecule. The formation of *N^2*-propano-deoxyguanosine from acetaldehyde and isolated DNA or deoxyguanosine is facilitated by histone (Inagaki et al. 2004; Sako et al. 2003), polyamines such as spermine and spermidine (Theruvathu et al. 2005) and basic amino acids such as arginine and lysine (Sako et al. 2002), which are available *in vivo*. *N^2*-propano-deoxyguanosine adducts are responsible for the genotoxic and carcinogenic effects of crotonaldehyde. As the same adduct is formed also by acetaldehyde *in vitro*, the carcinogenic effects of acetaldehyde could be connected with the occurrence of this adduct.

An adduct able to cross-link both DNA strands can be formed from *N^2*-propano-deoxyguanosine (Cho et al. 2006; Lao and Hecht 2005; Stein et al. 2006). Inter-

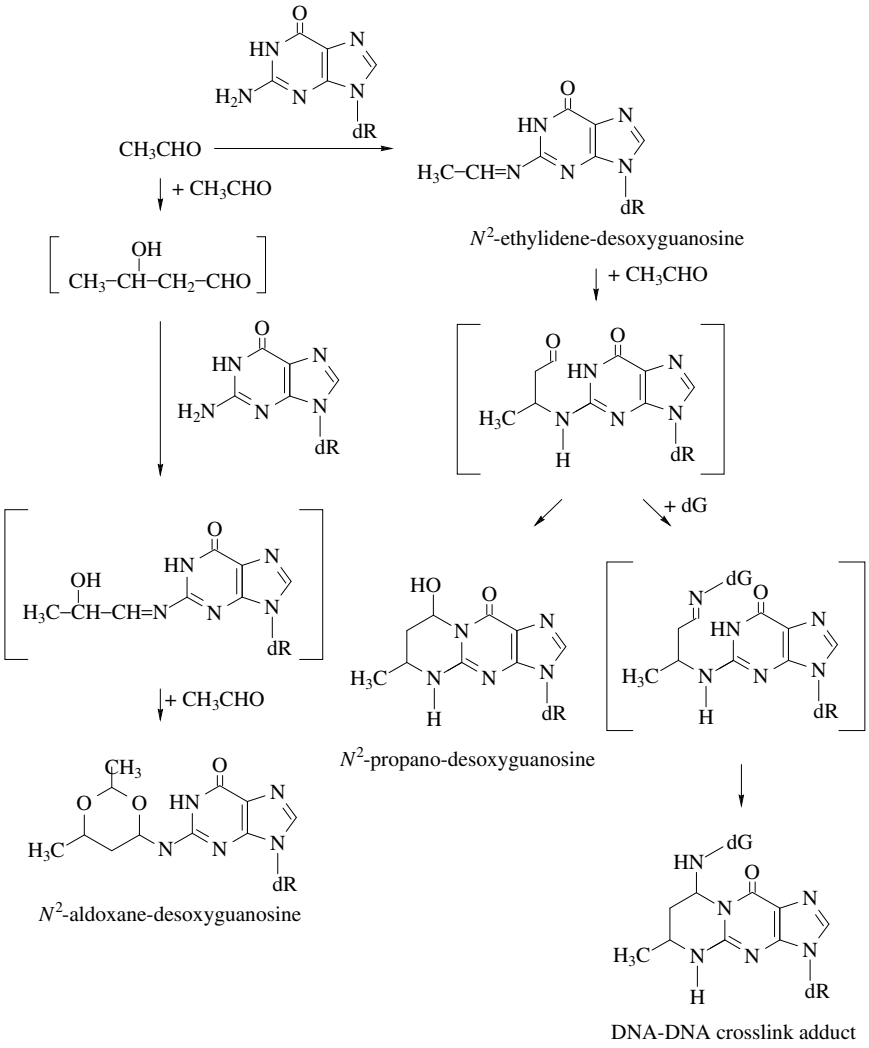

Figure 1 Products formed in the reaction of acetaldehyde *in vitro* with DNA, identified at the nucleoside level (according to Hecht et al. 2001 a). The metabolites in square brackets were not found.

strand crosslinks are lethal DNA damage if they are not repaired. They can cause point and deletion mutations during DNA repair (Lao and Hecht 2005).

– DNA adducts – *in vivo*

There are no animal studies available of the formation of N^2-ethylidene-deoxyguanosine and N^2-propano-deoxyguanosine by acetaldehyde.

– DNA adducts – endogenous

N^2-ethylidene-deoxyguanosine adducts occur endogenously: in the urine of 6 healthy volunteers, who were non-smokers and had consumed no alcohol for one week, N^2-ethylidene-deoxyguanosine concentrations of 0.059 ± 0.008 nmol/l were determined (0.012 ± 0.003 µmol/mol creatinine) (Matsuda et al. 1999). Increased N^2-ethylidene-deoxyguanosine adduct levels were detected in the lymphocytes and granulocytes of alcoholics (see Section 4.6). Smoking could be excluded as the cause of the increased adduct levels (Fang and Vaca 1997), which suggests that in alcoholics the adducts are formed from metabolically produced acetaldehyde. In histologically normal samples from the liver tissue of 12 volunteers, N^2-ethylidene-deoxyguanosine concentrations of 534 ± 245 fmol/µmol deoxyguanosine or 1 adduct/10^7 nucleotides were found. In this publication, no information is given about alcohol consumption or smoking (Wang et al. 2006).

Although the N^2-propano-deoxyguanosine adduct (Figure 1) is also present in endogenous form, its formation from acetaldehyde is unlikely for kinetic reasons (see below). It was formed *in vitro* and *in vivo* also by crotonaldehyde (2-butenal) (Chung et al. 1999 a, b; Hecht et al. 2001 a, b; Nath and Chung 1994; Nath et al. 1996, 1998; Wang et al. 2000; see documentation "Crotonaldehyde" 2007).

Investigations in humans of N^2-propano-deoxyguanosine adducts cannot, however, be used in the evaluation of acetaldehyde, as generally smokers were investigated, and in addition to acetaldehyde they are exposed also to crotonaldehyde. To form N^2-propano-deoxyguanosine with isolated DNA *in vitro*, relatively high concentrations up to 40 mM acetaldehyde are necessary (Wang et al. 2000). This concentration is not reached in the *in vivo* metabolism of ethanol even after oral ingestion of ethanol; the concentrations found are between 1 and 120 µM acetaldehyde (Inagaki et al. 2003). The *in vitro* investigation with a human leukaemia cell line in which this adduct was found was carried out using high concentrations (50 mM; Inagaki et al. 2004). The formation of N^2-propano-deoxyguanosine requires the presence of the primary adduct N^2-ethylidene-deoxyguanosine and a further molecule of acetaldehyde (see Figure 1). Because of the reaction kinetics, the formation of this adduct is disadvantaged at low acetaldehyde concentrations, as are to be expected *in vivo* (Inagaki et al. 2004), or the adduct may even not be formed at all (Fang and Vaca 1995). Unlike N^2-ethylidene-deoxyguanosine, this adduct should play no part in the carcinogenesis of acetaldehyde *in vivo*.

– Effects of the DNA adducts – base mismatch, DNA repair

Synthesized N^2-ethyldeoxyguanosine triphosphate was inserted during DNA synthesis opposite template dCytosin by DNA polymerase δ from calf thymus with the correct base pair (Matsuda et al. 1999). The Klenow fragment of the bacterial polymerase POL I inserted deoxycytosine and deoxyguanosine opposite an N^2-ethyldeoxyguanosine–DNA adduct (Terashima et al. 2001). Investigations with polymerases from mammalian cells showed that polymerase α is strongly blocked by the N^2-ethyldeoxyguanosine adduct, but polymerase η is able to bypass the damage and perform the accurate replication of base pairs (Perrino et al. 2003).

Spectra of acetaldehyde-induced mutations in supF genes of single and double-stranded shuttle vector plasmids, replicated in a human fibroblast cell line, were investigated. Of the 101 mutants obtained from the double-stranded plasmids, 63% had tandem base substitutions, of which the majority consisted of GG to TT transversions. Of the 44 mutants of the single-stranded plasmids, 39% had tandem mutations different to those of the double-stranded plasmids. The DNA damage in this system could be reduced by nucleotide excision repair (Matsuda et al. 1998).

Acetaldehyde thus led *in vitro* to DNA adducts which inhibit the correct replication of DNA, and to mutations with base mismatches. The damage can be repaired.

Other effects

It cannot be excluded that radicals make a contribution to the genotoxic effects of acetaldehyde. Methyl radicals were found in the bile of rats treated with acetaldehyde (gavage, 1000 mg/kg body weight). *In vitro*, also acetyl radicals can be formed from acetaldehyde—for example, by xanthine oxidase in the presence of transition metal ions such as Fe^{3+} (Fenton reaction)—and from these, methyl radicals via decarbonylation (Nakao et al. 2000).

Inactivation of acetaldehyde

In rats, the aldehyde dehydrogenase (ALDH) isoenzyme with the higher K_m value has a higher specific activity in the respiratory epithelium than in the olfactory epithelium (128 and 28 nmol/minute and mg protein, respectively; Casanova-Schmitz et al. 1984). The olfactory epithelium reacts more sensitively to acetaldehyde-mediated toxicity: hence, after 5 weeks exposure, degeneration of the olfactory epithelium occurred at concentrations of 243 ml/m³ and above (Saldiva et al. 1985), whereas in the respiratory epithelium, after 4 weeks exposure, degeneration was observed only after concentrations of about 2200 ml/m³ and above (Appelman et al. 1982). Tumours were found in the olfactory epithelium after exposure to concentrations of 750 ml/m³ and above, and in the respiratory epithelium after 1500 ml/m³ and above (Woutersen et al. 1985). Accordingly, it must be assumed that oxidation to acetate constitutes a detoxification reaction.

Conclusions

At present it is not possible to state whether genotoxic or cytotoxic effects play the main role in acetaldehyde-induced tumour formation as no investigations are available on its carcinogenicity at non-cytotoxic concentrations. Non-linear concentration–effect relationships have been described for DPX formation, tissue damage and tumours in the respiratory epithelium Morris 1997; Woutersen et al. 1985. It is, however, not clear whether the concentration–effect relationship found for tumours in the olfactory epithelium is non-linear in the concentration range below 500 ml/m³, which is relevant for the establishment of a threshold limit value. These concentrations have not been tested.

At least for single exposures to acetaldehyde via inhalation, a NOAEC of 300 ml/m³ can be derived for DPX formation in the respiratory epithelium of rats. It is not possible to give a NOAEC for DPX formation in the olfactory epithelium after repeated exposure; effects were observed at 1000 ml/m³ and above (Lam et al. 1986).

Unlike with formaldehyde, a wide variety of stable DNA adducts is formed with acetaldehyde. The quantitative contribution of the DNA adducts to the carcinogenicity of acetaldehyde is not clear at present, as their formation has not been investigated *in vivo* and determinations or calculations of the concentration of acetaldehyde in the nasal mucosal epithelium after exposure to acetaldehyde are not available. Therefore, comparison with *in vitro* data is not possible.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Animals

Acetaldehyde concentrations in the air of 1, 10, 100 or 1000 ml/m³ were drawn for up to a maximum of 40 minutes through the isolated upper respiratory tracts of male F344 rats anaesthetized with urethane. The acetaldehyde was drawn through the nose to the lungs at flow rates of 50, 100, 200 or 300 ml/minute, as well as bidirectionally at 207 ml/minute. Absorption efficiency in the upper respiratory tract decreased with flow rate and concentration. About 65%, 39%, 25% and 25% were absorbed at 1, 10, 100 and 1000 ml/m³, respectively, and a flow rate of 200 ml/minute. At concentrations of 100 and 1000 ml/m³ the acetaldehyde dosage rates were 5–100 µg/minute, 5–100 times higher than the V_{max} of the nasal ALDH (see Section 3.2). Therefore, the authors consider the limited enzyme capacity to be the reason for the lower absorption at higher concentrations. This assumption is supported by the fact that in animals pretreated with an aldehyde dehydrogenase inhibitor (cyanamide) the uptake was not dependent on the concentration (Morris 1999; Morris and Blanchard 1992). In another study by the same working group with the same species and acetaldehyde concentrations of 10, 300 and 1500 ml/m³, the delivered dosage rates exceeded the specific activity of the nasal ALDH after concentrations of 300 ml/m³ and above (Stanek and Morris 1999). It may be concluded from these investigations that acetaldehyde is transported from the nasal epithelium into the blood circulation as the concentration increases.

In 3 rats exposed for one hour to acetaldehyde (1–20 mM, about 44–882 mg/l = 24000–480000 ml/m³) by inhalation, there was more acetaldehyde in the blood (1210 nmol/ml) immediately after the end of exposure than in the liver (55 nmol/g) (Hobara et al. 1985).

In 6 male dogs given single acetaldehyde doses of 600 mg/kg body weight by gavage, no acetaldehyde was detected in the urine (detection limit: 2 ng/µl). The

acetaldehyde concentrations were close to the detection limit in the plasma of two animals, but below the detection limit in the plasma of the other four (Booze and Oehme 1986). This suggests that acetaldehyde is rapidly metabolized in the liver (first pass effect).

After the administration of a 20 mM acetaldehyde solution in single intragastric doses of 5 ml (4.4 mg/animal; 9 mg/kg body weight at a body weight of 500 g), or intracolonic doses of 3 ml to 4 rats (2.6 mg/animal; 5 mg/kg body weight), the highest acetaldehyde levels were found in the portal blood after five minutes. After intragastric administration, the acetaldehyde concentration in the portal blood was 235 µM, and after intracolonic administration it was 344 µM. The acetaldehyde concentration in the portal blood was about 17 times higher than that in the femoral vein (Matysiak-Budnik et al. 1996). This experiment proves that acetaldehyde does not react completely with macromolecules, but passes through membranes and is thus able to reach the liver via the portal circulation. In addition, the great difference in the acetaldehyde concentrations before and after passing through the liver indicates a highly effective first pass metabolism in the liver.

In CD-1 mice (number of animals not specified) given single intraperitoneal doses of acetaldehyde of 200 mg/kg body weight on day 10 of gestation, the maximum concentrations (77.3 ± 10.3 µg/g; mean value ± SD) were detected in embryo tissue five minutes after injection of the substance. At that time the concentration in the maternal blood was 185 ± 13.6 µg/ml. The concentrations decreased rapidly, and two hours after the treatment were below the detection limit (Blakley and Scott 1984 a).

In rats, a half-time for acetaldehyde in the blood of about three minutes was reported after exposure to extremely high acetaldehyde concentrations in the air (Hobara et al. 1985). Also after intragastric administration a half-time of about three minutes can be estimated for the substance in the blood of the portal vein in rats (Matysiak-Budnik et al. 1996).

There are no studies of dermal absorption available.

From the physico-chemical data (water solubility 1000 g/l, $\log K_{OW}$ –0.34 (SRC 2006)), it can be calculated using the models of Guy and Potts (1993) or Wilschut et al. (1995) that 1114 or 3848 mg of the substance, respectively, is absorbed in one hour from a skin surface of 2000 cm^2. This calculation applies for liquid acetaldehyde, and thus represents the worst-case assumption. A correspondingly lower amount is absorbed from diluted solutions.

Humans

In humans, 45% to 70% of the acetaldehyde inhaled via mouth or nose during exposure to 0.4–0.6 µg/ml (220–330 ml/m^3 inhaled air) for 45 to 75 seconds was retained in inverse relation to the respiratory rate. Steady state is not reached during such short-term exposure. From a figure in the publication, retention of 60% can be derived for a respiratory rate of 14/minute (Egle 1970). There are no data available for the half-time of acetaldehyde in humans.

Endogenous concentration of acetaldehyde in the blood

The earliest determinations of endogenous acetaldehyde concentrations in the blood of humans, oxen, horses and dogs, yielded concentrations in the range of 0.2–0.6 mg/l (4.5–13.5 µM; Fabre 1925; Gee and Chaikoff 1926). Also a series of more recent investigations using modern methods detected acetaldehyde concentrations in this range in human blood. However, the determination of acetaldehyde concentrations in blood is problematical, as acetaldehyde occurs as an artefact during sample preparation, mainly as a result of the oxidation of blood alcohol (Eriksson and Fukunaga 1993; Fukunaga et al. 1993). These authors therefore assumed that endogenous acetaldehyde may not be present at all. To reduce possible errors in the determination of acetaldehyde, a series of improvements were introduced (Baraona et al. 1987; Eriksson et al. 1982; Helander et al. 1993; Hernandez-Munoz et al. 1992; Lucas et al. 1986). After perchloric acid precipitation and separation of the proteins in the blood by centrifugation, the supernatant acetaldehyde concentration was less than 1 µM (Fukunaga et al. 1993; Helander et al. 1993). Together with that bound to protein, the acetaldehyde concentrations in whole blood were approximately three times higher: 3.6 ± 1.0 µM (n = 14) (Helander and Curvall 1991); > 2.5 µM (Helander et al. 1993); 2.2 ± 1.1 µM (n = 4) (Fukunaga et al. 1993). These findings contradict the assumption of Eriksson et al. (1982) that endogenous acetaldehyde could be produced from blood alcohol by artificial means only during sample preparation. As ethanol is distributed in the plasma and whole blood about equally (Jones 1983; Jones et al. 1992), higher acetaldehyde concentrations ought not to be determined in whole blood than in the supernatant fraction after centrifugation. Correspondingly, Helander et al. (1993) found that the artefactual formation of acetaldehyde interfered only with the determination of "free" or total acetaldehyde, but not, however, with the determination of the acetaldehyde "bound" in the blood. The fact that acetaldehyde is present in endogenous form is shown also by investigations of the air exhaled by fasting volunteers. In the exhaled air of 14 non-alcoholics and non-smokers, acetaldehyde concentrations between 0.7 and 11 ng/l (0.016 and 0.25 nmol/l) were determined (Dannecker et al. 1981).

In mammals, endogenous acetaldehyde is produced in the intermediary metabolism after oxidative decarboxylation of pyruvate, threonine aldolase-mediated degradation of threonine, and other metabolic processes. It is formed in intestinal bacteria after non-oxidative decarboxylation of pyruvate and after deamination of ethanolamine. Most of it is converted to ethanol by alcohol dehydrogenase (ADH), which on reaction tends to form ethanol. Ethanol acts toxicokinetically like a deep compartment for the acetaldehyde (Figure 2), and should thus be able to act as a buffer against the toxicity of endogenous acetaldehyde. Acetaldehyde is oxidized by aldehyde dehydrogenase (ALDH) to form acetate in a series of organs, and also in the blood, but mainly in the liver Lindros et al. 1978; Ostrovsky 1986.

Nuutinen et al. (1984) determined the K_m value of ALDH at 37°C *in vitro* with the whole blood of 4 control persons to be about 30 µmol/l. From Figure 3 of this publication, a V_{max} of 5.68 µmol/l and minute per litre whole blood can be derived. Based on the blood volume of an adult (5 l), this yields a V_{max} from blood of

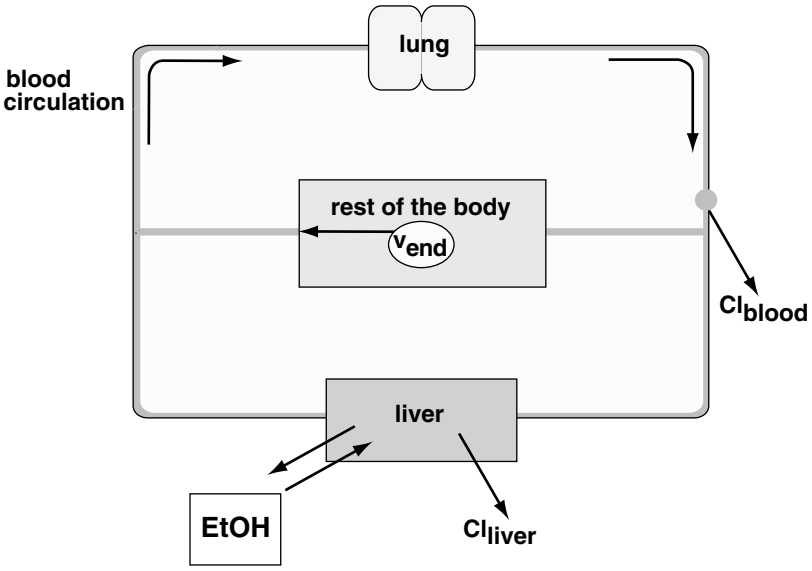

Figure 2 Formation, distribution and metabolism of endogenous acetaldehyde Physiological toxicokinetic model of the endogenous formation of acetaldehyde .v_{end} = rate of endogenous acetaldehyde formation; Cl_{blood} = clearance from the blood; Cl_{liver} = clearance from the liver; EtOH = ethanol

28.4 µmol/minute. Clearance of acetaldehyde from the blood of Caucasians (Cl_{blood}; Figure 2) is thus 28.4/30 = 0.95 l blood/minute. Acetaldehyde is oxidized in the liver very rapidly; for this reason it is assumed that the acetaldehyde present in blood does not originate from the liver, but from other organs (Lindros et al. 1978). If it is assumed that the acetaldehyde which reaches the liver via the circulation is eliminated quantitatively in this organ, then elimination by the liver (Cl_{liver}; Figure 2) corresponds to the blood flow through it (1.6 l blood/minute; Arms and Travis 1988). The rate of endogenous acetaldehyde formation (v_{end}; Figure 2) can be calculated approximately from the endogenous steady state concentration of acetaldehyde in blood ($[ACA]_{end}$) if the elimination of ethanol via respiration and urine is considered to be negligible and acetaldehyde clearance is considered only in the blood and liver (Figure 2). Using the lowest mean endogenous acetaldehyde concentration in whole blood ($[ACA]_{end}$ = **2.2 ± 1.1 µmol/l**; Fukunaga et al. 1993), this rate is calculated in Equation 1 (which applies to steady state conditions) as follows:

Equation 1 $v_{end} = [ACA]_{end} \times Cl_{liver} + [ACA]_{end} \times Cl_{blood}$ v_{end} = 2.2 [µmol/l] × (1.6 [l/minute] + 0.95 [l/minute]) = 5.6 µmol/minute per adult.

This means that at least 5.6 µmol acetaldehyde must be produced per minute in the adult organism in order to maintain a constant endogenous acetaldehyde concentration of 2.2 µmol/l in whole blood.

Estimated internal exposure after acetaldehyde inhalation

The basis is a volunteer study which showed that 60% of the substance is retained during the first 75 seconds of inhalation exposure to acetaldehyde (14 breaths/minute) (Egle 1970). To calculate the acetaldehyde uptake, the following assumptions were made: 60% of the inhaled substance reaches the lungs and is respirable; during physical exercise at 50 W, alveolar ventilation (V_{alv}) is 1170 l/hour (corresponding to about 10 m^3/8 hours) (Åstrand 1983). With continuous exposure to 10 ml/m^3 acetaldehyde gas (c_{ACA}) in the air (corresponding to 0.4 µmol acetaldehyde per litre air), the amount of acetaldehyde absorbed (v_i) per time unit in the steady state is:

Equation $2v_i = c_{ACA} \times V_{alv} \times 0.6 = 281$ µmol/hour or 4.7 µmol/minute

This rate is within the range of the endogenously produced acetaldehyde (v_{end} = 5.6 µmol/minute). As, in the corresponding concentration range ($[ACA]_{end}$ = 2.2 µmol/l), the oxidation of acetaldehyde takes place according to first order kinetics (Lindros et al. 1978), both v_{end} and v_i are proportional to the current steady state concentration of acetaldehyde ([ACA]) in the blood. Thus, in the steady state, a v_i of 4.7 µmol/minute corresponds to an additional blood ACA concentration of $2.2/5.6 \times 4.7 =$ **1.9 µmol/l**. For continuous exposure at the workplace to acetaldehyde concentrations of 50 ml/m^3, and assuming 8 hours work per day, on 5 days a week, for 48 weeks a year, over 40 years, and a lifespan of 80 years, the additional average lifetime concentration is 1.0 µmol/l. In relation to the unavoidable endogenous exposure, this represents an increase of 45%.

3.2 Metabolism

Acetaldehyde is oxidized mainly by aldehyde dehydrogenase (ALDH) to form acetate, which, after activation to acetyl-CoA, can enter the intermediary metabolism (WHO 1995). In the liver and other organs of humans, a number of isoenzymes of ALDH are present which have different kinetics and binding parameters (Goedde and Agarwal 1987; Klyosov et al. 1996). The mitochondrial NAD-dependent ALDH2 (EC 1.2.1.3.) oxidizes as a result of its high affinity at least 90% of the acetaldehyde; this can be blocked by disulfiram. The ALDH2 isoenzyme is inactive in at least 40% of Asians (WHO 1995). Also CYP2E1 and, to a lesser extent, CYP1A2 and CYP4A2 contribute to the oxidation of acetaldehyde (Bell-Parikh and Guengerich 1999; Kunitoh et al. 1997).

For the conversion of acetaldehyde by isoenzyme 1 of ALDH in F344 rats, V_{max} and K_m values of 128 nmol/minute and mg protein and 20 mM, respectively, were obtained in the respiratory mucosa, values of 28 nmol/minute and mg protein and 22 mM, respectively, in the olfactory mucosa. For isoenzyme 2, the corresponding

values were 0.8 nmol/minute and mg protein and 3×10^{-4} mM, respectively, in the respiratory mucosa, and 2.2 nmol/minute and mg protein and 0.1 mM, respectively, in the olfactory mucosa (Casanova-Schmitz et al. 1984). ALDH activity has been observed also in the renal cortex and renal tubules of dogs, rats, guinea pigs and baboons, and in the testes of the mouse (WHO 1995).

In the homogenate of olfactory and respiratory epithelium of F344 rats, ALDH activity of 1.2 µg/minute was determined for the oxidation of acetaldehyde (2 mM) (Morris and Blanchard 1992).

In another study of the same research group with the same species, the ALDH activity in the respiratory and the olfactory epithelium was determined to be 210 and 160 nmol/minute and animal (64 and 28 nmol/minute and mg protein), respectively, at acetaldehyde concentrations of 60 mM (Stanek and Morris 1999).

From *in vitro* and *in vivo* investigations in rats, the authors concluded that there is a minor, detoxifying metabolic pathway of acetaldehyde via 3-hydroxy-2-butanone (acetoin), which is reduced to 2,3-butanediol and subsequently conjugated with uridine diphosphate glucuronide to 2,3-butanediol-β-glucuronide. The presence of this glucuronide was detected in the urine of rats and humans given oral doses of 2,3-butanediol or ethanol (Otsuka et al. 1996).

4 Effects in Humans

4.1 Single exposures

Table 1 gives a summary of the data from volunteer studies with known exposure levels.

At concentrations of 50 ml/m³ and above, eye irritation occurred in the majority of 24 volunteers after exposure for 15 minutes. In sensitive persons, eye symptoms were seen even at concentrations as low as 25 ml/m³ (Silverman et al. 1946). The study does not meet present-day standards. Irritation of the upper respiratory tract is not described until concentrations of about 135 ml/m³ (ACGIH 2001; see Sim and Pattle 1957 in documentation "Acetaldehyde" 1972 (German)).

Twelve volunteers were exposed to intranasal acetaldehyde concentrations of 800 ml/m³ via impulse olfactometer for 200 ms (about 16 times) and the chemosensory potentials evoked were evaluated. The results suggest that the cortical correlates for the reaction to acetaldehyde resemble more those of the odorous substance vanilline than the irritants ammonia and sulfur dioxide. The volunteers described the odour of acetaldehyde as "fruity" and "chemical". The symptom "painful/stinging" was rated as relatively mild (Hummel and Kobal 1992).

Table 1 Effects of acetaldehyde in studies with volunteers exposed once via inhalation

Concentration ml/m3	Exposure duration	Number of exposed persons	Findings	References
25	15 minutes	24 (12 ♂, 12 ♂)	eye irritation in some persons (no other details)	Silverman et al. 1946
50	15 minutes	24 (12 ♂, 12 ♂)	eye irritation in the majority of volunteers (no other details)	Silverman et al. 1946
135	30 minutes	14	slight irritation of the upper respiratory tract	see Sim and Pattle 1957 in documentation "Acetaldehyd" 1972 (German)
>100–200	not specified	not specified	irritation of mucous membranes, effects on ciliary activity in the upper respiratory tract	ACGIH 2001
>200	15 minutes	24 (12 ♂, 12 ♂)	irritation in the nose and throat	Silverman et al. 1946

4.2 Repeated exposure

There are no studies available for repeated exposure to acetaldehyde.

4.3 Local effects on skin and mucous membranes

Acetaldehyde vapour and liquid caused eye irritation. Liquid acetaldehyde led also to skin irritation (von Burg and Stout 1991; see Section 4.1).

In a non-occlusive patch test, a 10% acetaldehyde preparation (vehicle not specified, probably water) caused erythema, which was limited to the test area, in all 12 tested persons (Haddock and Wilkin 1982).

In an investigation, a 5-minute patch test with 75% acetaldehyde in water (and with several primary alcohols and a number of other aldehydes) produced an immediate erythematous reaction in three oriental volunteers with medical histories indicating ethanol intolerance (flush) (Wilkin and Fortner 1985).

4.4 Allergenicity

In a study of intolerance reactions to air-oxidized and non-oxidized surface-active

ethoxylated (fatty) alcohols, 6 of 528 consecutive patients also tested with a 1% preparation of acetaldehyde in water produced reactions (erythema plus oedema, papules or vesicles). In 10 further patients, only erythematous reactions occurred. In the follow-up test, only 1 of the 6 patients still reacted to 1% and 0.33% acetaldehyde in water. The relevance of these reactions has not, however, been clarified, although the authors consider the presence of slight quantities of acetaldehyde in the oxidized surfactants to be possible (Matura et al. 2004).

No reactions to acetaldehyde were observed in patients with eczematous skin reactions to ethanol (Fregert et al. 1969; van Ketel and Tan-Lim 1975).

In a repeated insult patch test with 50% ethanol in water, 6 of 93 volunteers reacted in the challenge test with the same preparation (see documentation "Ethanol" 1999). In two of them, the reactions were reproducible after 18 months and one of them reacted also to a 1% preparation of acetaldehyde in water. To determine a non-irritant test concentration for acetaldehyde, one of the authors experimented on herself and applied over a period of eight days a 10% and a 5% solution of acetaldehyde for 3 hours followed by a 0.5% and a 1% solution for 24 hours. The challenge test with a 2% preparation of acetaldehyde in water produced a strong reaction, which the authors considered to be allergic, and prompted a flare at the area of skin treated with the 10% preparation 20 days earlier. In addition, reactions to a number of primary and secondary alcohols occurred (Stotts and Ely 1977).

In a maximization test with 2% acetaldehyde in petrolatum, five 48-hour occlusive applications to the forearm produced no reactions in any of the 28 volunteers. The 48-hour challenge test was carried out on the persons' backs after a 10 to 14-day pause. Prior to the induction treatment, the test area was pretreated occlusively for 24 hours with a 2% aqueous solution of sodium lauryl sulfate, and correspondingly before the challenge test for 30 minutes (SCCNFP 2004).

4.5 Reproductive toxicity

There are no studies available for the reproductive toxicity of acetaldehyde. Nevertheless, acetaldehyde is of importance in connection with the foetal alcohol syndrome.

Foetal alcohol syndrome is a disease in the offspring caused by alcohol consumption by the mother during pregnancy (see documentation "Ethanol" 1999). How ethanol produces the toxic effects on development has not been completely clarified. It is, however, generally assumed that acetaldehyde, as the primary metabolite of ethanol, can contribute to the effects (WHO 1995).

4.6 Genotoxicity

There are no studies available for the genotoxicity of acetaldehyde itself.

In 24 alcoholics, increased values were found for acetaldehyde adducts with the

DNA (N^2-ethylidene deoxyguanosine) in lymphocytes and granulocytes. The average adduct frequency was $3.4 \pm 3.8/10^7$ nucleotides in granulocytes and $2.1 \pm 0.8/10^7$ nucleotides in lymphocytes, but there was great interindividual variation. In 12 control subjects with no or moderate alcohol consumption (a maximum of 50 g ethanol/week), the adduct levels were below the detection limit of 0.5 adducts/10^7 nucleotides. The alcoholics were also heavy smokers. However, smoking could be excluded as the cause of the increased adduct levels as the N^2-ethylidene deoxyguanosine adduct levels were not increased in five non-alcoholics who were heavy smokers (Fang and Vaca 1997).

4.7 Carcinogenicity

No conclusions can be drawn as to the carcinogenicity of acetaldehyde from an epidemiological study with workers at an aldehyde factory in the former German Democratic Republic as a result of fundamental shortcomings (the number of persons investigated not specified, a low number of cases: 9 carcinomas, exposure to a mixture of substances, concentrations in departments with the supposedly highest concentrations not specified) (Bittersohl 1974, 1975).

In several studies, carriers of specific alleles in acetaldehyde-metabolizing enzymes were investigated to find out whether they have a greater risk of developing tumours. A number of enzymes that participate in the metabolism of acetaldehyde are polymorphic: ADH3, ALDH2 and glutathione *S*-transferase M1 (GSTM1). Particularly carriers of the $ADH3^1$, $ALDH2^2$ and $GSTM1^0$ alleles are likely to be exposed to higher levels of acetaldehyde than are people with the other alleles following the intake of a comparable amount of alcohol (IARC 1999; Salaspuro 2003). The increased odds ratios for tumours in the oral cavity and pharyngeal region in drinkers with the $ADH3^{1-1}$ genotype are to be emphasized (Coutelle et al. 1997; Harty et al. 1997). In homozygote carriers of the inactive $ALDH2^2$ allele and in heterozygotes, the level of acetaldehyde after ethanol administration is 19 and 6 times higher, respectively, than in homozygote carriers of the active $ALDH2^1$ allele. The odds ratio for oesophageal tumours in heterozygote ALDH2 carriers was clearly increased, regardless of alcohol consumption (Yokoyama et al. 1996). The results of Yokoyama et al. (1996) were confirmed in a meta-analysis of studies in which this influence of the ALDH2 genotype on the risk of oesophageal tumours was investigated. The relative risk for heavy drinkers with the $ALDH2^{1-2}$ genotype is up to 12 times higher than for drinkers with the $ALDH2^{1-1}$ genotype. In addition, it was shown that in the presence of the $ALDH2^{2-2}$ genotype the acetaldehyde concentration in the blood after alcohol intake is apparently so high that the acute symptoms prevent these subjects from drinking, so that the risk of oesophageal tumours in these subjects is not increased, but actually lower than in subjects with two $ALDH2^1$ alleles (Lewis and Smith 2005). The studies are to be regarded as

evidence of the critical role of acetaldehyde in the aetiology of ethanol-related tumours in the upper digestive tract.

5 Animal Experiments and *in vitro* Studies

5.1 Acute toxicity

5.1.1 Inhalation

From comparative studies of the sensory irritation of acetaldehyde and formaldehyde, a difference in the irritative effects of 1:1000 was determined. In mice, the RD_{50} values (the concentration which produces a 50% reduction in the respiratory rate) were about 2900 ml/m³ for acetaldehyde and between 3.2 and 4.9 ml/m³ for formaldehyde (Steinhagen and Barrow 1984 in the documentation "Acetaldehyde" 1992). In F344 rats, an RD_{50} of 3740 ml/m³ was determined. In the same species, exposure to 25 ml/m³ and above for 50 minutes produced significant vasodilation (Stanek et al. 2001).

In groups of five male Wistar rats exposed nose-only to 750 or 1500 ml/m³ for 6 hours, the percentage of non-protein sulfhydryl groups in the respiratory epithelium of the nose was increased compared with that in controls. Substance-related histopathological changes in the nasal epithelium were not observed. The unit length labelling indices used as a measure for both cell proliferation and the enzyme activities of GST, GPx, FDH, ALDH (see Table 2 for abbreviations) in the respiratory epithelium of the nose were not changed by acetaldehyde (compare 3-day exposure in Section 5.2.1; Cassee et al. 1996).

5.1.2 Ingestion

All six male dogs vomited after receiving single doses of acetaldehyde of 600 mg/kg body weight by gavage. The two animals with the highest plasma acetaldehyde concentrations trembled slightly. All clinical symptoms were reversible 24 hours after the treatment (Booze and Oehme 1986).

Male Wistar rats were given single oral doses of 17.9 or 35.8 mmol/kg body weight (788 or 1575 mg/kg body weight) (no other details). Five of six animals from the high dose group died. The triglyceride levels in the liver and the serum enzymes (aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase) were normal 24 hours after the treatment; in addition, no histological changes were observed in the liver (Strubelt et al. 1987).

5.1.3 Dermal absorption

There are no studies available for the dermal absorption of acetaldehyde.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Studies of repeated inhalation exposure to acetaldehyde are summarized in Table 2.

After repeated exposure to acetaldehyde, degeneration of the nasal epithelium, hyperplasia and metaplasia were observed in rats (see Table 2). The olfactory epithelium is affected at lower concentrations than is the respiratory epithelium. Thus, degeneration of the olfactory epithelium occurred after five weeks exposure to concentrations as low as 243 ml/m³ (Saldiva et al. 1985), whereas degeneration of the respiratory epithelium was not observed after exposure for four weeks until concentrations of around 2200 ml/m³ (Appelman et al. 1982). From a 4-week study with rats, a NOAEC of 150 ml/m³ can be derived for degenerative changes in the olfactory epithelium (Appelman *et al.* 1985 in documentation "Acetaldehyde"

Table 2 Effects of acetaldehyde after repeated inhalation exposure

Species, strain, number	Exposure	Findings	References
rat, Wistar, 5 ♂ per group	**3 days,** 0, 750, 1500 ml/m³, 6 hours/day, nose only	**750 ml/m³ and above**: **LOAEC**; incidence of single cell necrosis in the olfactory epithelium increased **1500 ml/m³**: non-protein sulfhydryl groups in the respiratory epithelium of the nose increased; no change in the enzyme activities of GST, GPx, FDH, ALDH in the respiratory epithelium of the nose, no change in the unit length labelling index as a measure of cell proliferation	Cassee et al. 1996
rat, Wistar, 10 ♂/10 ♀ per group	**4 weeks,** 0, 400, 1000, 2200, 5000 ml/m³, 6 hours/day, 5 days/week, whole-body exposure	**400 ml/m³**: **LOAEC**; ♂ and ♀: degeneration of the olfactory epithelium without hyperplasia and metaplasia **1000 ml/m³ and above**: growth retardation **2200 ml/m³ and above**: ♂ and ♀: degeneration of the olfactory epithelium of the nose with hyperplasia and metaplasia; degeneration of the respiratory epithelium of the nose without hyperplasia and metaplasia, degeneration of the epithelium of the	Appelman et al. 1982

Table 2 (Continued)

Species, strain, number	Exposure	Findings	References
		larynx, often with hyperplasia and metaplasia; degeneration of the epithelium of the trachea, often with hyperplasia and metaplasia	
		5000 ml/m³: ♂ and ♀: number of neutrophils increased, lymphocytes decreased, ♂: monocytes increased; ♂ and ♀: degeneration of the respiratory epithelium of the nose with hyperplasia and metaplasia; ♂: focal irritation of the interstitium of the lungs, focal haemorrhages in the lungs, small foci of compacted, alveolar septa with a high cell density in the lungs, with an increased number of macrophages	
rat, Wistar, 10 ♂ per group	**4 weeks,** 0, 150, 500 ml/m³, 6 hours/day, 5 days/week, whole-body exposure	**150 ml/m³**: **NOAEC**;	Appelman et al. 1985 in documentation "Acetaldehyde" 1992
		500 ml/m³: **LOAEC**; olfactory epithelium: loss of microvilli, thinning and disarrangement of the epithelium; no unusual findings in the remaining organs histologically investigated (planes of section: nose 4, larynx 3, trachea 3, lobes of the lungs 1)	
		peaks of 3000 ml/m³ (at 500 ml/m³): irritation of the eyes and nose	
		peaks of 660 ml/m³ (at 150 ml/m³): no histological changes; interruptions in the daily exposure of 1 1/2 hours had no influence on the histological changes;	
		biochemical parameters of lung lavage did not yield unusual findings	
rat, Wistar, 12 ♂ per group	**5 weeks,** 0, 243 ml/m3, 8 hours/day, 5 days/week, whole-body exposure	**243 ml/m3: LOAEC;** functional residual capacity, residual volume, total lung capacity, respiration rate increased, pronounced, subacute inflammatory reactions in the nasal cavities, hyperplasia in the nasal olfactory epithelium, polymorphonuclear and mononuclear infiltrations in the submucosa;	Saldiva et al. 1985
		lower respiratory tract and parenchyma of the lungs without noticeable findings	
rat, Wistar, 20 ♂/20 ♀ per group, see	**13–52 weeks,** 0, 750, 1500, 3000 ml/m3 (highest concentration: reduced to 1000 ml/m3	**1500 ml/m3 and above:** after 52 weeks: delayed growth;	Woutersen et al. 1985
		3000/1000 ml/m3: after 4 months: delayed growth, after 6 months: laboured breathing, salivation, breathing through the mouth, after 52 weeks: mortality increased	

Table 2 (Continued)

Species, strain, number	Exposure	Findings	References
Section 5.7.2	because of delayed growth, transient body weight loss and early mortality), 6 hours/day, 5 days/week, whole-body exposure, interim examinations after weeks 13, 26 and 52	**olfactory epithelium:** after 13/26 weeks: 750 ml/m3 and above: concentration-dependent degeneration (flattening, cell necroses, giant cells); after 52 weeks: 750 ml/m3 and above: degeneration, focal basal cell hyperplasia, 3000 ml/m3: loss of Bowman's glands and bundled nerve fibres **respiratory epithelium:** after 13 weeks: 3000 ml/m3: degeneration; after 26 weeks: 1500 ml/m3 and above: degeneration, hyperplasia and metaplasia, hyperkeratosis, 3000 ml/m3: rhinitis; after 52 weeks: 1500 ml/m3 and above: degeneration, 3000 ml/m3: hyperplastic and metaplastic changes with keratinization, papillomatous hyperplasia, proliferation of atypical basal cells, rhinitis, sinusitis **larynx:** after 13/26 weeks: 3000 ml/m3: hyperplasia, squamous cell metaplasia, lesions time-dependent; after 52 weeks: 1500 ml/m3 and above: hyperplasia, metaplasia, keratinization **no NOAEC**	
hamster, Syrian golden hamster, 10 ♂/10 ♀ per group	**90 days,** 0, 390, 1340, 4560 ml/m³, 6 hours/day, 5 days/week, whole-body exposure	**390 ml/m³: NOAEC** **1340 ml/m³ and above: LOAEC;** histological changes in the trachea: keratinization of the epithelia, presence of layered epithelia (metaplastic epithelium); ♂: relative kidney weights increased **4560 ml/m³:** delayed growth, irritation of the eyes and nose, relative heart and lung weights increased, alkaline phosphatase in serum increased, rhinitis, histological changes in the nasal cavity: necrosis and metaplasia in the respiratory and olfactory epithelium, disappearance of subepithelial glands, thinning of the bones of the nasal concha, keratinization of the epithelia; bronchi: focal bronchopneumonia, accumulation of macrophages containing pigment and focal irritation in	Kruysse et al. 1975

Table 2 (Continued)

Species, strain, number	Exposure	Findings	References
		the interstitium; larynx: respiratory epithelium transformed to squamous epithelium, squamous epithelium keratinized; ♀: number of erythrocytes increased, number of leucocytes decreased, relative weights of heart, kidneys, lungs, brain increased; ♂: relative testis weights increased	
hamster, Syrian golden hamster, 35 ♂ per group	**52 weeks**, 0, 1500 ml/m³, 7 hours/day, 5 days/week, whole-body exposure	**1500 ml/m³**: **LOAEC**; after 39 weeks mortality increased, slight anaemia, protein level in urine increased, activity of glutamate oxalacetate transaminase in urine increased, no histological changes in the kidneys, histological changes in the nasal mucosa and trachea (hyperplasia, squamous metaplasia, inflammation)	Feron et al. 1979 in 1982 supplement
hamster, Syrian golden hamster, 30 ♂/30 ♀ per group, see Section 5.7.2	**52 weeks**, 0, 2500 ml/m³, 7 hours/day, 5 days/week, whole-body exposure, after 9 weeks concentration reduced in steps to 1650 ml/m³ (from week 45) because of delayed growth, early mortality	**2500/1650 ml/m³**: **LOAEC**; mortality increased, body weights decreased; ♀: relative lung and kidney weights increased, activity of alkaline phosphatase in serum increased; nose: rhinitis, thinning and degeneration of the olfactory epithelium, hyperplasia and metaplasia of the respiratory epithelium and thickening of the submucosa, almost exclusively in the dorsomedial section of the nasal cavity, metaplastic layered squamous epithelium; larynx: slight to moderate focal metaplasia in the epithelium, atrophic, inflammatory, hyperplastic and metaplastic changes; trachea: slight to moderate focal epithelial metaplasia	Feron et al. 1982

ALDH: aldehyde dehydrogenase, FDH: formaldehyde dehydrogenase, GPx: glutathione peroxidase, GST: glutathione *S*-transferase

1992). After exposure for between 13 weeks to 2 years to concentrations of 750 ml/m³, degeneration, with or without hyperplasia and metaplasia, was found in the olfactory epithelium, and after 1500 ml/m³ and above degeneration of the respiratory epithelium with metaplasia and hyperkeratosis. A NOAEC was not obtained for this exposure period (Woutersen et al. 1985, see also Table 8).

In hamsters exposed for 90 days to concentrations of 1430 ml/m³ and above, inflammatory changes with hyperplasia and metaplasia were observed in the larynx. This yields a NOAEC of 390 ml/m³ for the histological changes in the larynx (Kruysse et al. 1975). After exposure for 52 weeks, also changes in the trachea were observed after concentrations of 1500 ml/m³, and changes in the nasal epithelium

after 2500/1650 ml/m³ (after 9 weeks the concentration was reduced in steps to 1650 ml/m³ by week 45 because of delayed growth and early mortality) (Feron et al. 1979 in documentation "Acetaldehyde", 1992; Feron et al. 1982).

In a 22-day study, Sprague Dawley rats were exposed continuously to increasing acetaldehyde concentrations (750–2500 mg/m³; 410–1365 ml/m³) (WHO 1995).

Table 3 Effects of acetaldehyde after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂/10 ♀ per group	**4 weeks** 0, 25, 125, 675 mg/kg body weight and day, in the drinking water	**125 mg/kg body weight and day**: NOAEL **675 mg/kg body weight and day**: ♂ and ♀: food and water consumption decreased, slight to moderate hyperkeratosis in the forestomach	Til et al. 1988
rat, Wistar, 10 ♂	**11 weeks** 0, 0.7% in the drinking water (about 0, 875 mg/kg body weight and day assuming 50 ml intake and a body weight of 400 g); controls: water	**875 mg/kg body weight and day:** immunohistochemically detectable acetaldehyde–protein adducts in the hepatocytes increased, periportal fat storage, aspartate aminotransferase and alanine aminotransferase in serum unchanged	Jokelainen et al. 2000
rat, Wistar, 4 ♂ low dose, 10 ♂ high dose, 10 ♂ controls	**11 weeks** 0, 20, 120 mM in the drinking water (0, 120, 500 mg/kg body weight); controls: water	**120 mg/kg body weight and day:** NOAEL **500 mg/kg body weight and day:** triglycerides in the liver increased; liver histology: microvesicular fatty degeneration and accumulation of fat, inflammatory changes; body weights and drinking water intake: no unusual findings	Matysiak-Budnik et al. 1996
rat, no other details	**6 months** 0.05% in the drinking water (about 40 mg/kg body weight and day according to WHO 1995)	**40 mg/kg body weight and day:** collagen synthesis in the liver increased; toxicological importance according to WHO not clear, no other investigations	WHO 1995

As it is not clear to which concentration the observed effects can be attributed, the study is not included in the evaluation.

5.2.2 Ingestion

Table 3 shows the studies of repeated oral administration of acetaldehyde.

In rats given acetaldehyde doses of 675 mg/kg body weight and day for 4 weeks, reduced food and water consumption and hyperkeratosis in the forestomach were observed. The NOAEL (no observed adverse effect level) was 125 mg/kg body weight and day (Til et al. 1988). In the same species, oral doses of 500 mg/kg body weight and day and above for 11 weeks led to the accumulation of fats and inflammatory changes in the liver (Jokelainen et al. 2000; Matysiak-Budnik et al. 1996). For these effects, a NOAEL of 120 mg/kg body weight and day can be derived (Matysiak-Budnik et al. 1996).

5.2.3 Dermal absorption

There are no studies available for the dermal absorption of acetaldehyde.

5.2.4 Intravenous injection

In 6 male Hartley guinea pigs per group given repeated intravenous acetaldehyde doses of 0, 20, 40 or 80 mg/kg body weight in sodium chloride solution (purity >95%) at intervals of 15 minutes, dose-dependent increases in intratracheal pressure and vascular permeability were observed (Berti et al. 1994).

5.3 Local effects on skin and mucous membranes

In a test with rabbits carried out according to OECD Test Guideline 404, acetaldehyde was not found to be irritating to the skin. In another test not conducted in accordance with test guidelines, 500 mg acetaldehyde produced slight irritation of the skin in the same species (no other details; ECB 2000).

In the rabbit eye, 40 mg acetaldehyde produced marked irritation (no other details; ECB 2000).

5.4 Allergenicity

In a modified cumulative contact enhancement test in female Dunkin-Hartley guinea pigs, acetaldehyde was found to be skin-sensitizing. The induction treatment

consisted of the 24-hour occlusive application of a 15% preparation of acetaldehyde in physiological saline on days 1, 3, 8 and 10, and two intradermal injections of 0.1 ml Freund's complete adjuvant (FCA) on day 7. Fourteen days later, a 24-hour occlusive challenge test was carried out in 15 animals with 15 µl of a 2.5%, a 5.0% and a 10.0% preparation of acetaldehyde in physiological saline. At the 48-hour reading, 4, 7 and 13 animals, respectively, reacted. At the 72-hour reading, 5, 9 and 13 animals reacted. In a repeated challenge test performed 78 days after the start of the study, however, none of the animals reacted to a 0.03% and a 2.5% acetaldehyde preparation in physiological saline. Of the animals induced with 5% formaldehyde in physiological saline, 8 reacted to 0.1% and 11 to 0.3% formaldehyde (72-hour reading) in the first challenge test and 0, 6 and 9 animals reacted to 0.1%, 0.3% and 1% formaldehyde in the repeated challenge test (72-hour reading). No cross-reactions between acetaldehyde and formaldehyde were observed in this study (Bergh and Karlberg 1999).

It is reported in an abstract that, in a maximization test, acetaldehyde had a weaker effect than formaldehyde and approximately the same effect as propionaldehyde and benzaldehyde (Momma et al. 1995). As none of the experimental data are available, these findings cannot be used in the evaluation.

5.5 Reproductive toxicity

5.5.1 Fertility

Groups of 5 to 10 male hybrid mice (C57BL/6J×C3H/He) were given intraperitoneal acetaldehyde doses of 0, 62.5, 125 or 250 mg/kg body weight in physiological saline on 5 consecutive days. Five weeks after the start of the treatment, the sperm count in the epididymis was significantly increased in the highest dose group relative to that in the controls. The relative testis weights and the relative weights of the seminal vesicles were unchanged after treatment (Lähdetie 1988). With the quantities of acetaldehyde used, these findings do not indicate substance-related impairment of the fertility of the male animals.

5.5.2 Developmental toxicity

As it is the main metabolite of ethanol, acetaldehyde has been suggested to be the cause of the developmental toxicity that occurs in the children of alcoholic mothers. Most of the investigations of the embryotoxicity of acetaldehyde have therefore been carried out in this context.

In vitro

Acetaldehyde concentrations of 100 µM and above produced a dose-dependent de-

crease in the cell count of cultured morulae blastocysts of mice. After concentrations as low as 10 µM, SCEs were induced in the cultured morulae blastocysts (Lau et al. 1991).

To investigate the development of rat embryos, whole embryo cultures were incubated from day 10 of gestation for 25 hours with acetaldehyde concentrations of between 5 and 100 µM. After concentrations of 25 µM and above, there was a statistically significant decrease in the total protein content, in the maximum absolute head length and that relative to the crown–rump length compared with the values for the controls. After 100 µM, only one of the 23 embryos survived. 5 µM had no effect (Campbell and Fantel 1983).

The cultivation of 10-day-old rat embryos for 30 to 48 hours in a medium with acetaldehyde concentrations of 0, 10 or 20 µg/ml (0, 0.23 and 0.46 mM) produced lethal effects in 100% of the embryos at 20 µg/ml and growth retardation and teratogenic effects at 10 µg/ml (Giavini et al. 1992).

Groups of 8 to 10, 10-day-old rat embryos were cultured in a medium containing acetaldehyde concentrations of 30 to 60 µg/ml (0.68–1.36 mM) for 8 hours. At 30 µg/ml there was a statistically significant increase in the number of malformed embryos compared with that in the controls, and at 45 and 60 µg/ml all embryos were affected. A clear correlation was observed between the malformed organs (encephalon, maxillary process, branchial arch) and the apoptotic regions (neuroepithelium, maxillary process, branchial arch), which were histologically determined using the TUNEL (3' terminal deoxynucleotide tranferase (TdT)-mediated dUTP-biotin nick end labeling) technique. The authors thus conclude that apoptosis plays a role in the malformations (Menegola et al. 2001).

The available data from *in vitro* test systems indicate an embryotoxic potential

Table 4 Developmental toxicity studies with acetaldehyde

Species, strain, number of animals per group	Exposure	Findings	References
rat,Wistar, 29 pregnant ♀, controls 25 ♀	**GD 5**, 150–200 nM, 0.5 ml/100 g body weight, (0.03–0.04 µg/kg body weight), intravenous, vehicle not specified, controls untreated, examined GD 6	**0.03–0.04 µg/kg body weight and day:** embryos: delayed formation of the blastocyst dams: toxicity not specified	Checiu et al. 1984

Table 4 (Continued)

Species, strain, number of animals per group	Exposure	Findings	References
rat, Wistar, 10–12 pregnant ♀	**GD 13,** 1, 10%, 0.02 ml/rat (1.3, 13 mg/kg body weight assuming a body weight of 200 g), injection into amniotic fluid, in physiological saline, controls: physiological saline, examined GD 20	**1.3 mg/kg body weight and day:** foetuses: mortality 70%; incidence of malformations (craniocele, hydrocephalus) increased **13 mg/kg body weight and day:** foetuses: mortality 100% dams: toxicity not specified	Bariliak and Kozachuk 1983
rat, strain and number of animals not specified	**GD 8–13,** 0, 10, 50 mg/kg body weight, intraperitoneal, in physiological saline, controls: physiological saline, postnatal examination (no other details)	**10 mg/kg body weight and day:** offspring: unusual findings in behavioural tests (surface righting); dams: toxicity not specified **50 mg/kg body weight and day:** offspring: unusual findings in behavioural tests (water maze, learning behaviour, auditory startle) dams: toxicity not specified	Schreiner et al. 1987
rat, CF, 7–9 pregnant ♀	**GD 8–15,** 0, 50, 75, 100, 150 mg/kg body weight and day, intraperitoneal, in physiological saline, controls physiological saline or untreated, examined GD 21	**50 mg/kg body weight and day and above:** foetuses: resorptions dose-dependently increased, number of dead foetuses dose-dependently increased, body weights decreased, incidence of malformations (microcephaly, micrognathia, micromelia, syndactylism, hydronephrosis, oedema and subcutaneous haemorrhages in face and feet) increased, delayed ossification dams: up to GD 16 food and water intake and body weight gains reduced **150 mg/kg body weight and day:** dams: lethal	Padmanabhan et al. 1983
rat,		50 mg/kg body weight and day and above:	

Table 4 (Continued)

Species, strain, number of animals per group	Exposure	Findings	References
CF, 6–10 pregnant ♀, controls 13	**GD 10, 11 or 12**, **GD 10–12**, 0, 50, 75, 100 mg/kg body weight and day, intraperitoneal, in physiological saline, controls physiological saline, examined GD 21	foetuses: resorptions increased, reduced growth rates, body weights decreased, placental weights decreased, incidence of malformations (microcephaly, micrognathia, micromelia, hydrocephaly, exencephaly, oedema and haemorrhages) increased dams: toxicity not specified	Sreenathan et al. 1982
rat, CF, number of animals not specified, evaluation of a total of 5–9 litters	**GD 8–15**, 0, 50 mg/kg body weight and day, intraperitoneal, in physiological saline, controls physiological saline, examined GD 16–21	50 mg/kg body weight and day: foetuses: malformations of the skeleton (wavy ribs), delayed ossification dams: toxicity not specified	Sreenathan et al. 1984
rat, Sprague Dawley, number of animals not specified	**GD 9–12**, 0, 1% solution, intraperitoneal (100 mg/kg body weight and day), in physiological saline, controls 0.9% physiological saline, examined GD 12	100 mg/kg body weight and day: foetuses: head lengths decreased, crown–rump lengths and morphological score unchanged dams: toxicity not specified	Ali and Persaud 1988
rat, Crl:COBS, CD®(SD)BR, 22 pregnant ♀	**GD 6–15**, 0, 400 mg/kg body weight and day, by gavage, in distilled water, controls corn oil, examined GD 20	400 mg/kg body weight and day: foetuses: NOAEL dams: water and food intake increased, otherwise no effects (regarding mortality, clinical pathology, body weights, macroscopic findings)	Rhône-Poulenc 1983

Table 4 (Continued)

Species, strain, number of animals per group	Exposure	Findings	References
mouse, CFLP, 12–16 pregnant ♀	**GD 7–9**, 1, 2% (v/v); 0.1 ml/25 g body weight, (about 31, 62 mg/kg body weight), intravenous, in physiological saline, controls: physiological saline, examined GD 10 and 19	31 mg/kg body weight and day and above: foetuses: resorptions increased (GD 10, 19), crown–rump lengths decreased (GD 10, 19), neural tube defects (GD 10); body weights decreased (GD 19), no externally visible anomalies (GD 19) 62 mg/kg body weight and day: dams: transient locomotor disturbances, no changes in body weight	O'Shea and Kaufman 1979
mouse, CFLP, 6–9 pregnant ♀	**GD 6, 7 or 8, GD 6–8, GD 7–8, GD 7–9**, 2% (v/v); 0.1 ml/25 g body weight, (about 62 mg/kg body weight), intravenous, in physiological saline, controls: physiological saline or untreated, examined GD 10 and 12	62 mg/kg body weight and day: foetuses: resorptions increased, crown–rump lengths decreased, protein content decreased, neural tube defects dams: no changes in body weights	O'Shea and Kaufman 1981
mouse, C57BL/6J, number of animals not specified, evaluation of 4–14 litters each examination time	**GD 7, 8, 9 or 10**, dose of 320 mg/kg body weight in arachis oil: once, twice (30 minutes apart) or twice (6 hours apart), intraperitoneal, controls: arachis oil, examined GD 18	320 mg/kg body weight and day: foetuses: incidence of malformations (omphaloceles, mandibular hypoplasia, polydactylism) increased, treatment on GD 7 or 8 produced facial abnormalities, treatment on GD 9 or 10 caused malformations of the forelimbs dams: toxicity not specified: number of resorptions unchanged	Webster et al. 1983

Table 4 (Continued)

Species, strain, number of animals per group	Exposure	Findings	References
mouse, LACA, number of animals not specified	**GD 9,** 0, 2, 4, 6%, 8 ml/kg body weight, (160, 320, 480 mg/kg body weight), intraperitoneal, in physiological saline, controls: physiological saline, examined GD 19	up to 480 mg/kg body weight and day: foetuses: microscopic examination did not yield unusual findings, no effects on DNA synthesis, no other investigations dams: toxicity not specified	Bannigan and Burke 1982
mouse, CD-1, number of animals not specified, evaluation of 8 litters per group, untreated controls 14 litters	**GD 9,** 5 × 200 mg/kg body weight (at intervals of 2 hours), intraperitoneal, in physiological saline, controls: physiological saline or untreated, examined GD 18	5 × 200 mg/kg body weight and day: foetuses: no effects (resorptions, number of dead foetuses, incidence of malformed foetuses, body weights) dams: toxicity not specified	Blakley and Scott 1984 b

GD: gestation day

for acetaldehyde, which can probably be attributed to its pronounced cytotoxic or genotoxic properties.

In vivo

Investigations of developmental toxicity in rats and mice are summarized in Table 4; in most studies administration of the substance was performed via intraperitoneal or intravenous injection, in only one study was oral administration used (see Table 4).

– Prenatal developmental toxicity

In rats given very low intravenous acetaldehyde concentrations of 0.15 to

0.2 µM, the delayed formation of blastocysts was reported on day 5 of gestation (Checiu et al. 1984). The translation of these findings to humans is not plausible, as the endogenous concentration of acetaldehyde in human blood is approximately 10 times higher. In addition, the study is poorly documented and, as only one dose was tested, cannot be used for evaluation. In comparison, 5 µM acetaldehyde produced no effects in *in vitro* studies with 10-day-old rat embryos (Campbell and Fantel 1983).

The high embryonic and foetal mortality observed in a study in which acetaldehyde was injected into the amniotic fluid of pregnant rats (Bariliak and Kozachuk 1983) can be assumed to be the result of the unusual method of substance administration. The results can therefore not be used for quantitative evaluation.

Even at the lowest dose of 50 mg/kg body weight and day, the intraperitoneal administration of acetaldehyde to rats from days 8 to 15 of gestation or on individual days within this period resulted in increased resorption, foetal mortality and malformations; in the dams, body weight gains were reduced at this dose. Doses of 150 mg/kg body weight and day were lethal for the dams (Padmanabhan et al. 1983; Sreenathan et al. 1982, 1984).

In the only available oral developmental toxicity study, 22 pregnant Sprague Dawley rats were given acetaldehyde doses of 400 mg/kg body weight and day by gavage in distilled water from days 6 to 15 of gestation. The controls received corn oil. Upon examination on day 20 of gestation, there were no unusual findings in the dams as regards the number of pregnancies, the number of corpora lutea, implantations and resorptions, or in the skeleton and organs of the foetuses. No maternal toxicity was observed, although the food and water intake of the dams was increased (Rhône-Poulenc 1983; Table 4).

In mice given intravenous acetaldehyde doses of 31 mg/kg body weight and above from days 7 to 9 of gestation, the number of resorptions was increased, the crown–rump lengths were reduced, and abnormalities such as neural tube defects were increased (O'Shea and Kaufman 1979). It must nevertheless be taken into account that in mice the intravenous injection of the substance causes stress in the dams; particularly in the mouse, stress alone (such as heat) has been demonstrated to cause various malformations (for example, cleft palate and neural tube defects) in the offspring (Shiota 1988). In addition, the duration of the daily injection is not given. As short-term symptoms of intoxication were seen in the dams, rapid injection and thus bolus administration must be assumed. The study is therefore not suitable for evaluating continuous inhalation exposure at the workplace.

An increase in malformations such as microcephaly, micrognathia, micromelia, syndactyly, hydronephrosis, oedema and subcutaneous haemorrhage was observed after the intraperitoneal administration of acetaldehyde doses of 320 mg/kg body weight on one of the days 7 to 10 of gestation (Webster et al. 1983). Five intraperitoneal acetaldehyde doses of 200 mg/kg body weight at intervals of 2 hours, corre-

sponding to 1000 mg/kg body weight, on day 10 of gestation did not cause any effects in the foetuses, however (Blakley and Scott 1984 b).

– Postnatal developmental toxicity

After intraperitoneal administration of acetaldehyde on days 8 to 13 of gestation, abnormalities in behavioural tests were observed in the offspring both at

Table 5 Studies of the genotoxicity of acetaldehyde *in vitro*

Test system		Concentration	Result		Comment	References
			–	+		
			m. a.	m. a.		
Bacteria						
differential killing	*Escherichia coli* K-12 343/636 and 343/591	up to 370 mM (16.3 mg/ml)	–	n.d.	no surviving colony at 123 mM (5.4 mg/ml)	Hellmér and Bolcsfoldi 1992
differential killing	*E. coli* pol A^+/ pol A^-	10 µl/plate (7830 µg/plate)	weak +	n.d.	cytotoxicity not specified	Rosenkranz 1977
BMT (plate incorporation)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA	0.5% in air, no other details	–	–	data not usable as not specified whether a closed system or not	IARC 1999
BMT (plate incorporation)	*S. typhimurium* TA1535	10 µg/plate	–	–	cytotoxicity not specified	Dellarco 1988
BMT (plate incorporation)	*S. typhimurium* TA100	concentration not specified	–	n.d.	cytotoxicity not specified	Dellarco 1988
BMT (plate incorporation)	*S. typhimurium* TA1535	0.01–2.5 µmol/ plate (0.44–110 µg/plate)	–	–	cytotoxicity not specified	Pool and Wiessler 1981
BMT (plate incorporation)	*S. typhimurium* TA1535, TA1538	10 µl/plate (7830 µg/plate)	–	n.d.	cytotoxicity not specified	Rosenkranz 1977
BMT (preincubation)	*S. typhimurium* TA98, TA100, TA1535, TA1537	up to 10000 µg/ plate, diluted in 95% ethanol	–	–	cytotoxicity at 10000 µg/ plate	Mortelmans et al. 1986
BMT (preincubation)	*S. typhimurium*	up to 1 mg/plate	–	n.d.	highest non-toxic	Marnett et al. 1985

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			–	+		
			m. a.	m. a.		
	TA102, TA104				dose at > 114 µmol (5 mg)	
BMT (preincubation)	*S. typhimurium* TA100	concentration not specified	n.d.	–	cytotoxicity not specified	Sasaki and Endo 1978
BMT (preincubation)	*E. coli* WP2 uvrA	880 µM (39 µg/ml)	+	n.d.	lethal for 31% of the culture after 30 minutes	Véghelyi et al. 1978
BMT (preincubation)	*E. coli* WP2 uvrA	20–10000 µM (0.88–441 µg/ml)	–	n.d.	cytotoxicity not specified	Hemminki et al. 1980
BMT (preincubation)	*E. coli* WP2 uvrA trp$^-$	0.1% (780 µg/ml)	+	n.d.	cytotoxicity not specified	Igali and Gazsó 1980
Mammalian cells						
SCE	human lymphocytes	2×10^{-3}, 1×10^{-2}% (v/v) (16, 78 µg/ml)	+	n.d.	cytotoxicity not specified	Obe et al. 1986
SCE	human lymphocytes	0.0005–0.001% (v/v) (4–8 µg/ml)	+ at 4 µg/ml and above	n.d.	> 0.001% (8 µg/ml) cytotoxicity	Jansson 1982
SCE	human lymphocytes	0.063–2 mM (2.8–88 µg/ml)	+ at 0.25 mM (11 µg/ml) and above	n.d.	proliferation index decreased at 0.5 mM and above (22 µg/ml)	Norppa et al. 1985
SCE	human lymphocytes	0.0005–0.002% (4–16 µg/ml)	+ at 0.001% (8 µg/ml) and above	n.d.	cytotoxicity not specified	Ristow and Obe 1978

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			– m. a.	+ m. a.		
SCE	human lymphocytes	90–1080 µM (4–48 µg/ml)	+ at 0.72 mM (29 µg/ml) and above	n.d.	cytotoxicity at > 1080 µM (48 µg/ml)	Böhlke et al. 1983
SCE	human lymphocytes	1–100 µM (0.04–4.4 µg/ml)	+ at 0.1 mM (4.4 µg/ml)	n.d.	no cytotoxicity in the tested concentration range	Knadle 1985
SCE	human lymphocytes	100–400 µM (4.4–18 µg/ml)	+ at 0.1 mM (4.4 µg/ml) and above	n.d.	no cytotoxicity in the tested concentration range	Helander and Lindahl-Kiessling 1991
SCE	human lymphocytes	250–500 µM (11–22 µg/ml)	n.d. + at 0.25 mM (11 µg/ml) and above	– n.d.	no cytotoxicity in tested concentration range	Sipi et al. 1992
SCE	human lymphocytes	20, 40 µg/ml (0.45, 0.91 mM)	+ 20 µg/ml (0.45 mM)	n.d.	cytotoxicity at > 1 mg/ml (23 mM)	Badr and Hussain 1977
SCE	human lymphocytes	0.1–0.3 mM (4.4–13 µg/ml) 70 hours; 0.6–2.4 mM (26–106 µg/ml) 1 hour	+ at 0.1 mM (4.4 µg/ml) and above at 70 hours, at 0.6 mM (26 µg/ml) and above in 1 hour	n.d.	no drastic decrease in proliferation indices in tested concentration range	He and Lambert 1985

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			– m. a.	+ m. a.		
SCE	human lymphocytes	0.1–2.4 mM (4.4–106 µg/ml)	+ at 0.1 mM (4.4 µg/ml) and above	n.d.	cytotoxicity not specified	Lambert and He 1988
SCE	human lymphocytes	20–400 µM (0.9–18 µg/ml)	+ at 40 µM (1.8 µg/ml) and above	n.d.	400 µM (18 µg/ml) cytotoxic	Véghelyi et al. 1978
SCE	CHO cells	20–400 µM (0.9–18 µg/ml)	+ at 40 µM (1.8 µg/ml) and above	n.d.	880 µM (39 µg/ml) 100% of cells dead	Véghelyi et al. 1978
SCE	CHO cells	30–300 µM (1.3–13 µg/ml)	+ at 30 µM (1.3 µg/ml) and above	n.d.	cytotoxicity not specified	Brambilla et al. 1986
SCE	CHO cells	8–80 µg/ml (0.18–1.8 mM) (–m. a.); 0.8–40 µg/ml (0.02–0.9 mM) (+ m. a.)	+ at 40 µg/ml (0.9 mM) and above	+ at 40 µg/ml (0.9 mM) and above	no cytotoxicity in the tested concentration range	de Raat et al. 1983
SCE	CHO cells	0.00025–0.0015% (2–12 µg/ml)	+ at 0.00025% (2 µg/ml) and above	n.d.	cytotoxicity not specified	Obe and Beek 1979
SCE	CHO cells	0.0005–0.004% (3.9–31 µg/ml)	+ at 0.0005% (3.9 µg/ml) and above	n.d.	cytotoxicity at 0.003% (23 µg/ml) and above	Obe and Ristow 1977

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			– m. a.	+ m. a.		
comet assay	human lymphocytes	1.56–100 mM (69–4400 µg/ml)	+ at 1.56 mM single strand breaks, at 100 mM double strand breaks	n.d.	100 mM (4400 µg/ml) (1 hour): < 20% surviving cells	Singh and Khan 1995
comet assay	human lymphocytes	3–200 mM (132–8800 µg/ml)	+ at 3 mM (132 µg/ml) and above	n.d.	> 70% survivors at 200 mM (8800 µg/ml)	Blasiak et al. 2000
comet assay	mucosa cells, stomach, human	3–200 mM (132–8800 µg/ml)	+ at 3 mM (132 µg/ml) and above	n.d.	> 70% survivors at 200 mM (8800 µg/ml)	Blasiak et al. 2000
comet assay	mucosa cells, colon, human	3–200 mM (132–8800 µg/ml)	+ at 3 mM (132 µg/ml) and above	n.d.	70% survivors at 200 mM (8800 µg/ml)	Blasiak et al. 2000
alkaline elution	human lymphocytes	10, 20 mM (440, 880 µg/ml)	– strand breaks + DNA crosslinks at 10 mM (440 µg/ml) and above	n.d.	no other details	Lambert et al. 1985
alkaline elution	bronchial epithelial cells, human	1 mM (44 µg/ml)	–	n.d.	ID50 (concentration which decreases the growth rate by 50%): 30 mM	Saladino et al. 1985

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			–	+		
			m. a.	m. a.		
					(1320 µg/ml)	
alkaline elution	bronchial epithelial cells, human	1–100 mM (44–4400 µg/ml)	– single strand breaks; + DNA crosslinks at 3 mM (132 µg/ml) and above	n.d.	ID50 (concentrations which lead to 50% inhibition): 25 mM (1100 µg/ml) (colony-forming efficiency); 125 mM (5500 µg/ml) viability	Grafström et al. 1994
alkaline elution	CHO cells	0.5–4.5 mM (22–198 µg/ml)	– single strand breaks; + DNA crosslinks at 1.5 mM (66 µg/ml) and above	n.d.	viability (% of controls) over the entire concentration range 100%	Marinari et al. 1984
alkaline elution	rat hepatocytes	0.03–3 mM (1.3–132 µg/ml)	–	n.d.	viability (% of controls) > 58%	Sina et al. 1983
alkaline unwinding	mouse lymphoma cells	1.5–44 mM (66–1900 µg/ml)	–	n.d.	84% not viable at 44 mM (1900 µg/ml)	Garberg et al. 1988
CA	rat fibroblasts	0.01–1 mM (0.44–44 µg/ml)	+ at 0.1 mM (4.4 µg/ml) and above	n.d.	cytotoxicity not specified	Bird et al. 1982

10 mg/kg and at 50 mg/kg body weight and day (Schreiner et al. 1987). No data

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			– m. a.	+ m. a.		
CA	human lymphocytes	0.001; 0.002% (v/v) 0.18–0.36 mM (8–16 µg/ml)	– 3 persons + in human lymphocytes of 1 person with Fanconi's anaemia	n.d.	cytotoxicity not specified	Obe et al. 1979
CA	human lymphocytes	0.8 µg/ml (0.02 mM), 2×/day, 4 days	+	n.d.	cytotoxicity not specified	WHO 1995
CA	human lymphocytes	0.1–20 mM (4–880 µg/ml) 2×/day, 5 days	+ not specified whether m.a.		cytotoxicity not specified	WHO 1995
CA	human lymphocytes, human fibroblasts	40–800 µM (1.8–35 µg/ml)	+ at 0.4 mM (70 µg/ml) and above	n.d.	cytotoxicity at 800 µM (35 µg/ml) and above	Véghelyi and Osztovics 1978
CA	human lymphocytes	90–1080 µM (4–48 µg/ml)	+ at 0.72 mM (33 µg/ml) and above	n.d.	cytotoxicity at > 1080 µM (48 µg/ml)	Böhlke et al. 1983
CA	embryo cells, Chinese hamster	0.002–0.006% (0.35–1.1 mM; 16–48 µg/ml)	+ at 0.006% (1.1 mM) aneuploidy (usually hypodiploidy, but also hyperdiploidy)	n.d.	highest concentration: mitosis index decreased	Dulout and Furnus 1988

were given for maternal toxicity. As the abstract provides no other details, and no information is available about the body weight gains of the offspring, which

Table 5 (Continued)

Test system		Concentration	Result		Comment	References
			–	+		
			m. a.	m. a.		
CA	CHO cells	88–5000 µg/ml (2–114 mM)	+ at 2 mM (88 µg/ml) and above	n.d.	cytotoxicity not specified	WHO 1995
MN	human lymphocytes	0.2–2.0 mM (8.8–88 µg/ml)	+ at 0.8 mM (35 µg/ml) and above	n.d.	cytotoxicity at > 1 mM	Migliore and Nieri 1991
MN	human lymphocytes	0.6–1 mM (26–44 µg/ml)	+ at 0.6 mM (26 µg/ml) and above	n.d.	no cytotoxicity; additional test (FISH) showed aneugenic effects possible	Migliore et al. 1996
MN	rat fibroblasts	0.1–10 mM (4.4–440 µg/ml)	+ at 0.5 mM (22 µg/ml) and above	n.d.	cytotoxicity not specified	Bird et al. 1982
HPRT	human lymphocytes	0.6–2.4 mM (27–106 µg/ml) (24 hours); 0.2–0.6 mM (8.8–27 µg/ml) (48 hours)	+ at 1.2 mM and above (after 24 hours); at 0.2 mM and above (after 48 hours)	n.d.	relative survivors: 0.6% at 3.6 mM (158 µg/ml) (24 hours)	He and Lambert 1990
HPRT	human fibroblasts	1–12 mM (44–528 µg/ml)	+ at 5 mM (220 µg/ml) and above	n.d.	50% survivors at 5 mM (220 µg/ml)	Grafström et al. 1994
$TK^{+/-}$	L5178Y mouse lymphoma cells	4–8 mM (176–352 µg/ml)	+ at 4 mM (176 µg/	n.d.	toxic at highest	Wangenheim and

could have influenced the behavioural parameters, these findings cannot be evaluated.

Table 5 (Continued)

Test system	Concentration	Result		Comment	References
		–	+		
		m. a.	m. a.		
		ml) and above		concentration, colony size not specified	Bolcsfoldi 1988

BMT: bacterial mutagenicity test, CA: chromosomal aberrations, HPRT: hypoxanthine-phosphoribosyl-transferase test, m. a.: metabolic activation, MN: micronucleus test, n. d.: not determined, SCE: sister chromatid exchange, TK: thymidine kinase

Table 6 Studies of the genotoxicity of acetaldehyde *in vivo*

5.6 Genotoxicity

The many results available for the genotoxicity of acetaldehyde *in vitro* are summarized in Table 5.

5.6.1 In vitro

DNA adducts

With isolated DNA (Fang and Vaca 1995; Fraenkel-Conrat and Singer 1988; Inagaki et al. 2003; Vaca et al. 1995; Wang et al. 2000; see also Section 2) and mammalian cells (Inagaki et al. 2003), exposure to acetaldehyde resulted in the formation of DNA adducts. Incubation of human buccal epithelial cells with acetaldehyde in concentrations of 0, 10, 30 or 100 mM led to the formation of 0.7, 1.9, 2.2 and 2.7 N^2-ethyl deoxyguanosine adducts per 10^7 nucleotides. No other DNA adducts were investigated. The acetaldehyde concentrations used were relatively nontoxic to the cells (Vaca et al. 1998).

Bacteria

In tests for differential killing, contradictory results were obtained with *Escherichia coli*. In all *Salmonella* mutagenicity tests, acetaldehyde yielded negative results with and without the addition of a metabolic activation system.

Mammalian cells

In numerous SCE tests with human lymphocytes and CHO cells (Table 5), acetaldehyde produced only positive results. In the comet assay to determine the induc-

tion of DNA strand breaks in different types of human cells (lymphocytes, mucosa cells of stomach and colon), acetaldehyde again produced only positive results (Blasiak et al. 2000; Singh and Khan 1995). In tests with lymphocytes and bronchial epithelial cells of humans and CHO cells carried out with the alkaline elution technique, no single strand breaks were found, although DNA crosslinks did occur (Grafström et al. 1994; Lambert et al. 1985; Marinari et al. 1984; Saladino et al. 1985; Sina et al. 1983). Acetaldehyde was found to be clastogenic in a number of chromosomal aberration tests with human lymphocytes, human fibroblasts and CHO cells (Bird et al. 1982; Böhlke et al. 1983; Dulout and Furnus 1988; Véghelyi and Osztovics 1978; WHO 1995). In several micronucleus tests with human lymphocytes (Migliore and Nieri 1991; Migliore et al. 1996) and rat fibroblasts (Bird et al. 1982), acetaldehyde yielded positive results. The authors concluded from the results of a micronucleus test which included an additional investigation (FISH) that aneugenic effects cannot be excluded (Migliore et al. 1996). In gene mutation tests with human fibroblasts and human lymphocytes (HPRT; Grafström et al. 1994; He and Lambert 1990) and mouse lymphoma cells ($TK^{+/-}$; Wangenheim and Bolcsfoldi 1988) without the addition of a metabolic activation system, acetaldehyde induced mutations.

Test system	Species, strain, number per group	Exposure	Result	Comment	References
Soma cells					
SMART	***Drosophila melanogaster***, mwh-flr^3 CROSS, 160 wings evaluated	**48 hours**, 0.18 mM in diet	weakly +, but reproducible		Graf et al. 1989
SCE, bone marrow	**mouse**, CBA, 1 ♂	**single**, intraperitoneal, 0, 0.5, 1 ml 10^{-4}% (v/v)	after 28 hours: +	non-standardized test; toxicity not specified	Obe et al. 1979
SCE, bone marrow	**hamster**, Chinese, 6–7	**single**, intraperitoneal, 0, 0.01, 0.1, 0.5 mg/kg body weight	+ at 0.5 mg/kg body weight	non-standardized test; mortality at 0.6 mg/kg body weight and above	Korte and Obe / et al. 1981

Table 6 (Continued)

Test system	Species, strain, number per group	Exposure	Result	Comment	References
MN, bone marrow, peripheral blood	**mouse**, CD-1, 6 ♂/dose	**single**, intraperitoneal, 0, 95, 190, 380 mg/kg body weight in sodium chloride solution, purity: 89.4%	after 24 hours: + at 190 mg/kg body weight and above	LD_{50} 470 mg/kg body weight	Morita et al. 1997
MN, bone marrow, peripheral blood	**mouse**, CD-1, 5 ♂	**single**, intraperitoneal, 0, 100, 200, 300, 400 mg/kg body weight in sodium chloride solution, purity: > 99.5%	after 24 hours: + at 200 mg/kg body weight and above	LD_{50} 338 mg/kg body weight	Morita et al. 1997
MN, peripheral blood	**mouse**, C57BL/6J, 4 ♂, control animals: 2 ♂	**5 days**, intraperitoneal, 0, 6, 12 mg/kg body weight in sodium chloride solution, purity: not specified	+	toxicity not specified	Ma et al. 1985
Germ cells					
SLRL (Basc-technique)	***Drosophila melanogaster***, > 20 ♂/brood (total of 3), 1 ♂ mated with 3 ♀	**3 days**, diet, 25 µl/ml in 10% ethanol	–	mortality 3%	Woodruff et al. 1985
SLRL (Basc-technique)	***Drosophila melanogaster***, > 20 ♂/brood (total of 3), 1 ♂ mated with 3 ♀	**single**, injection, 22.5 µl/ml in 10% ethanol	+	mortality 29%	Woodruff et al. 1985

Table 6 (Continued)

Test system	Species, strain, number per group	Exposure	Result	Comment	References
MN, early spermatids	**mouse**, hybrid (C57BL/6J×C3H/He) 4 ♂, control animals: 7 ♂	**single**, intraperitoneal, 0, 125, 250, 500 mg/kg body weight in sodium chloride solution	after 13 days: –	only one specific stage investigated, not the entire spermatogenesis	Lähdetie 1988

SLRL: sex-linked recessive lethal mutations, SMART: somatic mutagenicity and recombination test, MN: micronucleus test, SCE: sister chromatid exchange

5.6.2 In vivo

The results of tests of the genotoxicity of acetaldehyde *in vivo* are shown in Table 6. There are no investigations available of DNA adduct formation *in vivo*.

All the investigations in rodents involved intraperitoneal injection.

Somatic cells

In a *Drosophila* test for somatic mutations and recombinations, acetaldehyde yielded weakly positive results (Graf et al. 1989). In the bone marrow of the mouse, acetaldehyde (purity: > 99.5%) was found to be clastogenic in a valid micronucleus test (Morita et al. 1997). In two other micronucleus tests (Ma et al. 1985; Morita et al. 1997) and two tests for the induction of SCE (Korte and Obe et al. 1981; Obe et al. 1979), acetaldehyde also yielded positive results. In these tests, however, shortcomings were evident (methodological shortcomings, insufficient data regarding toxicity or the inadequate purity of the test substance of 89%).

Germ cells

In an SLRL (sex-linked recessive lethal) test with *Drosophila melanogaster*, acetaldehyde induced lethal mutations after injection, though not after dietary intake (Woodruff et al. 1985). A micronucleus test in early spermatids of mice yielded negative results (Lähdetie 1988).

Table 7 Cell transformation tests with acetaldehyde

Test system	Concentration	Result		Comment	References
		– m. a.	+ m. a.		
C3H/10Tl/2 cells, mouse	10–100 µg/ml	–	n.d.	LC_{50}: 25 µg/ml	Abernethy et al. 1982
		+ at 10 µg/ml together with 0.25 µg/ml TPA and above			
cell line, HRRT, kidney, rat	up to 3 mM (132 µg/ml)	–	n.d.	no cytotoxicity up to 3 mM (132 µg/ml)	Eker and Sanner 1986
		+ at 3 mM with 0.1 µg/ml TPA			

HRRT: hereditary renal rat tumour; m. a.: metabolic activation; n.d.: not determined; TPA: 12-*O*-tetradecanoyl phorbol-13-acetate

Table 8 Carcinogenicity studies with inhalation exposure to acetaldehyde

Author:	Woutersen et al. 1985
Substance:	acetaldehyde (purity: 99.8%)
Species:	rat, Wistar, 105 ♂/105 ♀ per concentration group: 5 ♂/5 ♀ for interim investigations (weeks 13 and 26); 10 ♂/10 ♀ for interim investigation (week 52); 30 ♂/30 ♀ for observation; i.e. only 55 ♂/55 ♀ remaining, exposed for 27 months
Administration route:	whole-body exposure
Concentration:	0, 750, 1500, 3000 ml/m³, 6 hours/day, 5 days/week,
	highest concentration decreased graduallyrom day 141 to 1000 ml/m³ by day 360 because of delayed growth, body weight loss, early mortality
Duration:	27 months
Toxicity:	**750 ml/m³**: mortality increased, delayed growth; olfactory epithelium: basal cell hyperplasia
	1500 ml/m³: mortality increased, delayed growth; olfactory epithelium: basal cell hyperplasia with atypical cells, focal squamous cell metaplasia with and without hyperkeratosis, gland-like structures

Table 8 (Continued)

		in connective tissue of the submucosa; respiratory epithelium: squamous cell metaplasia and hyperkeratosis, papillomatous hyperplasia, severity of effects on respiratory epithelium increasing from week 13 over week 26 to week 52; larynx: hyperplasia, squamous cell metaplasia **3000 ml/m³**: mortality increased, delayed growth; olfactory epithelium: focal squamous cell metaplasia with and without hyperkeratosis, no hyperplasia of basal cells up to the observation period in week 52 although in the interim investigation in week 52 hyperplasia of the basal cells in the olfactory epithelium were observed; respiratory epithelium: squamous cell metaplasia with keratinization; larynx: hyperplasia, squamous cell metaplasia; severity of the effects in the nose were concentration-dependent, all animals in the high concentration group had died after about 23 months; see Section 5.2.1			
		Concentration (ml/m³)			
		0	750	1500	3000/1000
Survivors	♂	52/55 (94.5%)	51/55 (92.7%)	49/55 (89.1%)	27/55 (49.1%)
(on day 468):	♀	54/55 (98.2%)	53/55 (96.4%)	53/55 (96.4%)	48/55 (56.4%)
Tumours:					
Nose:					
adenocarcinomas	♂	0/49	16/52 (30.8%)**	30/53 (56.6%)**	20/49 (40.8%)**
	♀	0/50	6/48 (12.5%)*	26/53 (49.1%)**	20/53 (37.7%)**
squamous cell carcinomas	♂	1/49 (2.0%)	1/52 (1.9%)	10/53 (18.9%)**	14/49 (28.6%)**
	♀	0/50	0/48	5/53 (9.4%)*	17/53 (32.1%)**
Author:		Feron et al. 1982; Feron *et al.* 1980 in documentation "Acetaldehyde" 1972 (German)			
Substance:		acetaldehyde ("purity checked", no other details)			
Species:		Syrian golden hamster, 30 ♂/30 ♀ per concentration group			
Administration route:		whole-body exposure			
Dose:		0, 2500 ml/m³, 7 hours/day, 5 days/week, after 9 weeks the concentration was decreased in steps to 1650 ml/m³ by week 45 and thereafter because of delayed growth and early mortality			
Duration:		52 weeks, observation period up to week 81			
Toxicity:		mortality increased, body weight decreased; ♀: relative lung and kidney weights increased, activity of alkaline phosphatase in serum increased;			

Table 8 (Continued)

		nose: rhinitis, decrease in thickness and degeneration of the olfactory epithelium, hyperplasia/metaplasia of the respiratory epithelium and thickening of the submucosa, almost exclusively in dorsomedial section of the nasal cavity, metaplastic squamous epithelium; larynx: slight to moderate focal metaplasia of the epithelium, atrophic, inflammatory, hyperplastic and metaplastic changes; trachea: slight to moderate focal metaplasia of the epithelium; see Section 5.2.1	
		Concentration (ml/m^3)	
		0	2500/1650
Survivors (week 52)	♂ ♀	26/30 (86.7%) 26/30 (86.7%)	24/30 (80.0%) 21/30 (70.0%)
Tumours:			
Nose:			
epithelial hyperplasia/ metaplasia	♂	slight/moderate: 0/24	slight/moderate: 10/27 (37.0%)
		severe: 0/24	severe: 4/27 (14.8%)
	♀	slight/moderate: 0/23	slight/moderate: 10/26 (38.5%)
		severe: 0/23	severe: 11/26 (42.3%)
Larynx:			
epithelial hyperplasia/ metaplasia	♂	without atypia [a]: 1/20 (5.0%)	without atypia: 6/23 (26.1%)
		with atypia: 0/20	with atypia: 4/23 (17.4%)
	♀	without atypia: 0/22	without atypia: 4/20 (20.0%)
		with atypia: 0/22	with atypia: 3/20 (15.0%)
carcinomas *in situ*	♂ ♀	0/20 0/22	3/23 (13.0%) 0/20
squamous cell carcinomas or adenomatous squamous cell carcinomas	♂ ♀	0/20 0/22	2/23 (8.7%) 3/20 (15.0%)
		The increases in the tumour incidences in exposed animals compared with in the controls are not statistically significant (Fisher's exact test, one-sided). The authors conclude that acetaldehyde has both irritative and carcinogenic effects in the nose and larynx, as even after a 29-week recovery period the hyperplasia and metaplasia in the epithelia of nose and larynx remained irreversible and tumours developed	

* $p < 0.05$,** $p < 0.01$ (Fisher's exact test),[a] nuclear or cellular atypia

5.7 Carcinogenicity

5.7.1 Short-term studies

The results of cell transformation tests with acetaldehyde are shown in Table 7. In two cell transformation tests with different test systems, acetaldehyde produced negative results. After the addition of 12-*O*-tetradecanoyl phorbol-13-acetate, however, the frequency of cell transformations increased Abernethy et al. 1982; Eker and Sanner 1986

5.7.2 Long-term studies

A carcinogenicity study with rats was already described in detail in the supplement from 1986 (documentation "Acetaldehyde" 1992). The most important findings are presented again here (Table 8). In this study 55 male and 55 female Wistar rats per group were exposed to acetaldehyde concentrations of 0, 750, 1500 or 3000 ml/m^3 (purity 99.8%) for 27 months in whole-body exposure chambers. On account of delayed growth, occasional loss of body weight and early mortality, the highest concentration was decreased in steps from day 141 to 1000 ml/m^3 on day 360. In both

Table 9 Oral carcinogenicity study with acetaldehyde

Author:	Soffritti et al. 2002
Substance:	acetaldehyde (purity: > 99.0%)
Species:	rat, Sprague Dawley, 50 ♂/50 ♀ per concentration group
Administration route:	oral, drinking water
Dose:	0, 50, 250, 500, 1500, 2500 mg/1 (about 0, 2.5, 12.5, 25, 75, 125 mg/kg body weight and day assuming a daily intake of 20 ml drinking water and a body weight of 400 g)
Duration:	administration from week 6 after birth up to death (last animal died in week 161)
Toxicity:	drinking water consumption, behaviour, body weight and survival of the treated animals were not significantly different to in the controls; histological and histopathological investigations (about 35 organs and tissue), with the exception of the tumours, did not yield unusual findings; no figures given for mortality
Tumours:	except in the 12.5 mg/kg group, the total number of malignant tumours was increased in all dose groups, although not dose-dependently. The incidences of tumours of the Zymbal gland, auditory canal, nasal and oral cavities, stomach, intestine, lungs and mammary gland were not significantly increased. Osteosarcomas significantly increased in ♂ after 125 mg/kg body weight and day

male and female animals the incidence of adenocarcinomas in the nose was increased after concentrations of 750 ml/m³ and above. Increased incidences of squamous cell carcinomas in the nose were observed in the males of the middle and high concentration groups and in the females of the high concentration group (Woutersen et al. 1985).

Also a study with hamsters was already quoted in documentation "Acetaldehyde" 1983 (German). This is again presented here in greater detail (Table 8). The incidences of carcinomas of the larynx were increased after inhalation exposure to 2500 ml/m³ (reduction to 1650 ml/m³ between week 9 and week 45 because of delayed growth and to avoid early mortality) for 52 weeks in whole-body exposure chambers. In addition, acetaldehyde markedly increased the incidence of benzo[*a*] pyrene-induced tracheobronchiolar carcinomas (Feron et al. 1982; Feron *et al.* 1980 in documentation "Acetaldehyde" 1983 (German).

A carcinogenicity study with lifetime administration of acetaldehyde with the drinking water to SD rats produced increases in the incidence of malignant tumours in all treated groups except for the females in the 12.5 mg/kg group. The increased incidences in the high dose group and in the female animals of the low dose group were significant. With the exception of the high dose group, however, the increases were not dose dependent. Affected were the Zymbal gland, auditory canal, nasal and oral cavities, stomach, intestine, lungs and mammary gland, but the increases were not statistically significant. The incidence of osteosarcomas in the males of the high dose group was significantly increased (Table 9; Soffritti et al. 2002). The study provides evidence of carcinogenic effects also after the administration of acetaldehyde with the drinking water, at least in the high dose group (about 125 mg/kg body weight and day), but cannot be used in the evaluation as a result of the absence of dose-dependency in most cases.

5.8 Other effects

"Normal" bronchi (3–4 mm in diameter) were obtained from lung tissue surgically removed from 11 patients with lung tumours. After incubation of the bronchi with 0.5 mM acetaldehyde for 24 hours, an increase in granulocyte macrophage colony-stimulating factor and nuclear factor κB was determined immunohistochemically in the epithelia. The authors concluded that acetaldehyde potentially causes inflammation in the respiratory tract via the production of these two factors (Machida et al. 2003).

"Normal" bronchi were isolated from 23 patients. After concentrations of 0.3 mM and above, acetaldehyde increased the muscle tone in the bronchi, which was accompanied by the release of increased amounts of histamine, but not of thromboxane B_2 or cysteinyl leukotrienes. One histamine receptor antagonist (H1 receptor) completely inhibited acetaldehyde-induced muscle contraction. Also in isolated mast cells, acetaldehyde induced the release of significant amounts of histamine and degranulation of these cells. The authors explain the development of

ethanol-induced asthma by the release of histamine and possible bronchoconstriction (Kawano et al. 2004).

In vitro, acetaldehyde concentrations of 0.2 mM and above decreased the motility and ciliary beat frequency of ciliated epithelial cells isolated from the bronchi of cattle. Cyanamide, an inhibitor of aldehyde dehydrogenase, caused these effects to take place earlier. The authors regard this as an indication of the presence of an aldehyde dehydrogenase in cultured ciliated cells (Sisson and Tuma 1994).

6 Manifesto (MAK value, classification)

Inhalation exposure of rats to acetaldehyde concentrations of 750 ml/m³ and above produces adenocarcinomas in the olfactory epithelium, while concentrations of 1500 ml/m³ and above lead to squamous cell carcinomas of the respiratory epithelium of the nasal mucosa. In hamsters, tumours occur in the nose and larynx.

Acetaldehyde is clastogenic, aneugenic and weakly mutagenic *in vitro* and clastogenic *in vivo*. At tumor-inducing concentrations, also cytotoxic effects are observed in the nasal mucosa.

In the 1986 supplement (documentation "Acetaldehyde" 1992) to the MAK documentation for acetaldehyde, it was assumed that chronic local tissue damage, caused by cytotoxic effects, is a precondition for the development of tumours in the nasal mucosa of rats, in analogy to formaldehyde. Therefore, the MAK value was based on the avoidance of irritant effects in the nasal mucosa. Since the 1986 supplement, no more recent data have become available for the NOAEC for these effects: the NOAEC from a 4-week study with rats is 150 ml/m³. In analogy to formaldehyde, an increase in the effects over time is unlikely, as the NOAECs for the local, histopathologically detectable irritation in the nasal epithelium of animals after short, medium and long-term exposure are within the range of 1–2 ml/m³ for formaldehyde (WHO 2002). For formaldehyde, the difference between the NOAEC for sensory irritation obtained in animal studies and the MAK value of 0.3 ml/m³ derived from results with humans is thus a factor of 3. The situation should be similar also with acetaldehyde. For this reason, the MAK value of 50 ml/m³ for acetaldehyde has been retained. However, a volunteer study with modern methods is required to confirm this value.

If the systemic availability of acetaldehyde is taken into account and the retained acetaldehyde is assumed to be completely available, the additional lifetime exposure is 1.0 µmol/l blood (compared with an endogenous lifetime exposure to acetaldehyde of 2.2 ± 1.1 µmol/l blood) when the MAK value of 50 ml/m³ is observed (Fukunaga et al. 1993). This means that the contribution made by occupational exposure to acetaldehyde is, even in the worst case, within the range of the standard deviation of endogenous exposure, so that no notable contribution to the systemic cancer risk in humans is to be expected. This assumption is supported by the absence of systemic tumours in animal studies at concentrations which never-

theless produced local tumours. Acetaldehyde is therefore assigned to Carcinogen Category 5. Nevertheless, it remains unclear whether local genotoxic effects are to be expected at 50 ml/m³, as no investigations of DNA crosslinks or DNA adducts in the nasal mucosa at this concentration are available.

As irritation is the critical effect, the limitation of exposure peaks according to Category I, with an excursion factor of 1 still applies (see the Supplement "Acetaldehyde" 2000 (German)).

As more recent data are not available, the momentary value of 100 ml/m³ has been retained (see the Supplement "Acetaldehyde" 2000 (German)).

There are no studies of dermal absorption. The systemic NOAEC is about 750 ml/m³ (1365 mg/m³) (Woutersen et al. 1985). From the physico-chemical data, it can be calculated that 1114 or 3848 mg is absorbed in one hour by 2000 cm² of skin. This calculation applies for liquid acetaldehyde and thus represents the worst-case assumption. As the systemic NOAEC corresponds to the absorption of 13650 mg in 8 hours, the contribution of dermal exposure to systemic toxicity is low, and acetaldehyde is therefore still not designated with an "H".

Apart from one report about sensitization caused by repeated application of acetaldehyde and a few reports of positive patch test reactions to acetaldehyde with unclear clinical relevance in most instances, there are no data available for the contact-sensitizing effects of acetaldehyde in humans. Findings from animal studies not carried out according to current guidelines indicate contact-sensitizing potential, but provide no clear evidence. Thus, despite suspected contact-sensitizing potential, acetaldehyde is still not designated with "Sh". As there are no data available for respiratory sensitization, the substance is also not designated with "Sa".

The available studies of developmental toxicity with intraperitoneal and intravenous administration indicate—like the *in vitro* studies—an embryotoxic (teratogenic) potential of acetaldehyde. Because of the local cytotoxic properties of acetaldehyde, intraperitoneal administration is not suitable for the quantitative evaluation of possible embryotoxic effects after inhalation exposure to acetaldehyde; also the study with intravenous administration is not suitable as a result of the method used. The oral administration of 400 mg/kg body weight and day from days 6 to 15 of gestation, in contrast, did not lead to developmental toxicity in rats. Using this NOAEL, a NOAEC of 2800 mg/m³ or 1538 ml/m³ can be calculated for humans. The difference between this and the MAK value is sufficient to justify classification in Pregnancy Risk Group C. This is supported by a developmental toxicity study with inhalation exposure to ethanol (see the 1998 documentation for ethanol), in which the metabolite acetaldehyde is held responsible for the embryotoxic effects. In this study, even ethanol concentrations of 20000 ml/m³ were not found to be embryotoxic, for which reason ethanol is classified in Pregnancy Risk Group C. Consequently, acetaldehyde is also classified in Pregnancy Risk Group C.

Acetaldehyde was found to be genotoxic both *in vitro* and *in vivo* and caused the induction of micronuclei in the bone marrow of mice (Morita et al. 1997). In toxicokinetic studies it was shown that acetaldehyde is systemically available after inhalation. A micronucleus test in the mouse with early spermatids yielded negative

results (Lähdetie 1988). This test cannot, however, be used in the evaluation, as the entire spermatogenesis was not investigated. Acetaldehyde is suspected of causing germ cell mutagenicity. The concentrations that produced positive results *in vitro* are 20 times higher than the additional body burden calculated above after exposure to concentrations of 50 ml/m³. As the *in vivo* tests were carried out with relatively high intraperitoneal doses and the inhalation studies produced no systemic tumours at high concentrations, the possible systemic genotoxic potency of acetaldehyde is considered to be so low that, when the MAK value is observed, no notable contribution to the genetic risk for humans is to be expected. Acetaldehyde is therefore classified in Germ Cell Mutagen Category 5.

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completed 28.03.2006

Acetaldehyde: Human health tier II assessment

30 June 2017

CAS Number: 75-07-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

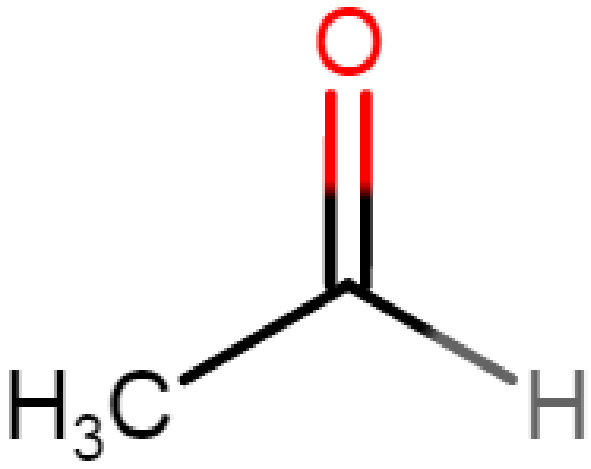
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ethanal acetic aldehyde ethyl aldehyde
Structural Formula	
Molecular Formula	C2H4O
Molecular Weight (g/mol)	44.05
Appearance and Odour (where available)	clear, colourless fuming liquid pungent, fruity odour
SMILES	C(C)=O

Import, Manufacture and Use

Australian

The total volume of the chemical introduced into Australia as reported under previous voluntary calls for information was less than 100 tonnes per annum. No specific Australian use information was provided or has been identified.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Substances and Ingredients (CosIng) database; United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory; and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic uses as a:

- masking and nail conditioning agent; and
- fragrance or flavour compound in decorative cosmetics, perfumes, toiletries, essential oils and oral care products.

The chemical has reported domestic uses including in:

- household cleaning/washing agents such as disinfectants and detergents;
- room air deodorisers;
- lacquers and varnishes; and
- adhesives and binding agents.

The chemical has reported commercial uses including:

- silvering of mirrors;
- leather tanning;
- fuel mixtures;
- denaturant for alcohol;
- finishing agent such as a hardener for gelatin fibres;
- glue casein products; and
- reprographic and photographic chemicals.

The chemical has reported site-limited uses including 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; and
- intermediate in the manufacture of aniline dyes, plastics and synthetic rubber.

Restrictions

Australian

The chemical is listed in the *Code of Practice for Supply Diversion into Illicit Drug Manufacture* as an Illicit Drug Precursors/Reagents—Category II: Requires an End User Declaration.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Carc. Cat. 3; R40 (Carcinogenicity)

Xi; R36/37 (Irritation)

Exposure Standards

Australian

The chemical has an exposure standard of 36 mg/m^3 (20 ppm) time weighted average (TWA) and 91 mg/m^3 (50 ppm) short term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica).

TWA: 37 mg/m^3 (20 ppm) [Netherlands, UK Workplace Exposure Limits (WELs)]

TWA: 45 mg/m^3 (25 ppm) [Ireland]

TWA: 90 mg/m^3 (50 ppm) [Austria maximum workplace concentration (MAK), Korea (South), Switzerland]

TWA: 91 mg/m^3 (50 ppm) [Germany]

TWA: 180 mg/m^3 (100 ppm) [Argentina, Canada (North West Territories, Yukon), Egypt, France, India, South Africa, USA (Alaska, Hawaii, Michigan, Minnesota, North Carolina, Tennessee, Vermont, Washington)]

STEL: 45 mg/m^3 (25 ppm) [Ireland, Singapore]

STEL: 90 mg/m^3 (50 ppm) [Austria (MAK), Switzerland]

STEL: 92 mg/m^3 (50 ppm) [Netherlands, USA (WELs)]

STEL: 270 mg/m^3 (150 ppm) [Argentina, Canada (North West Territories, Yukon), Egypt, India, Korea (South), South Africa, USA (Alaska, Hawaii, Michigan, Minnesota, North Carolina, Tennessee, Vermont, Washington)]

Health Hazard Information

Toxicokinetics

The European Commission Scientific Committee on Consumer Safety (SCCS) reported that the chemical is the first metabolite found in the oxidation of ethanol (SCCS, 2012). Ethanol is metabolised to the chemical by three major pathways: the alcohol dehydrogenase pathway; the microsomal ethanol oxidising cytochrome P450 pathway; and the catalase–H2O2 system. The chemical is oxidised to acetate primarily by acetaldehyde dehydrogenases. Several degradation reactions are known to produce the chemical endogenously in the human body. Inter-individual and genetic variations will affect the metabolism and levels of the chemical. Without external alcohol ingestion, the chemical is expected to be at concentrations below the level of detection, except in the gastrointestinal tract.

Acute Toxicity

Oral

Based on the available data, the chemical is considered to have moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section).

Median oral lethal dose (LD50) values in rats were between 660 and 1930 mg/kg bw. The oral LD50 value in mice was 1230 mg/kg bw (SCCS, 2012).

Dermal

The chemical was reported to have low acute toxicity via the dermal route (LD50 in rabbits of 3540 mg/kg bw) (SCCS, 2012).

Inhalation

The chemical was reported to have low acute toxicity via inhalation (median lethal concentration (LC50) in rats has been calculated as 24040 mg/m^3 (13300 ppm)) (REACH).

A 4 hour inhalation toxicity study was conducted with exposure levels of 10436 ppm, 12673 ppm, 15683 ppm and 16801 ppm. The experimental study was similar to the method described in OECD Test Guideline (TG) 403. Clinical signs of toxicity reported included restlessness and laboured respiration.

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to the respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The data available from observations in humans support this classification (see **Observation in humans** below).

Skin Irritation

Based on the available data, the chemical is not considered to cause skin irritation.

The chemical was reported to cause slight skin irritation when tested in rabbits for 4 hours under occlusive conditions in a guideline (OECD TG 404) study (REACH). In a non-guideline study on rabbits, 500 mg of the chemical produced slight irritation of the skin.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The data available from observations in humans support this classification (see **Observation in humans** below).

Observation in humans

In an inhalation exposure study, 24 volunteers were exposed to the chemical for 15 minutes at concentrations ≥91 mg/m^3 (SCCS, 2012). Eye irritation was reported for the majority of the volunteers, with effects observed in some cases at concentrations as low as 45 mg/m^3. Irritation of the upper respiratory tract was reported at concentrations ≥246 mg/m^3. Mild irritation to the upper respiratory tract was also reported in 14 humans exposed to the chemical vapour at 135 ppm (240 mg/m^3) for 30 minutes.

In a skin patch test (non-occlusive), all 13 volunteers were reported with erythema following application of a 10 % preparation of the chemical. The test vehicle is not specified, therefore it is unclear whether concurrent exposure to other chemicals in the preparation contributed to the effects reported.

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not considered to cause skin sensitisation.

The chemical was not found to induce dermal sensitisation when tested according to OECD TG 406 (REACH). Several skin sensitisation studies were also considered by the SCCS who concluded there is limited evidence of skin sensitisation following exposure to the chemical (SCCS, 2012).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause serious health effects from repeated oral exposure.

In a 4 week drinking water study in rats, the no observed adverse effect level (NOAEL) of 125 mg/kg bw/day was reported (SCCS, 2012). At the higher dose (675 mg/kg bw/day), relative kidney weights were slightly increased in males, while urine production was decreased. The effects and variations in serum biochemistry were considered to be attributed to reduced water intake. Effects on liver function or histology were not reported.

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is not considered to cause serious health effects from repeated inhalation exposure.

In a 4 week repeat dose inhalation toxicity study in male Wistar rats, the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 270 mg/m^3 (150 ppm) (REACH). At higher concentrations (900 mg/m^3 (500 ppm)), degeneration of the olfactory epithelium was reported.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic, warranting hazard classification (see **Recommendation** section).

In vitro

The chemical did not exhibit mutagenic activity in *Salmonella typhimurium* with and without metabolic activation (REACH). The chemical was reported to induce chromosomal aberrations and micronuclei in SD rat primary skin fibroblasts (CERI, 2007). The chemical also induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells, aneuploidy 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. The chemical 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. In a modified OECD TG 471 assay (a single test was performed with one plate per strain and concentration), the chemical induced chromosomal aberrations in human TK6 cells without metabolic activation at levels ≥0.25 mM and was cytotoxic at 1 mM.

In vivo

The chemical induced sister chromatid exchanges in Chinese hamster and mouse bone marrow (CERI, 2007). Chromosomal aberrations were also reported in a study using rat embryo cells administered the chemical through the amnion. In studies using intraperitoneal administration, micronuclei were induced in rat bone marrow cells, rat peripheral lymphocytes and mouse bone marrow cells. Induced micronuclei or morphological abnormalities were not found in mouse spermatids.

Although effects were not seen in the single study examining germ calls, there is sufficient evidence to classify the chemical as possibly causing mutagenic effects.

Carcinogenicity

The chemical is classified as hazardous, with the risk phrase 'Limited evidence of carcinogenic effect' (Carc. Cat. 3; R40) in HSIS (Safe Work Australia). The available data support this classification.

The chemical is classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals (IARC, 1999). The chemical produced tumours of the respiratory tract in rats and hamsters following inhalation exposure at concentrations as low as 750 ppm, particularly adenocarcinomas and squamous cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters.

Tumour formation at the site of exposure suggests a threshold (non-genotoxic) mechanism of carcinogenicity. The US EPA Integrated Risk Information System (IRIS) Chemical Assessment Summary for acetaldehyde calculated a quantitative cancer risk of 1:10 000 at an air concentration of 50 µg/m^3 (equivalent to 28 ppb) (US EPA IRIS, 1988).

In a subsequent report, IARC also classified the chemical as a Group 1 (Carcinogenic to Humans) when associated with the consumption of alcoholic beverages (IARC, 2012; REACH). However, it must be noted that this IARC Group 1 classification relates to a non-industrial use of the chemical.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to cause reproductive and developmental toxicity. A NOAEL of greater than 400 mg/kg bw/day was reported for reproductive and developmental toxicity in rats (REACH).

In a reproductive and developmental toxicity screening test the chemical was administered orally to 22 rats at 400 mg/kg bw/day from day 6 through to day 15 of gestation. There were no maternal or developmental effects recorded at that dose level.

The chemical was also investigated in several studies for developmental effects following intraperitoneal injection of either a single dose of 0, 50, 75 or 100 mg/kg bw/day on gestation day 10, 11 or 12, or repeated doses of 0, 50, 75 or 100 mg/kg bw/day on gestation days 10 to 12 (CERI, 2007). Foetal resorptions, malformation (oedema, microcephaly, micrognathia, exencephaly and hydrocephaly), retarded development, and decreases in foetal body and placenta weight were observed in the groups given 50 mg/kg and above. However, exposure via the intraperitoneal route is not appropriate for the evaluation of a hazard or risk to humans from industrial use of the chemical. One CERI reported study did examine the developmental effects of the chemical after oral exposure to rats. Pregnant rats were administered a dose of 200 mg/kg/day (3 % water solution) on gestation days 6 to 18. An anomaly of the ribs and vertebrae was observed in the foetuses. In addition, delayed ossification and hypoplasia of the cranial bones and sternum were observed. However, a reliable NOAEL could not be derived from this study due to insufficient data.

Other Health Effects

Neurotoxicity

There is limited evidence to indicate that the chemical causes neurological effects in animals, including central nervous system depression and neural degeneration (US EPA, 1994).

In dogs exposed to levels of >134 ppm for 30 minutes, inhibition of the central nervous system and subsequent decrease in respiratory rate were reported. A single intraperitoneal injection (dose not reported) of the chemical produced sustained neural degeneration in the cerebral cortex of rats.

The results of one study in human volunteers indicated that the chemical penetrates the human blood-cerebrospinal fluid barrier. However, the neurotoxic potential of the chemical in humans cannot be determined from the available information.

Risk Characterisation

Critical Health Effects

The main critical effects to human health for risk characterisation are carcinogenicity and potential genotoxicity. On acute exposure to vapours, eye and respiratory system irritation may occur. The chemical is also acutely toxic via the oral route.

Public Risk Characterisation

Although use in cosmetic or domestic products in Australia is not known, the chemical is reported to be used in cosmetic and domestic products overseas. Currently there are no restrictions identified in the use of this chemical in Australia.

Considering the health effects and the bioavailability of the chemical, there is concern regarding the use of this chemical as an ingredient in cosmetics products in the absence of any regulatory controls.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and domestic products be managed through changes to poisons scheduling.

The chemical is recommended for Tier III quantitative risk assessment to characterise the carcinogenic risk from exposure to vapours from use of cosmetic and domestic products.

Regulatory Control

Public Health

It is recommended that the use of this chemical in cosmetic products such as perfumes, toiletries and essential oils, be restricted through scheduling.

Matters for consideration for scheduling include the carcinogenicity, in addition to the European Commission Scientific Committee on Consumer Safety (SCCS) recommendation that the chemical can be safely used as a cosmetic fragrance or flavour ingredient at a maximum concentration of 0.0025% (25 ppm) of a fragrance compound, resulting in approximately a 5 ppm concentration in the final finished product.

The US EPA IRIS Chemical Assessment Summary for acetaldehyde includes quantitative estimates of carcinogenic risk from inhalation exposure (US EPA IRIS, 1988) that will be used in the Tier III assessment, in conjunction with an inhalation exposure model.

Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of closed systems or isolation of operations;
- use of local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of protective equipment that is designed, constructed, and operated to ensure that, the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;

- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health and physicochemical (physical) hazards) of chemicals are prepared; and
- management of risks arising from storage, handling and use of a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant Codes of Practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals—Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These Codes of Practice are available from the Safe Work Australia website.

A review of physical hazards of the chemical has not been undertaken as part of this assessment.

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Last update 30 June 2017

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Acetaldehyde: Human health tier III assessment

8 March 2019

CAS Number: 75-07-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

For more detail on this program please visit: www.nicnas.gov.au

Synopsis

The Human Health Tier II IMAP assessment of acetaldehyde determined that further work is required to fully evaluate the carcinogenic risk arising from vapour exposure during use of cosmetic and domestic products that contain the chemical. Therefore, a Human Health Tier III IMAP assessment was recommended (NICNAS, 2017).

A quantitative risk assessment was conducted using a margin of exposure (MOE) approach, to evaluate the carcinogenic risk from inhalation exposure to the chemical in cosmetic and domestic products under typical exposure scenarios. Qualitative estimates of carcinogenic risk using the same inhalation exposure scenarios were also determined.

In this Human Health Tier III IMAP assessment, it was determined that use of cosmetic and domestic products containing the chemical is unlikely to pose an unreasonable carcinogenicity risk to public health. Acetaldehyde concentrations in products are expected to be orders of magnitude lower than levels that may pose a risk, or there will be a comparatively lower frequency of use of products with potentially higher concentrations.

The Human Health Tier II IMAP report for the chemical is available here and contains detailed assessment information that remains valid (NICNAS, 2017). New or updated information is included in the Human Health Tier III IMAP report, in the relevant sections. The Human Health Tier II and Tier III IMAP reports for this chemical should be read together.

Rationale for Tier III Assessment

In order to characterise the carcinogenic risk to public health and safety from exposure to consumer products containing acetaldehyde, NICNAS analysed existing toxicity and exposure data for the chemical, and conducted a quantitative risk assessment. Both MOE and qualitative approaches were used, specifically in relation to exposure to the chemical vapour in air space from consumer product use (cosmetic and domestic products) and the critical health effect of carcinogenicity.

Carcinogenicity studies, and studies relevant to the mechanism of carcinogenicity, were evaluated. A 13-week repeated dose inhalation toxicity study in rodents (Dorman et al., 2003) was considered critical, as it provided clear evidence of a dose-response curve for the local respiratory tract lesions relevant to the development of carcinogenicity. Mechanistic information was supported by toxicokinetics data on the relative absorption of acetaldehyde at differing concentrations, in different respiratory tract compartments, following acute exposure.

The scope of this risk assessment is to determine if the concentration of acetaldehyde in consumer products is at a level that minimises the risk of carcinogenicity, or other adverse effects, in humans.

Chemical Identity

Synonyms	ethanal acetic aldehyde ethyl aldehyde
Structural Formula	
Molecular Formula	C2H4O
Molecular Weight (g/mol)	44.05
Appearance and Odour (where available)	clear, colourless fuming liquid pungent, fruity odour
SMILES	C(C)=O

Import, Manufacture and Use

International

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

According to the US National Library of Medicine Household Products Database, the chemical is used in approximately 30 different domestic products. The types of products include:

- glues and adhesives – for arts and crafts, as well as home maintenance;
- caulks and sealants;
- primers and sealers;
- paints and stains – for arts and crafts, as well as home maintenance; and
- cleaning products – including car wax.

There are similar numbers of products in the different categories. The highest listed concentration is up to 1.0 % or 10000 ppm (range 0.01–1 % or 100–10000 ppm) in a leather cleaning product, but concentrations typically ranged from <0.002 % to <0.01 % (20–100 ppm) where reported for other products (US National Library of Medicine Household Products Database).

The chemical has reported non-industrial use as a flavouring agent (WHO, 1997; SCCNFP, 2004; SCCS, 2012a).

Restrictions

Australian

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) as an approved active constituent for use in veterinary chemical products. Active constituents 'are primarily responsible for a product's biological or other effects' (APVMA).

International

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is listed on the Europe Commission Regulation (EU) No 10/2011 Annex I on plastic materials and articles intended to come into contact with food—the total specific migration limit (SML (T)) is 6 mg acetaldehyde/kg food (Galleria Chemica).

Aldehydes are listed on the Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles—Limits for finished articles; a limit of 15 mg/kg applies (Galleria Chemica).

Exposure

Public Exposure

In this assessment, public exposure to the chemical is presented as estimates of inhalation exposure from use, by the general population, of consumer products that contain the chemical. For comparison, information on general environmental inhalation exposure to the chemical is also included. Non-industrial exposure to the chemical from alcohol consumption is not within the scope of this assessment. Exposure to the chemical as a by-product of indoor combustion sources such as tobacco smoking and cooking or heating (wood or gas stoves, kerosene heaters) is also not within the scope of this assessment.

Physico-chemical properties relevant to exposure

The chemical has a high vapour pressure of approximately 100 kPa (approximately 1 atmosphere) at 20 °C. The half-life of the chemical in air is 10–60 hours and the odour threshold of the chemical in air is 90 μg/m^3 (EHC, 1995; HSG, 1995). In aqueous solution, the chemical can undergo reversible hydration (gem-diol formation) on the carbonyl group, but to a much lesser extent than formaldehyde. Therefore, it is relatively more volatile from aqueous solutions than formaldehyde (Herbert and Lauder, 1938; Chemistry LibreTexts, 2018). On this basis, it is assumed that there can be 100 % volatilisation of the chemical from consumer products.

Consumer product exposure

According to the US National Library of Medicine Household Product Database, the chemical is an ingredient in domestic products (e.g. school glue, adhesives, car wax, cleaners, stains and sealants) at concentrations ranging <0.0003–1.0 % (equivalent to 3–10000 ppm). The products with the highest concentrations include leather cleaner (up to 1.0 % or 10000 ppm) and sealant (up to 0.1 % or 1000 ppm), both of which are used comparatively infrequently by consumers.

The Research Institute for Fragrance Materials (RIFM) calculated total dermal exposure to the chemical from a typical range of cosmetic products that may be used over a week. This was based on the quantity and frequency of application of the different products identified, and numerous conservative assumptions or technical input from industry as specified in the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) opinion on acetaldehyde. The RIFM calculated that dermal exposure to the chemical from cosmetic product use was approximately 4.3 μg/day or 0.1 μg/kg bw/day for a 60 kg person. This was derived from measurements where a total of approximately 52 g cosmetic products are used per application, with differing application frequencies and retention factors leading to a daily estimated application amount of approximately 13.2 g. The 13.2 g of cosmetic products contained an estimated 5.3 ppm total acetaldehyde, based on industry data on the proportion of fragrance compound in the different products and acetaldehyde within the fragrance compound (SCCNFP, 2004).

In the 8th revision of the SCCS Notes of Guidance for the Testing of Cosmetic Substances and their Safety Evaluation, 17.4 g was considered to be the aggregate value of cosmetic products that are applied daily (SCCS, 2012b). Assuming a product acetaldehyde concentration of 100 ppm (instead of using fragrance industry data based on commercial formulations, as in the previous opinion), dermal acetaldehyde exposure from cosmetic products use was calculated for a 60 kg person (29 μg/kg bw/day) in the most recent SCCS opinion on acetaldehyde (SCCS, 2012a).

The difference in the estimated systemic exposure value to acetaldehyde by the RIFM (SCCNFP, 2004) and the SCCS (2012a) is likely from the use of industry estimates of product acetaldehyde concentrations compared with a worst-case scenario, respectively. For an equivalent 100 ppm product acetaldehyde concentration, an exposure estimate of 1.9 μg/kg bw/day can be calculated for the 13.2 g SCCNFP scenario, which is still approximately 15-fold lower than for the 17.4 g SCCS scenario (29 μg/kg bw/day). While systemic exposure via the dermal route is not relevant for carcinogenicity via the inhalation route, the assumptions behind the 17.4 g aggregate value represent a more conservative exposure scenario and will be used to estimate airborne concentrations of acetaldehyde from cosmetic products use for the MOE estimations.

General environmental exposure

The chemical is a highly volatile organic compound (VOC). In Australia, it was one of nine VOCs that accounted for 68 % of the sum of all VOCs identified in a study of 40 dwellings in south-eastern suburban Melbourne. The 7-day concentration was measured to be 7.6 ± 3.6 μg/m^3 and 0.7 ± 0.4 μg/m^3 for indoor and outdoor environments, respectively. Time spent indoors accounts for 90 % of the day (Cheng et al., 2016).

In the European Union (EU), inhalation exposure to the chemical measured using personal monitors was 11.8 ± 5.3 μg/m^3 and concentrations in different indoor and outdoor microenvironments ranged 1.5–11.7 μg/m^3 (Bruinen de Bruin et al., 2008). In Canada, the median range of personal inhalation exposure to the chemical was measured as 18.6–39.3 μg/m^3 in one study. The median indoor level range was 10.5–48.7 μg/m^3 and the median outdoor level range was 2.4–7.2 μg/m^3 in studies in four cities during winter and summer from 2005–2010 (Government of Canada, 2017). In North America, average indoor concentrations were 15–36 μg/m^3 for existing homes, but up to 103 μg/m^3 for new homes. The average concentration of the chemical in outdoor air was reported to be approximately 5 μg/m^3 (range 2.0–8.3 μg/m^3) (EHC, 1995; HSG, 1995; OEHHA, 2008).

Based on the above measurements, and assuming a lifetime average adult body weight of 70 kg and an average adult daily inhalation rate of 15 m^3 (for long term exposures) (enHealth, 2012), mean acetaldehyde intake from indoor air is estimated to range 7–46 μg/kg bw/day (or up to 98 μg/kg bw/day in new homes).

Indoor air quality guidelines

Indoor air quality guidelines (IAQGs) set chemical concentrations below which adverse human health effects are not expected for the general population. There are no IAQGs in Australia. The World Health Organisation (WHO) included acetaldehyde in a list of chemical 'pollutants of potential interest', but for which data were uncertain or insufficient to derive an IAQG at the time (WHO, 2010).

In 2014, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) included acetaldehyde in their list of IAQGs, with a short-term reference value (for 1 hour, one-time or intermittent exposures) of 3000 µg/m^3 and a long-term reference value (for regular exposure, lasting longer than 1 year, to permanent or background levels) of 160 µg/m^3 (ANSES, 2014). Residential IAQGs were also derived by Health Canada in 2017, with maximum exposure limits of 1420 µg/m^3 for short- term (1 hour) and 280 µg/m^3 for long-term (24 hours, over months or years up to a lifetime) (Government of Canada, 2017). In both instances, the 1 hour values relate to bronchoconstriction effects in humans; whereas the long-term values relate to the critical health effect of nasal olfactory and respiratory epithelium degeneration in rats, which can occur following repeated exposure at irritating levels and may lead to carcinogenicity (ANSES, 2014; Government of Canada, 2017).

In this risk assessment, intermittent but repeated exposures to domestic or cosmetic products is considered most likely given the use scenarios. The lower 1 hour IAQG of 1420 µg/m^3 is the more conservative value for short-term exposure and will be used for qualitative risk estimations.

Health Hazard Information

The critical health effect for risk characterisation is carcinogenicity via the inhalation route, associated with local respiratory irritation effects. The chemical may also cause other systemic long-term effects (mutagenicity), local effects (ocular irritation) and harmful systemic acute effects following a single exposure through the oral route (NICNAS). Following the Human Health Tier II IMAP assessment of this chemical, it is listed on the Hazardous Chemicals Information System (HCIS) with the following hazard categories and hazard statements for human health (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Eye irritation – Category 2A; H319 (Causes serious eye irritation)
- Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)
- Germ cell mutagenicity – Category 2; H341 (Suspected of causing genetic defects)
- Carcinogenicity – Category 2; H351 (Suspected of causing cancer)

The chemical has an exposure standard of 36 mg/m^3 (20 ppm) time weighted average (TWA) and 91 mg/m^3 (50 ppm) short-term exposure limit (STEL).

Since the Human Health Tier II IMAP assessment of acetaldehyde, more detailed information has become available in the harmonised classification and labelling proposal for the chemical (CLH, 2015) and the final opinion on this proposal published by the European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC, 2016). Relevant details have now been further considered for this risk assessment (see **Carcinogenicity** section). For the purpose of quantitative risk assessment, inhalation is the relevant route of exposure. The studies used to derive the lowest observed adverse effect concentration (LOAEC) for carcinogenicity and the no observed adverse effect concentration (NOAEC) for respiratory tract lesions leading to carcinogenicity are described. Relevant toxicokinetics data are also included. The resulting dose estimates are compared with exposure estimates, and safety margins determined. Calculated risk estimates are also compared with published risk estimates (see **Public risk characterisation: Risk assessment – Quantitative** section).

For clarity, product acetaldehyde concentrations will be described using ppm units and air acetaldehyde concentrations using mg/m^3 units.

Toxicokinetics

The chemical reacts at the site of contact and is systemically absorbed through the lungs and gastrointestinal tract. Its physico-chemical properties (e.g. low molecular weight) suggest that dermal absorption is also possible (EHC, 1995; HSG, 1995).

The chemical is an electrophile that can react with nucleophilic groups of proteins and DNA, to form stable and unstable adducts. Interaction of the chemical with macromolecules can affect their biological activity (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

The chemical is rapidly metabolised by oxidation to form the acetate ion, via the aldehyde dehydrogenase (ALDH) enzyme. This occurs primarily in liver mitochondria, but can also occur in the nasal respiratory epithelium and kidneys. Acetate can then enter the citric acid cycle, to ultimately be metabolised to carbon dioxide and water (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

Systemic availability of the chemical is expected to be minimal due to its rapid metabolism. This is confirmed by limited data showing that there is only minor urinary excretion of the chemical in dogs following gastric exposure; in rats and rabbits, urinary metabolites were measurable following intravenous exposure (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

In an inhalation study in human volunteers (n = 8) exposed (nasally or orally) to the chemical at 100–800 mg/m^3 for 45–70 seconds, there was 45–70 % uptake via the respiratory tract. In another inhalation study, male Sprague Dawley (SD) rats (n = 3) were exposed (whole body) to the chemical for 1 hour. Tissue distribution of the chemical was highest in blood, followed by skeletal muscle, cardiac muscle, kidney, spleen and liver. The half-life in blood was reported to be 3.1 minutes, and the low levels in liver were attributed to rapid metabolism of the chemical in that organ. The chemical may also cross the maternal– foetal barrier and blood–brain barrier at low levels (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

Vapour uptake studies

In a study examining vapour uptake in the upper respiratory tract, anaesthetised male F344 rats (n = 5/group) were exposed (nose only) to the chemical at 1.8, 18, 180 or 1800 mg/m^3 for up to 40 min. Exposure was also varied by differing inspiratory conditions and flow rates—uni-directional at 50, 100, 200 or 300 mL/min and cyclic at 207 mL/min. The airflow regimes were chosen to be within the physiological range (50–275 %) of the predicted minute ventilation of rats (uni-directional) or to mimic the tidal volume and breathing frequencies of rats (cyclic). In this model, deposition efficiency (relative vapour uptake) was higher (at least 2-fold) at lower exposure concentrations compared with higher exposure concentrations. This was attributed to local nasal metabolism of the chemical via ALDH, since the effect was diminished with pre-treatment of animals with an ALDH inhibitor. Conversely, it was reported that at higher exposure concentrations the capacity for metabolism was saturated and uptake reflected solubility (Morris, 1999). Similar observations (2–3-fold higher relative vapour uptake at 1.8 or 18 mg/m^3, compared with 1800 mg/m^3) were made using the chemical in SD rats, B6C3F1 mice, Syrian golden hamsters and Hartley guinea pigs following the same experimental protocol as described above, but with physiologically relevant airflow regimes for each of the tested rodent species (Morris, 1997a).

Using computational fluid dynamic models simulating the nasolaryngeal airways and conducting (extrathoracic and tracheobronchial) airway walls, predictions on the transient absorption of acetaldehyde vapours in the upper respiratory tract were made. Air-phase transport of inhaled acetaldehyde vapours and its absorption in a mucous membrane–tissue–blood scenario were modelled. Over the time course of an inhalation cycle (1–2 seconds, considered transient exposure), the concentration of acetaldehyde was higher in the mucous membrane compared with either air or tissue. Transient exposure also resulted in approximately 2- to 5-fold higher uptake in mucous membrane, 2- to 3-fold higher uptake in tissue and 4- to 25-fold lower uptake in blood compared with steady-state exposure conditions. Based on these results, it was predicted that local tissue concentrations would be higher following transient exposure than during steady state exposure (Tian and Longest, 2010).

These studies suggest that there is relatively higher absorption at vapour concentrations consistent with those from consumer products, and that with acute exposure there is relatively higher absorption in the local mucous membranes.

Respiratory and eye irritation

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with the following hazard categories and hazard statements:

Eye irritation – Category 2A; Causes serious eye irritation (H319)

Specific target organ toxicity (single exposure) – Category 3; May cause respiratory irritation (H335)

The available data supports the eye and respiratory irritation classifications and emphasises that the chemical is a mucous membrane irritant.

Using a crossover study design, humans (n = 20 subjects) were each exposed to air or the chemical vapour at 91 mg/m^3 for 4 hours on separate occasions. Measurements of irritation symptoms by questionnaire, olfactory threshold, mucociliary transport, and inflammatory markers (e.g. various interleukins) in nasal secretions and nasal epithelium were made after each exposure. There were no differences in the measured parameters and it was concluded that acute exposure at 91 mg/m3 did not cause adverse respiratory effects (SCCCS, 2012).

In an inhalation study using 14 volunteers, exposure to the chemical vapour at 243 mg/m3 for 30 minutes resulted in mild irritation to the upper respiratory tract (SCCS, 2012a).

In an inhalation study, 24 volunteers were exposed to the chemical at ≥45 mg/m3 for 15 minutes. Eye irritation was reported in 'sensitive persons' at 45 mg/m^3 and 'in the majority' at ≥91 mg/m3. Upper respiratory tract irritation was a less sensitive effect, occurring only at concentrations >246 mg/m^3 (SCCS, 2012a). Based on the concentration at which the most sensitive human subjects experienced eye irritation (LOAEC = 45 mg/m^3), a tolerable concentration for irritation in humans was determined to be approximately 2 mg / m^3 as per:

Tolerable concentration
= LOAEC / uncertainty factors
= 45 mg/m^3 / 10 x 2
= 2.25 mg /m^3

where the uncertainty factors were 10 for intraspecies variation and 2 for low data quality (EHC, 1995).

In a study using 12 volunteers (both sexes) exposed to the chemical vapour at 45, 90 or 360 mg/m^3 for 15 minutes, reddened eyelids and bloodshot eyes were reported at the highest concentration (REACH).

In an occupational incident report, 33 patients suffered corneal burns due to accidental ocular acetaldehyde exposure. In 30 patients, healing occurred within 48 hours and in the remaining 3 patients, healing occurred within 3–10 days. There was no vision loss (REACH).

Data from longer term rodent studies also supports the human observations, with exposure to acetaldehyde vapour resulting in eye, nose and upper respiratory tract irritation (SCCS, 2012a; see also **Carcinogenicity** section).

Genotoxicity

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with hazard category Germ cell mutagenicity – Category 2 and hazard statement 'Suspected of causing genetic defects (H341) in the HCIS. The available data support this classification and highlight that the chemical can cause direct DNA damage.

In vitro, the chemical was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* WP2 *uvrA*, but induced chromosome aberrations in *Aspergillus nidulans* and forward mutations in yeast. Positive results were reported using the chemical in mammalian cell in vitro mutagenicity assays, e.g. gene mutations in mouse lymphoma cells and human lymphocytes; chromosome aberrations in Chinese hamster ovary cells, primary rat skin fibroblasts and human lymphocytes; and micronucleus formation in Chinese hamster lung fibroblast (V79) cells, primary rat skin fibroblasts, human hepatoma cells and human lymphocytes. Positive results were also reported in mammalian cell in vitro DNA damage assays, e.g. sister chromatid exchange (SCE) in Chinese hamster V79 and ovary cells, as well as human lymphocytes; DNA adducts in calf thymus DNA; and DNA strand breaks or cross-links in human lymphocytes, and human gastric and colonic mucosa cells (CLH, 2015).

In vivo, DNA-protein crosslinks were reported to occur in rat nasal respiratory mucosa and olfactory cells following inhalation exposure to the chemical in a short term study (single exposure or 5-day repeated exposure), but not in another study (4 or 65 day exposure). The chemical induced SCE in bone marrow and spermatogonial cells, as well as micronucleus formation in erythrocytes and bone marrow, from rodents (mice, rats or Chinese hamsters) exposed to the chemical by intraperitoneal (i.p.) injection. Chromosome aberrations were observed in rat embryos exposed to the chemical by an intra-amniotic injection; and sex-linked recessive lethal mutations were seen in *Drosophila melanogaster* exposed to the chemical by injection (but not via feed). In contrast, there were no meiotic micronuclei in early spermatids from mice exposed to the chemical by i.p. injection (CLH, 2015).

Carcinogenicity

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with hazard category Carcinogenicity – Category 2 and hazard statement 'Suspected of causing cancer' (H351) in the HCIS. The available data support an amendment to this classification (see **Carcinogenicity summary** below and **Recommendation** section).

Relevant rodent data

In a carcinogenicity study, albino Wistar rats (n = 105/sex/dose) were exposed (whole body) to vapour at 0, 1350, 2700 or 5400 mg/m^3 for 6 hours/day, 5 days/week, for 27 months. Subsets of animals were euthanised at 13, 26 and 52 weeks. Due to overt toxicity (severe growth retardation, intermittent body weight loss and early mortality) in rats exposed at 5400 mg/m^3 during the first 20 weeks, this exposure concentration was gradually reduced to 1800 mg/m^3 over the next 32 weeks (from week 20 to week 52). In rats initially exposed at the highest concentration, mortality was 50 % and 42 % in males and females, respectively, at day 468; and 100 % at day 715. Mortality was often associated with excess inflammatory exudate (secretions) blocking the nasal cavity. Rats exposed to the chemical also had lower body weight gain (reduced in males at all concentrations and in females at ≥2700 mg/m^3), nasal olfactory epithelium thinning, and sensory plus sustentacular (or structural support) cell loss, compared with controls. In rats exposed at ≥2700 mg/m^3, there were significant increases in the non-neoplastic lesions, hyperplasia and metaplasia, of the respiratory tract epithelium, compared with controls. At the highest concentration, there was excess salivation and dyspnoea (laboured breathing). Neoplastic lesions included increased malignant nasal carcinoma (carcinoma in situ, squamous cell carcinoma arising from the respiratory epithelium and adenocarcinoma arising from the olfactory epithelium) seen in animals exposed to the chemical at all of the concentrations tested. The total incidences of carcinoma were 33 %, 77 % and 76 % in males, and 13 %, 64 % and 81 % in females, exposed to the chemical at 1350, 2700 and 5400 mg/m^3, respectively. A no observed adverse effect concentration (NOAEC) for carcinogenicity could not be established in this study. It was reported that the nasal tumours arose from the progressive nasal epithelium degeneration, including chronic and permanent inflammation (US EPA IRIS, 1988; SCCNFP, 2004; CERI, 2007; SCCS, 2012a; CLH, 2015).

Carcinogenicity (increased incidence of nasal tumours) was also reported in a shorter duration study in Wistar rats (n = 30/sex/dose) exposed to vapour at ≥1350 mg/m^3 for 52 weeks, with a 26 or 52 week recovery period. In this study, nasal tumours developed even during the recovery period, suggesting that progression of nasal lesions to cancer can occur in the absence of continued exposure. In hamsters (n = 10/sex/dose) exposed to the chemical vapour at ≥702 mg/m^3 for 90 days, histopathological changes that precede carcinogenicity were observed in the nasal cavity and turbinates, larynx, trachea and lung. These included focal hyperplasia and metaplasia, as well as severe degeneration in the various tissues and organs (US EPA IRIS, 1988; SCCNFP, 2004; CERI, 2007; CLH, 2015).

A NOAEC for carcinogenicity was not determined with the doses used in the aforementioned studies, and the US EPA considered two sub-acute studies, examining lesions relevant to the development of carcinogenicity, to establish an NOAEC. Male Wistar rats (n = 10/group) were exposed to vapour at 0, 270 or 900 mg/m^3, and in another study, Wistar rats (n = 10/sex/dose) were exposed to vapour at 0, 720, 1800, 3960 or 9000 mg/m^3—both for 6 hours/day, 5 days/week for 4 weeks. It was reported that the combined findings from these studies represented a dose-response curve for the lesions that cause carcinogenicity, as they were similar to that associated with pre-cancerous lesions and carcinogenicity in chronic studies of longer duration and higher exposure concentrations. The NOAEC was 270 mg/m^3, based on concentration-dependent degeneration in the nasal olfactory and respiratory epithelium in rats exposed at ≥720 mg/m^3, and in the nasal, laryngeal and tracheal epithelium (including hyperplasia and metaplasia) in rats exposed at ≥1800 mg/m^3. Body weight gain was reduced in males exposed at ≥1800 mg/m^3 and in females exposed at 9000 mg/m^3. Dyspnoea was observed in rats in the first 30 minutes of exposure at 9000 mg/m^3. Mortality was reported at ≥3960 mg/m^3 (one male at 3960 mg/m^3, and one male and one female at 9000 mg/m^3) (US EPA IRIS, 1988). In the SCCS report on acetaldehyde, it was stated that these studies were not compliant with OECD Test Guidelines or good laboratory practice (GLP) (SCCS, 2012a). Nonetheless, from these data, the US EPA derived a reference concentration (RfC)—'a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects [(in this instance, olfactory epithelium degeneration)] during a lifetime' of 9 µg/m^3 (US EPA IRIS, 1988). The US EPA quantitative carcinogenicity risk estimates are described in more detail later (see **Appendix: Other quantitative risk estimates** section).

Male F344 rats (n = 24–36/dose) were exposed (whole body) to vapour at 0, 90, 270, 900 or 2700 mg/m^3 for 6 hours/day, 5 days/week for up to 13 weeks. Subsets of rats (n = 12/dose) were euthanised after 4, 9, 14, 30 or 65 exposure days to examine the upper respiratory tract (histopathology, cell proliferation and DNA–protein crosslinking). There was no mortality or signs of systemic toxicity. Body weight gain and terminal body weights were not affected by exposure to the chemical. There were no abnormal findings in the lung and trachea. Respiratory epithelium inflammation, hyperplasia and squamous metaplasia were reported to increase in site-, concentration- and time-dependent manners. The more external areas of the nasal cavity were most sensitive to respiratory epithelial lesions, including the dorsal meatus tip and lateral wall, and anterior maxilloturbinate regions. These lesions were reported as significantly increased at concentrations ≥900 mg/m^3 for hyperplasia and metaplasia; and at 2700 mg/m^3 for inflammation. Inflammation was noted on exposure day 14 in the dorsal meatus lateral wall, and on exposure day 65 in the dorsal meatus tip. Hyperplasia was noted from exposure day 14 at 900 mg/m^3 and from exposure day 4 at 2700 mg/m^3 in the dorsal meatus tip. Metaplasia was noted from exposure day 4 at ≥900 mg/m^3 in the anterior maxilloturbinate and from exposure day 4 at 2700 mg/m^3 in the dorsal meatus tip. Significantly increased metaplasia was also reported in the larynx on exposure day 65 at ≥900 mg/m^3 and from exposure day 4 at ≥2700 mg/m^3. The severity of these effects was reported to be minimal to slight/mild. Olfactory epithelial degeneration (also reported as neuronal loss) was significantly increased in the posterior dorsal meatus from exposure day 4 and at concentrations ≥270 mg/m^3. There were concentration- and time-dependent increases in the severity of these effects, ranging from minimal at lower concentrations/shorter exposure durations to moderately severe in the highest concentration/longest exposure duration group. Olfactory epithelial vacuolation was reported as 'present' in rats exposed at 270 mg/m^3 from exposure day 9, but this effect was sporadic in rats exposed at ≥900 mg/m^3. In all groups of rats, DNA–protein crosslinking was comparatively higher (approximately 4-fold or greater) in respiratory compared with olfactory epithelium, when measured on both 4 and 65 days. In exposed groups compared with controls, DNA–protein crosslinking in the upper respiratory was unchanged (4 days) or intermittently changed (65 days), and cell proliferation in the respiratory and olfactory epithelium was reported as minimal, but the results were variable making interpretation difficult. An NOAEC of 90 mg/m3 was reported, based on olfactory epithelial lesions at concentrations ≥270 mg/m^3 (Dorman et al., 2008). This study is considered the most reliable study for subsequent quantitative risk assessment.

Using the above study, an alternative derivation of the RfC for olfactory degeneration was reported. A physiologically based pharmacokinetic (PBPK) model of the upper respiratory tract was developed for acetaldehyde, to take into consideration interspecies differences and provide chemical-specific dosimetric adjustment parameters. The RfC for quantitative risk assessment of olfactory degeneration (specifically, epithelial cell atrophy and neuronal loss), that can lead to cancer was 810 µg/m^3 (Teeguarden at al., 2008). This model is described in more detail later (see **Appendix: Other quantitative risk estimates** section).

Observations in humans

Nine cases of cancer have been reported in factory workers from the former East Germany, who were exposed during the process of acetaldehyde dimerisation. The cancers included bronchial tumours (n = 5) and oral cavity carcinomas (n = 2), and the incidence of these in the workers was reported to be higher than the incidence in the general population of East Germany. These cases are confounded by exposure to other chemicals, cigarette smoking and no available information on the total workers exposed or other general characteristics (e.g. duration of exposure, age and sex) (US EPA IRIS, 1988; SCCNFP, 2004; SCCS, 2012a; CLH, 2015).

Information related to the potential mechanism of carcinogenicity

Inhalation exposure of F344 rats to the chemical at up to 5400 mg/m^3 once for 6 hours resulted in a non- linear dose-response curve for DNA–protein crosslinking in nasal respiratory epithelium. There was no change at 180 mg/m^3, non-significant increases at 540 mg/m^3 and significant increases only at concentrations ≥1800 mg/m^3. No dose-related changes were seen in nasal olfactory epithelium. Repeated exposure to the chemical at 1800 mg/m^3 for 6 hours/day, 5 days/week induced DNA–protein crosslinking in the nasal olfactory epithelium and it was suggested that this effect might be dependent on cytotoxicity-induced regeneration. Alternatively, since the chemical can be metabolised by ALDH in the upper respiratory tract, and the enzyme is comparatively enriched in respiratory epithelium compared with olfactory epithelium, regional differences in reactivity of the chemical may account for differences in local lesion formation following exposure. In addition, the hydrogen ions released during acetaldehyde metabolism may lead to the formation of acid metabolites that can be injurious to the nasal cavity, via a carboxylesterase-dependent mechanism. Many of these properties of acetaldehyde are similar to those of formaldehyde, another reactive aldehyde that is a known carcinogen with irritant properties. Carcinogenicity was reported for both acetaldehyde and formaldehyde, at concentrations estimated to saturate the metabolic detoxification pathways, and therefore resulting in cytotoxicity (Morris, 1997b).

In the ECHA final opinion on the proposal for classification and labelling of acetaldehyde, the proposed mechanism of carcinogenicity of the chemical was considered to include both site of contact irritation and potential for local somatic cell genotoxicity (RAC, 2016). This can lead to mutation, cytotoxicity and enhanced proliferation in the nasal cavity, and both the mutations and the resulting chronic tissue damage ultimately contribute to tumour formation (Government of Canada, 2017).

Carcinogenicity summary

Based on the weight of evidence of the available data, a threshold-based mechanism of carcinogenicity for acetaldehyde is likely following inhalation exposure. Genotoxicity has generally only been reported at the point of contact in somatic cells (with such changes unlikely to be heritable or critical toxicity initiating events), and other lesions leading to tumour formation also occur at the point of contact. From a toxicological perspective, acetaldehyde is considered to be similar to formaldehyde (NICNAS, 2006), with differences in toxicity potency related to differences in physico-chemical and toxicokinetic properties. Overall, the relevance of acetaldehyde-induced carcinogenicity to humans is considered clear, supporting classification as a probable human carcinogen.

Risk Characterisation

Public Risk Characterisation

In this assessment, MOE methodology and qualitative comparisons were used for characterising the public health risks from acetaldehyde exposure through use of consumer products containing the chemical. The critical health effect is carcinogenicity, and it is considered that upper respiratory tract lesions precede the development of cancer. The MOE methodology is appropriate for a chemical with a threshold-based mechanism of carcinogenicity.

Methodology

An MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB, 2003). The risk characterisation is conducted by comparing quantitative exposure information with a NOAEC selected from appropriate animal studies and deriving an MOE as follows:

1. Identification of critical health effect(s).
2. Identification of the most appropriate/reliable NOAEC for the critical health effect(s). If NOAEC was not identified, an LOAEC can also be used but will require a higher margin of safety.

3. Comparison of the estimated or measured dose or exposure (Dose) with the appropriate/reliable NOAEC (or LOAEC) to provide an MOE calculation (MOE = NOAEC (or LOAEC)/Dose).
4. Evaluation as to whether the MOE obtained by this method indicates a health concern for the human population under consideration, taking into account relevant safety factors.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. Higher MOE values indicate lower risk of potential adverse effects. To decide whether the MOE is of sufficient magnitude, expert judgement is required. Such judgements are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability. The acceptable MOE for NOAEC-based assessment is generally 100 or greater, comprised of an uncertainty factor (UF) of 10 for interspecies variability (due to potentially increased sensitivity of humans compared to laboratory test animals) and 10 for intraspecies variability (to account for potential differences in toxicokinetic and toxicodynamic parameters in the human population). If an LOAEC instead of an NOAEC is used, an additional UF of 3 is applied and the acceptable MOE for LOAEC-based assessments is 300 or greater. Default UFs are considered appropriate to be used in most MOE estimations and presumed to be protective to human health.

Uncertainty factors can also be used to reduce the required MOE, by taking into account chemical or route-specific toxicology knowledge (ECETOC, 2003; WHO, 2005), provided that the scientific rationale is transparent. For example, in this quantitative assessment, since the local effects in the upper respiratory tract are believed to be associated with concentrations of acetaldehyde exceeding the metabolic capacity of cells, and do not occur following longer-term exposure to concentrations below this threshold, the following alterations to uncertainty factors may instead apply:

- a reduced adjustment for rat to human extrapolation can be applied, since rodents are relatively more sensitive than humans to the local effects of soluble vapours in the nasal cavity by a factor of 2 to 4-fold (ECETOC, 2003)—the UF can be considered to be equivalent to 5 (i.e. 10 / 2) for interspecies variation; and
- a reduced adjustment for intraspecies variation can be applied, since toxicokinetic variability is not relevant because the toxic effects of the chemical are local—the UF can be considered to be equivalent to 3.16 (i.e. $10^{0.5}$) for intraspecies variation (WHO, 2005), only accounting for toxicodynamic variability between individuals.

An adjustment for database adequacy is not needed, since the study that defines the critical health effect for risk assessment (i.e. olfactory epithelial lesions that can lead to carcinogenicity; Dorman et al., 2008) is considered sufficiently reliable. Furthermore, an adjustment for exposure duration (between sub-chronic and chronic) is not needed, since the toxic effects of the chemical are local and threshold-based. Overall, this may allow an MOE of 15.8 (i.e. 5 x 3.16) to be used, instead of the standard 100.

For estimations of exposure within a home setting, the following criteria and conservative assumptions were used:

- the volume of a bathroom is 10 m^3 (RIVM, 2014);
- the volume of a lounge room is 58 m^3 (RIVM, 2014);
- 100 % of the chemical in the consumer product will be released instantaneously into the respective spaces for each use scenario; and
- the 1 hour IAQG of 1.42 mg/m^3 (1420 $\mu g/m^3$) was considered a limiting peak exposure for domestic and cosmetic product for acute irritancy.

As a final conservative measure, to ensure safety estimations are ultimately protective of carcinogenicity, an MOE of 100 will be used in this quantitative risk assessment.

Risk assessment – Quantitative

The NOAEC value used in the calculations below (90 mg/m^3) is from the sub-chronic study by Dorman et al., 2008 and reflects olfactory epithelial tissue damage in F344 rats exposed to the chemical for up to 13 weeks. This study was considered the most robust for quantitative risk assessment purposes. Teeguarden et al., 2008 derived a human equivalent NOAEC, taking into account anatomical parameters (e.g. respiration rate, tissue thickness and surface area), that was higher (approximately 121 mg/m^3) than this rat NOAEC. The rat value will be used in this quantitative risk assessment to ensure estimations are protective of carcinogenicity.

Cosmetic products

Based on the SCCS' Notes of Guidance for the testing of Cosmetic Substances and their Safety Evaluation (8^{th} and 9^{th} revision; SCCS, 2012b and SCCS, 2016), the SCCS considers a daily aggregate exposure value for all cosmetic products to be 17.4 g/day. Depending on the product concentration (ppm) of acetaldehyde in 17.4 g cosmetics, and assuming that these cosmetics will mostly be applied remotely on the body; release in a 10 m3 bathroom air space during application, with 100 % release of acetaldehyde in this space, is considered a reasonable worst-case exposure scenario. The acetaldehyde air concentration is calculated as per:

Air concentration = 17.4 g corrected for acetaldehyde ppm in products / 10 m^3 bathroom

The MOE can then be determined as per:

MOE
= NOAEC / air concentration
= 90 mg/m^3 / air concentration

Acetaldehyde is reported to not be intentionally used in cosmetic products (rather it may occur as an unavoidable trace from plant extracts, botanicals or ethanol ingredients contained within the product), but it is present as an ingredient in fragrance compounds that are used in cosmetic compounds (SCCNFP, 2004; SCCS, 2012a). In fragrance compounds, it is recommended that acetaldehyde only be used at a maximum of 25 ppm (SCCNFP, 2004). As an ingredient in cosmetics, this acetaldehyde concentration would be further diluted by formulation of the fragrance compound with the other components of the cosmetic product. The SCCS (2012a) estimates that a final finished product contains approximately 5 ppm of acetaldehyde.

Based on the SCCS (2012a) modelling parameters using a worst-case scenario of 100 ppm product acetaldehyde concentration, the MOE estimation for acetaldehyde exposure through daily cosmetic use is 517. This is based on an air concentration of 0.174 mg/m^3 in a typical bathroom space for this total product acetaldehyde amount. Based on the expected 5 ppm maximum product acetaldehyde concentration (SCCS, 2012a), the MOE estimation for acetaldehyde exposure through daily cosmetic use is 10345. This is based on an air concentration of 0.009 mg/m3 in a typical bathroom space for this total product acetaldehyde amount.

Domestic products

Since a leather cleaner was listed as containing the highest amount of acetaldehyde (up to 10000 ppm or 1 %) in the US Household Products Database, this type of product will be used in further calculations and represents a worst-case scenario. There is low certainty in the typical acetaldehyde amounts in these product types, as the range given was 100–10000 ppm (0.01–1 %) and these figures could not be confirmed in the product material safety data sheet (MSDS). Values covering the range of concentrations provided in the US Household Products Database for this product (100–10000 ppm) will be used in the calculations.

Using default parameters for leather cleaners from the ConsExpo Cleaning Products Fact Sheet (RIVM, 2018), aerosol-type products are used 5 times per year, mainly in lounge rooms and the released mass is 109 g per use with an exposure duration lasting 4 hours. For exposure duration, the ConsExpo default assumption is that the user will remain in the room for 4 hours after cleaning, and this is based on expert judgement. It is acknowledged that the quality of this assumption is low (Q-factor = 1; RIVM, 2018); therefore, increasing uncertainty. A more reasonable situation may be that the user will be in the lounge room for the time taken to clean the couch, after spraying the set amount of cleaning product on the couch.

For domestic products, exposure to vapour was simulated using ConsExpo Web (version 1.0.5), to estimate the mean acetaldehyde air concentration on the day of exposure. Total product acetaldehyde concentration and duration of use were varied as indicated below (Table 1). Both parameters can contribute to the mean acetaldehyde air concentration on the day of exposure, to influence the potential absorption amount. All other parameters (i.e. released mass per use (109 g), room volume (58 m^3), ventilation rate (0.5 room air change/hour) and inhalation rate (1.49 m^3/hr, representing light exercise)) were kept static in the model. The MOE was then determined:

MOE
= NOAEC / air concentration
= 90 mg/m^3 / air concentration

Table 1 contains the calculated MOE estimations for the different scenarios.

Table 1: MOE estimations for acetaldehyde exposure through a typical single domestic use

Total product acetaldehyde (ppm)	Duration of use (minutes)	Acetaldehyde air concentration – mean concentration on day of exposure (mg/m^3)	MOE
10000	15	0.18	500
	30	0.35	257
	60	0.62	145
	90	0.83	108
	120	0.99	90
	240	1.40	64
6500	240	0.88	102
5000	240	0.68	132
1000	240	0.14	643
500	240	0.068	1324
100	240	0.014	6429

At the highest reported product acetaldehyde concentration (10000 ppm) for leather cleaner, a duration of use 90 minutes or less achieves protection. This is a reasonable time-frame for a task such as leather cleaning in a lounge room. Lower product acetaldehyde concentrations, with the default duration of use time of 240 minutes, also provide sufficient protection from the risk of adverse effects.

A sealant was listed as containing the second highest amount of acetaldehyde (up to 1000 ppm) in the US Household Products Database. Using default parameters for joint sealants from the ConsExpo Do-It-Yourself Fact Sheet, a typical use scenario is 75 g sealant applied 3 times per year. Sealants typically have high viscosity and harden rapidly on application (RIVM, 2007), making volatile chemicals less able to diffuse to the product surface over time. Therefore, complete release of acetaldehyde from these products is not expected, and combined with their more specialised use (limited exposure); overall risk is considered low.

Summary – Quantitative

The MOE estimations above represent safety margins for acute exposure from a single application of consumer products. Since the acute toxicity effects (local irritation) of the chemical can lead to the critical health effect of carcinogenicity, these MOE values are considered protective for repeated exposures. These values likely represent overestimates of the carcinogenicity risk arising from inhalation of acetaldehyde under these use scenarios, given the conservative approach used in the calculations.

Based on these estimations, the expected maximum product acetaldehyde concentration of 5 ppm in cosmetics is considered not to pose an unreasonable risk. For domestic products such as leather cleaner, a duration of use of approximately 90 minutes is also considered not to pose an unreasonable risk, if the product contained the maximum listed acetaldehyde concentration of 10000 ppm. Furthermore, irregular exposures to domestic products containing acetaldehyde should be protective of carcinogenicity based on the mean acetaldehyde air concentration on the day of exposure not exceeding the short-term IAQG of 1.42 mg/m^3 (1420 µg/m^3). This is because repeated insults to the upper respiratory tract, which may lead to the lesions preceding carcinogenicity, are avoided.

It is also considered unlikely that domestic products will contain such high amounts of acetaldehyde. The acetaldehyde air concentrations arising from domestic product use, as described in the above MOE estimations, may exceed the odour threshold for acetaldehyde (0.09 mg/m^3 or 90 µg/m^3; see **Public exposure: Physico-chemical properties relevant to exposure** section); and they are approaching the tolerable irritancy threshold for acetaldehyde (2 mg/m^3 or 2000 µg/m^3; see **Respiratory and eye irritation** section). This indicates that the highest potential acetaldehyde concentration in leather cleaner is a large overestimate of the true concentration.

Risk assessment – Qualitative

The following calculations describe air concentrations of acetaldehyde following use of cosmetic or domestic products, compared with the recently published IAQG values. The lowest available 1 hour IAQG value of 1420 µg/m^3 (see **Public exposure: Indoor air quality guidelines** section) is used, as it is derived based on bronchoconstriction effects in humans and; therefore, represents the most conservative approach to protecting against developing the lesions that may lead to carcinogenicity.

For cosmetics, a 17.4 g daily aggregate exposure value is used (SCCS, 2016), and a worst-case scenario of 100 ppm acetaldehyde concentration or a maximum expected 5 ppm acetaldehyde concentration is considered (SCCS, 2012a). Assuming 100 % release and exposure of acetaldehyde in cosmetics in a 10 mg/m^3 bathroom air space during application, acetaldehyde air concentrations of 174 µg/m^3 and 8.7 µg/m^3 are calculated for the 100 ppm and 5 ppm scenarios, respectively. These are both below the 1 hour IAQG value of 1420 µg/m^3.

For domestic products, a leather cleaner is listed as containing the highest product concentration of acetaldehyde (up to 10000 ppm) (US National Library of Medicine Household Products Database) and using default parameters for leather cleaners from the ConsExpo Cleaning Products Fact Sheet, the released mass is 109 g per use (RIVM, 2018). At this concentration in this mass, the air concentrations exceed the odour threshold and approach the tolerable irritancy threshold (see **Risk Assessment: Quantitative – Domestic products** and **Summary – Quantitative** sections above). Therefore, it is considered unlikely that domestic products will contain such high amounts of acetaldehyde.

The product concentration range provided for leather cleaner was 100–10000 ppm; the lower limit of this range (i.e. 100 ppm) is the upper limit of the more typical concentration range listed (20–100 ppm) for all domestic products in the US National Library of Medicine Household Products Database (see **Import, manufacture and use: International** section). Considering 100 % release and exposure of acetaldehyde at a more typical 100 ppm concentration in a leather cleaning product, used in a 58 mg/m3 lounge room air space during a single application, an acetaldehyde air concentration of 188 µg/m^3 is calculated, which is below the 1 hour IAQG value of 1420 µg/m^3.

Summary – Qualitative

Based on the available exposure information for acetaldehyde in cosmetics (SCCS, 2012a) and domestic products (US National Library of Medicine Household Products Database), use is not expected to result in an air concentration that would approach the IAQG. This is based on cosmetic products containing a maximum of 5 ppm acetaldehyde; and domestic products such as leather cleaner with an acetaldehyde concentration of 100 ppm, that is considered reasonable and more typical of most other domestic products on the market. This domestic product concentration also takes into consideration odour threshold and tolerable irritancy threshold information for the chemical. Overall, through cosmetic and domestic use, exceeding the IAQG is considered unlikely.

Risk assessment conclusion

Although use in cosmetic and domestic products in Australia is not known, the chemical is reported to be used overseas and is likely to be available in similar products in Australia.

Quantitative risk assessment determined that acetaldehyde in cosmetic products at the expected maximum concentration of 5 ppm would avoid carcinogenicity risk (MOE >100) from inhalation exposure when used in a bathroom. Using a leather cleaner with the maximum listed product concentration (10000 ppm) and a reasonable duration of use time (90 min) in a domestic setting (leather lounge cleaning in a lounge room) would also avoid carcinogenicity risk (MOE >100) from inhalation exposure. However, at the 10000 ppm concentration in this use scenario, the air concentrations exceeded the odour threshold and approached the tolerable irritancy threshold. This suggests that domestic products will not likely contain such high amounts of acetaldehyde.

By qualitative risk assessment, via comparison with the most conservative 1 hour IAQG value, exposure to cosmetic products at 5 ppm and domestic products at 100 ppm (considered the most reasonable product concentration) would not result in an air concentration that would approach this value. Therefore, there is adequate protection against the risk of developing the respiratory lesions that precede carcinogenicity.

In the most recent SCCS opinion, it was recommended that the chemical not be used intentionally in cosmetic products, and that the use of fragrance compounds containing the chemical at a maximum 25 ppm would result in an acetaldehyde product concentration of approximately 5 ppm (SCCS, 2012a). Based on this information, the chemical is not expected to be used in cosmetic products at concentrations that would pose a risk for carcinogenicity via the inhalation route.

Regarding domestic products, the chemical was listed in a leather cleaning product with a concentration range of 100–10000 ppm. Acetaldehyde does not likely exist in domestic products at the high end of this range of concentrations – the typical range was 20–100 ppm (US National Library of Medicine Household Products Database). There would also be a low frequency of use of leather cleaner in a lounge room (assumed to be 5 times per year in ConsExpo models, considered a low quality assumption with a Q-factor of 2; RIVM, 2018), suggesting a low likelihood for exposure to concentrations that would pose a carcinogenicity risk via the inhalation route.

Hence, the public risk from this chemical is not considered to be unreasonable.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification
Acute toxicity	Not Applicable	Harmful if swallowed – Cat.4 (H302)*
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation – Cat. 2A (H319)* May cause respiratory irritation – Specific target organ tox, single exp Cat. 3 (H335)*
Genotoxicity	Not Applicable	Suspected of causing genetic defects – Cat. 2 (H341)*
Carcinogenicity	Not Applicable	May cause cancer – Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[*] Existing Hazard Classification. No change recommended to this classification

Public health

Acetaldehyde is naturally present in the air we breathe, from a wide range of human activities. The chemical is also present in cosmetic products, mainly as a component of fragrance compounds, and in a variety of domestic products that are typically used infrequently. The principal route of public exposure is by inhalation, via indoor and outdoor (ambient) air. Acetaldehyde concentrations in indoor air are higher than outdoor levels.

Should the recommendation for an indoor air guidance value for formaldehyde be adopted (NICNAS, 2006), similar consideration should be given to acetaldehyde. This should be based on respiratory irritation, an acute effect that may lead to the development of carcinogenicity, using an approach similar to the French or Canadian IAQG values (ANSES, 2014; Government of Canada, 2017). Therefore, the sampling duration should be short (such as hourly). This value will provide guidance for the public and regulatory authorities so that the results of monitoring studies can be considered and action taken where appropriate.

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

The advice provided in the Human Health Tier II IMAP report remains unchanged.

While the assumptions used in this assessment are considered to be conservative, industry is requested to advise NICNAS if higher concentrations are in use in cosmetic or domestic products.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment. The chemical is, however, classified in the HCIS for the following physical hazard: Flammable liquid – Category 1; H224 (Extremely flammable liquid and vapour).

Appendix: Other quantitative risk estimates

Comparison of the current quantitative risk assessment with previous quantitative risk assessments is difficult, as different assumptions have been made. The various available models are presented below for completeness, and summarised for transparency.

US EPA IRIS – Acetaldehyde

Based on the NOAEC and LOAEC values determined for degeneration of olfactory epithelium in Wistar rats exposed to acetaldehyde in two sub-acute (28-day) inhalation toxicity studies (see **Carcinogenicity** section), an inhalation RfC of 9 µg/m^3 was determined. Confidence in the RfC estimation was 'low', primarily based on the short duration of the studies and the use of only one species (US EPA IRIS, 1988).

Based on the lifetime (27-month) inhalation exposure study in Wistar rats (see **Carcinogenicity** section), the inhalation unit risk was estimated to be 2.2 x 10-6 per µg/m^3 above the RfC. By a linearised multistage variable exposure extrapolation method (designed by Crump and Howe, 1984), the quantitative estimate of extra carcinogenic risk from lifetime inhalation exposure to acetaldehyde was determined to be:

- 1 in 10000 at an air concentration of 50 µg/m^3
- 1 in 100000 at an air concentration of 5 µg/m^3
- 1 in 1000000 at an air concentration of 0.5 µg/m^3

This relationship remains linear up to an air concentration of 5000 µg/m^3, where the maximum risk that can be determined by this model would be 1 in 100. It is emphasised that these risks are based on lifetime exposure.

PBPK modelling (Teeguarden et al., 2008)

Based on the NOAEC determined in the study by Dorman et al. (2008) (see **Carcinogenicity** section), 50 ppm exposure for 6 hours/day, 5 days/week for 13 weeks in rats was estimated to result in an average olfactory epithelial tissue concentration of 73 nmol/mL. An UF of 30 was applied (elements not specified), resulting in a human equivalent concentration (HEC) of 2.43 nmol/mL. It was determined that the RfC was 810 µg/m^3, since continuous exposure at this concentration is required to attain the HEC under steady-state conditions (Dorman at al., 2008).

Government of Canada, Residential indoor air quality guideline: Acetaldehyde

Based on the opinion that 'a strong body of evidence has … emerged to support the notion that acetaldehyde exerts its carcinogenic effect through a non-linear MOA, with non-neoplastic effects being precursors to a carcinogenic response ... derivation of an RfC for the neoplastic effects of acetaldehyde is based on the observation of the non-neoplastic effects'. Using the NOAEC of 89 mg/m^3 for degeneration of olfactory epithelium determined in the study by Dorman et al. (2008) (see **Carcinogenicity** section) in an upper respiratory tract PBPK model, the HEC was calculated to be 120 mg/m^3. This value was adjusted for continuous exposure, resulting in a HEC of 21 mg/m^3. An UF of 75 was applied (2.5 for toxicodynamic differences between animals and humans, 10 for sensitive human populations and 3 for uncertainty of the dose- response curve shape), to give a long-term (24 hour) RfC of 280 µg/m^3 for residential indoor air exposure (Government of Canada, 2017).

A short-term (1 hr) RfC was also determined based on bronchoconstriction effects in asthmatic subjects exposed to the chemical for 2 minutes. A concentration of 142 mg/m^3, equivalent to the lower 95 % confidence interval of the LOAEC in the study, was used as the point of departure concentration. An UF of 100 was applied (10 for use of an LOAEC instead of an NOAEC and 10 for sensitive human populations), to give an RfC of 1420 µg/m^3 for residential indoor air exposure (Government of Canada, 2017).

SCCS opinion on acetaldehyde

Quantitative risk assessment was performed using the dose descriptor T25 method, and assuming a genotoxic (non-threshold) mechanism of cancer, where all routes of exposure are considered relevant. The T25 represents the dose at which there is a 25 % cancer incidence rate in an animal study (SCCS, 2012a).

Multiple similar T25 values were presented to support their hypothesis for a genotoxic mode of action of cancer. These were 116 mg/kg bw/day or 127 mg/kg bw/day following oral exposure to the chemical for combined lymphomas and leukaemias, and total malignant tumours, respectively; and 121 mg/kg bw/day derived from an inhalation study (see below) for nasal carcinomas in male Wistar rats. The inhalation study T25 (i.e. 121 mg/kg bw/day) was selected for further calculations. The chosen T25 value was calculated as described in SCCNFP, 2004:

- there was a net 31 % higher cancer (nasal carcinoma) incidence rate at a concentration of 1350 mg/m^3 (or 1.35 mg/L) in treated males (17/52) compared with controls (1/49)
- rats were exposed for 6 hours/day, 5 days/week, for 27 months
- an inhalation rate of 20.5 L/hour is assumed
- Dose (mg/kg bw/day) = concentration (mg/L) x inhalation rate (L/hour) x exposure time (hours per day x days per week) x duration of experiment (or standard lifetime) = 150 mg/kg bw/day
- T25 = Dose x (25 % / net cancer incidence rate) = 150 x (25 / 31) = 121 mg/kg bw/day

[It is noted that in the Dose formula above, a correction for rat body weight is apparently missing, but it is assumed that this was factored in given the final units presented. It is also unclear why there are apparently two total experiment durations (or standard lifetimes) factored into the calculation, as presented in the report detailing this derivation (SCCNFP, 2004). If these elements are indeed incorrect, and assuming a terminal rat body weight of approximately 500 g (0.5 kg; as per the HT25 calculation below), a dose of 267 mg/kg bw/day and a T25 of 215 mg/kg bw/day can be determined (using the same methodology as described in Sanner et al., 2001).]

Assuming 100 % absorption, the rat dose descriptor (T25) was converted to the human dose descriptor (HT25) using a body weight adjustment factor as per:

HT25
= T25 / (kg body weight$_{human}$ / kg body weight$_{animal}$) $^{0.25}$
= 121 / (60 / 0.5) $^{0.25}$
= 121 / 3.3
= 37 mg/kg bw/day

In this quantitative risk assessment, a product concentration of up to 100 ppm acetaldehyde was considered, corresponding to 1.74 mg acetaldehyde/day. Assuming an adult human body weight of 60 kg, a daily lifetime systemic exposure dose (SED) of 0.029 mg/kg bw/day was determined (i.e. SED = 1.74 / 60).

The lifetime cancer risk (LCR) for a 100 ppm product exposure was calculated by linear extrapolation, assuming 100 % dermal absorption and that this will cover all routes of absorption, as per:

LCR
= SED / (HT25 / 0.25)
= 0.029 / (37 / 0.25)
= 0.029 / 148
= 2 x 10^{-4} (or 1 in 5000)

It was reported that a 20-fold reduction of the measured LCR, to take it down to 10^{-5} (or 1 in 100000), provided 'a safe concentration … [of] 5 ppm in all cosmetic products' (SCCS, 2012a). The SCCS concluded that the unintentional use of the chemical was safe as a cosmetic fragrance or flavour ingredient at a maximum final concentration of 5 ppm acetaldehyde in a finished product, derived from 0.0025 % (25 ppm) in the fragrance compound (SCCS, 2012a).

SCCNFP opinion on acetaldehyde

In an earlier opinion on the chemical (SCCNFP, 2004), acetaldehyde was again considered to be safe as a fragrance/flavour ingredient at a maximum concentration of 0.0025 % (25 ppm) in the fragrance compound.

Weekly use data on typical cosmetic products containing the chemical were provided from the Research Institute for Fragrance Materials (RIFM). Using a conservative approach, and based on an adult human body weight of 60 kg, the SCCNFP estimated maximum exposure to the chemical to be 0.1 µg/kg bw/day. Using the T25 method exactly as described above, the LCR was calculated as per:

LCR
= SED / (HT25 / 0.25)
= 0.0001 / (37 / 0.25)
= 0.0001 / 148
= 7 x 10^{-7}

It was reported that this 'exposure … does not represent any cancer risk' (SCCNFP, 2004).

EHC – Acetaldehyde

Two distinct approaches were described in the EHC report (1995) for cancer risk following inhalation exposure to the chemical.

Based on the 2-year inhalation carcinogenicity study in Wistar rats (see **Carcinogenicity** section) and using a linearised multistage model (Global 82), a 10^{-5} (or 1 in 100000) excess LCR was reported for nasal tumours at lifetime exposure concentrations of 11–65 µg/m^3.

Based on the NOAEC for irritation in a sub-acute (28-day) inhalation toxicity study in Wistar rats (see **Carcinogenicity** section), and assuming a threshold (non-genotoxic) mechanism of carcinogenicity associated with irritation, a tolerable concentration for carcinogenicity was determined as per:

Tolerable concentration
= NOAEC / UF
= 275 mg/m^3 / 10 x 10 x 10
= 275 µg /m^3

where the UFs used were 10 for interspecies variation, 10 for intraspecies variation and 10 for the sub-acute study duration.

Summary

The US EPA modelling is likely to over-estimate the carcinogenicity risk of the chemical, by assuming a non-threshold mechanism and using a linear extrapolation model to fit carcinogenicity study data to a dose-response curve. Compared with the US EPA modelling approach, and considering that two discrete PBPK modelling approaches (Teeguarden et al., 2008 and Government of Canada, 2017) based on the most sensitive lesion (olfactory epithelial degeneration) considered to precede carcinogenicity resulted in RfC values in the same order of magnitude, it is likely that these latter figures more accurately reflect excess carcinogenicity risk.

The indicative tolerable cancer risk level for the general population according to REACH guidelines is 10^{-6} (or 1 in 1000000) (SCCS, 2016). For continuous acetaldehyde exposure, this can only be achieved at an air concentration of 0.5 µg/m^3 according to the US EPA modelling, or approximately 16–45 µg/m^3 if PBPK modelling has predicted more accurate RfC values that are 31- to 90-fold higher (Teeguarden et al., 2008; Government of Canada, 2017). The higher RfC values are also more sensible considering that general indoor environmental inhalation exposures measured in Australia, the EU, Canada and North America range 7–46 µg/m^3 and this has not been reported to contribute to increased carcinogenicity risk (see **Public exposure** section).

In the SCCS opinion on acetaldehyde, based on an estimated daily exposure dose of 29 µg/kg bw/day, it is stated that at a final product concentration of 5 ppm (derived from 25 ppm in the fragrance compound) there would be a 10^{-5} (or 1 in 100000) LCR (SCCS, 2012a). Prior to this, and based on a lower estimated daily exposure dose of 0.1 µg/kg bw/day, an LCR of 7 x 10^{-7} was estimated by the SCCNFP for 25 ppm in the fragrance compound (SCCNFP, 2004). The quantitative risk assessment approaches used by the SCCS (2012a) and SCCNFP (2004) are not aligned with current knowledge of the chemical's expected MOA. However, the conclusion on a 'safe' level of acetaldehyde in cosmetic products is sufficiently conservative to mitigate any risk.

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Related content

Acetaldehyde: Human health tier II assessment

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

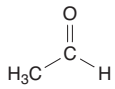
Acetaldehyde

CAS No. 75-07-0

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as ethanal



Carcinogenicity

Acetaldehyde is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to acetaldehyde by inhalation caused tumors in two rodent species and at two different tissue sites. In rats of both sexes, it caused cancer of the nasal mucosa (squamous-cell carcinoma and adenocarcinoma), and in hamsters of both sexes, it caused cancer of the larynx (carcinoma) (IARC 1985, 1987). Inhalation of acetaldehyde also promoted the induction of respiratory-tract tumors by intratracheal instillation of the known carcinogen benzo[*a*]pyrene in hamsters of both sexes.

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens,* an additional study in rats has been identified. Administration of acetaldehyde in drinking water increased the incidences of hemolymphoreticular cancer (leukemia and lymphoma combined), benign tumors of the pancreas (islet-cell adenoma), and cancer of the bone (osteosarcoma) and nasal cavity (carcinoma) in males and benign mammary-gland tumors (fibroma or fibroadenoma) in females (Soffritti *et al.* 2002). Increased incidences of tumors observed at other sites occurred only at one of the lower doses tested.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acetaldehyde. A survey of workers producing acetaldehyde and other aldehydes in Germany reported 9 cases of cancer, including 5 of lung cancer and 2 of oral-cavity cancer, among an unspecified number of workers; these incidences reportedly were higher than expected, but the observations were confounded by the fact that all cases of cancer occurred in tobacco smokers (IARC 1985, 1987).

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens,* additional epidemiological studies have been identified, primarily case-control studies of populations exposed to acetaldehyde (the main initial metabolite of alcohol) following consumption of alcoholic beverages. Alcoholic beverage consumption is listed in the Report on Carcinogens as *known to be a human carcinogen*. In its 1999 review, the International Agency for Research on Cancer noted that three small case-control studies found increased risks of alcohol-related cancer (of the oral cavity, pharynx, larynx, and esophagus) among individuals with genetic variations (polymorphisms) that result in increased levels of acetaldehyde after alcohol consumption. However, IARC concluded that the data available were inadequate to evaluate the carcinogenicity of acetaldehyde (IARC 1999). Since then, a number of review articles and meta-analyses have summarized the results of subsequent studies that found dose-response relationships between alcohol consumption and cancer of the oral cavity, pharynx, larynx, and esophagus, and possibly the stomach and colorectum, among individuals with genetic polymorphisms that increase blood or salivary levels of acetaldehyde (Bagnardi *et al.* 2001, Zeka *et al.* 2003, Boffetta and Hashibe 2006, Baan *et al.* 2007, Boccia *et al.* 2009, Salaspuro 2009). In 2009, IARC concluded that acetaldehyde associated with alcohol consumption was carcinogenic to humans (Secretan *et al.* 2009). Few studies have been conducted on the association of these polymorphisms with cancer at other tissue sites, and the role of acetaldehyde in pancreatic, liver, bladder, or breast cancer is not clear (van Dijk *et al.* 2001, Terry *et al.* 2006, Seitz and Becker 2007, Visvanathan *et al.* 2007, Druesne-Pecollo *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenases (ADH), and acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenases (ALDH). In some individuals, genetic polymorphisms in these enzymes can result in either higher rates of acetaldehyde production from alcohol or lower rates of acetaldehyde metabolism to acetic acid, resulting in higher blood acetaldehyde levels after a given level of alcohol intake than in individuals without these polymorphisms. Five ADH genes have been identified in humans, two of which have been shown to be polymorphic. The variant allele of the *ALDH2* gene, which is prevalent in Asians, encodes an enzyme that has almost no ability to detoxify acetaldehyde (IARC 1999).

Properties

Acetaldehyde is an aliphatic aldehyde that exists at room temperature as a colorless gas with a fruity, pungent odor. It is miscible with water, ether, benzene, gasoline, solvent naphtha, toluene, xylene, turpentine, and acetone. It is very flammable and is unstable in air (Akron 2009, HSDB 2009). Physical and chemical properties of acetaldehyde are listed in the following table.

Property	Information
Molecular weight	44.0[a]
Specific gravity	0.79 at 16°C/4°C[a]
Melting point	–124°C[a]
Boiling point	21°C[a]
Log K_{ow}	–0.34[b]
Water solubility	1,000 g/L at 25°C[a]
Vapor pressure	902 mm Hg at 25°C[a]
Vapor density relative to air	1.5[a]
Dissociation constant (pK_a)	13.6 at 25°C[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Acetaldehyde is used primarily as a chemical intermediate in the production of acetic acid, pyridine and pyridine bases, peracetic acid, pentaerythritol, butylene glycol, and chloral. It is also used in the synthesis of crotonaldehyde, flavor and fragrance acetals, acetaldehyde 1,1-dimethylhydrazone, acetaldehyde cyanohydrin, acetaldehyde oxime, various acetic acid esters, paraldehyde, metaldehyde (a molluscicide widely used to kill slugs and snails), polymers, and various halogenated derivatives (IARC 1985, 1999). Acetaldehyde has been used in the manufacture of aniline dyes, plastics, and synthetic rubber, to silver mirrors, and to harden gelatin fibers. It has also been used in the production of polyvinyl acetal resins, in fuel compositions, to inhibit mold growth on leather, and in the manufacture of disinfectants, pesticides, drugs, explosives, lacquers and varnishes, photographic chemicals, phenolic and urea resins, and rubber accelerators and antioxidants (EPA 1994).

Acetaldehyde is considered by the U.S. Food and Drug Administration to be generally recognized as safe for use as a flavoring agent and adjuvant (Furia and Bellanca 1975, HSDB 2009). It is an important component of food flavorings and is added to milk products, baked

goods, fruit juices, candy, desserts, and soft drinks; it is especially useful for imparting orange, apple, and butter flavors. The concentration of acetaldehyde in food generally is up to 0.047%. In 1976, about 8,600 kg (19,000 lb) of acetaldehyde was used as food additives. Acetaldehyde is also used in the manufacture of vinegar and as a fruit and fish preservative. It is approved for use in phenolic resins in molded containers for contact with non-acidic foods. Acetaldehyde is no longer registered as an active ingredient in any pesticide. When it was used as a fumigant for storage of apples and strawberries, it was exempted from a residue tolerance (IARC 1985, EPA 1994, HSDB 2009).

Production

Acetaldehyde was first produced commercially in 1916, and its U.S. production peaked at 1.65 billion pounds in 1969 (IARC 1985). In 2015, combined U.S. production and imports were in the range of 250 million to 500 million pounds (EPA 2016), similar to the range of 100 million to 500 million pounds reported from 1994 to 2002 (EPA 2004). Data on U.S. imports and exports of acetaldehyde indicated that although exports have decreased substantially from the 42.6 million pounds reported in 1989 (USITC 2009), they have continued to greatly exceed imports (as shown in the table below). In 2009, acetaldehyde was available from 49 suppliers, including 21 U.S. suppliers (ChemSources 2009).

Category	Year	Quantity (lb)
Production + imports[a]	2015	250 million to 500 million
U.S. imports[b]	2017	177,000
U.S. exports[b]	2017	4.5 million

Sources: [a]EPA 2016. [b]USITC 2018.

Exposure

There is high potential for exposure of the general population to acetaldehyde through ingestion, inhalation, and dermal contact and of workers through inhalation and dermal contact. The main source of exposure of the general population is through consumption of alcoholic beverages and the subsequent metabolism of alcohol to form acetaldehyde (HSDB 2009). Because acetaldehyde may form in wine and other alcoholic beverages after exposure to air (Hagemeyer 2002), alcoholic beverages (including wines, beer, and spirits) also frequently contain acetaldehyde as a volatile component (HSDB 2009).

Acetaldehyde is a product of most hydrocarbon oxidation reactions and is a normal intermediate in the respiration of most higher plants. It is found in trace amounts in many plant products, including apples, broccoli, coffee, grapefruit, grapes, lemons, mushrooms, onions, oranges, peaches, nectarines, pears, pineapples, raspberries, strawberries, cranberries, sour cherries, and mango. It has been detected in the essential oils of alfalfa, rosemary, balm, clary sage, daffodil, bitter orange, camphor, angelica, fennel, mustard, peppermint, and lychee, and in oak and tobacco leaves and cotton leaves and blossoms (IARC 1985, Burdon *et al.* 1996, Gorny *et al.* 1999, Gunes *et al.* 2002, Bonerz *et al.* 2007, Mahattanatawee *et al.* 2007). Acetaldehyde has also been detected in breast milk. Consumers may be exposed to acetaldehyde in many milk products, including all types of cheese, yogurt, and milk of varying fat content (Mistry and Hassan 1992, Barbieri *et al.* 1994, Jandal 1996, Beshkova *et al.* 1998, Van Aardt *et al.* 2001, Kondyli *et al.* 2002, Boscaini *et al.* 2003, Di Cagno *et al.* 2004, Fernandez-Garcia *et al.* 2004, Blagden and Gilliland 2005, Gadaga *et al.* 2007, Kaminarides *et al.* 2007). Acetaldehyde has also been detected in cooked beef, chicken, and fish (HSDB 2009, Yasuhara and Shibamoto 1995) and is used as a synthetic flavoring ingredient in processed foods, especially margarine (HSDB 2009).

According to EPA's Toxics Release Inventory, environmental releases of acetaldehyde have increased slightly since 1988, when 9.5 million pounds was released, 73% to air, 23% to underground injection wells, and the remainder to surface water and landfills. Since then, releases to underground injection wells have decreased, and releases to surface water have increased. In 2007, 11.4 million pounds of acetaldehyde was released from 336 facilities that processed, produced, or used the chemical; 29 facilities each released more than 100,000 lb. Of the total amount, 94% was released to air, 3.1% to underground injection wells, and 2.8% to water (TRI 2009). Acetaldehyde will volatilize rapidly from water or land, and it will leach into the ground, where it will biodegrade (HSDB 2009). Acetaldehyde is also degraded readily in soil, sewage, and natural waters by microorganisms (EPA 1987).

Acetaldehyde is a natural product of photooxidation of hydrocarbons commonly found in the atmosphere and occurs naturally as emissions from forest fires, volcanoes, and animal wastes. In the 1990s, annual emissions of acetaldehyde from all sources in the United States were estimated at 12.1 million kilograms (27 million pounds) (IPCS 1995). Burning wood produces acetaldehyde at approximately 0.7 g/kg of wood, and fireplace emissions range from 0.083 to 0.20 g/kg of wood burned (HSDB 2009). In the 1990s, annual emissions from residential burning in the United States were estimated at 5,000 metric tons (11 million pounds) (IPCS 1995). Acetaldehyde is also a combustion product of some plastics (e.g., polycarbonate) and some hard and soft polyurethane foams. It also occurs in gasoline exhaust (1.4 to 8.8 mg/m^3) and diesel exhaust (0.05 to 6.4 mg/m^3); however, very little is emitted from small engines such as lawn mowers or leaf blowers (IARC 1985, Baldauf *et al.* 2006).

Many individuals are exposed to acetaldehyde by inhalation. The highest ambient-air concentrations of acetaldehyde were reported for urban or suburban areas or near sources of combustion (HSDB 2009). In ambient air, concentrations of acetaldehyde generally averaged 5 μg/m^3. Indoor air concentrations were higher than ambient concentrations in all locations where acetaldehyde air concentrations were measured, both in the United States and in other countries (Miguel *et al.* 1995, Mukund *et al.* 1996, Brickus *et al.* 1998, MacIntosh *et al.* 2000, Possanzini *et al.* 2002, Baez *et al.* 2003, Hellen *et al.* 2004, Hodgson *et al.* 2004, Park and Ikeda 2004, Saijo *et al.* 2004, Sax *et al.* 2004, Shendell *et al.* 2004, Gilbert *et al.* 2005, Cavalcante *et al.* 2006, Ohura *et al.* 2006, Pang and Mu 2006, Sax *et al.* 2006, Hodgson *et al.* 2007, Possanzini *et al.* 2007). Acetaldehyde is also found in tobacco and marijuana cigarette smoke (1,220 μg per cigarette) and tobacco cigarettes (980 to 1,370 μg per cigarette).

In 1988–89, acetaldehyde was detected in 4 of 10 surveyed water supplies (EPA 1987). In surface water, concentrations generally are less than 0.1 μg/L, and the contribution from drinking water to human exposure is considered negligible (IPCS 1995).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 216,533 workers, including 97,770 women, potentially were exposed to acetaldehyde (NIOSH 1990). Workers potentially exposed include those involved in the manufacture or use of industrial organic chemicals, dyes, fabricated rubber, plastics, urea-formaldehyde foam insulation, fuels, drugs, explosives, varnishes, pesticides, food additives, leather goods, and mirrors (IARC 1985, EPA 1994).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acetaldehyde on ships and barges.

Department of Transportation (DOT)

Acetaldehyde is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.
National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of acetaldehyde is subject to certain provisions for the control of volatile organic compound emissions.
Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of acetaldehyde = U001.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 200 ppm (360 mg/m^3).
Considered a highly hazardous chemical: Threshold quantity (TQ) = 2,500 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 25 ppm.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 2,000 ppm.
Listed as a potential occupational carcinogen.

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Scientific Committee on Consumer Safety

SCCS

OPINION ON

Acetaldehyde

The SCCS adopted this opinion at its 16th Plenary meeting

of 18 September 2012

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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This opinion has been subject to a commenting period of four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged.

Revised opinions carry the date of revision.

TABLE OF CONTENTS

1. BACKGROUND

Acetaldehyde is classified as carcinogen category 2 (CMR substance according to Regulation 1272/2008 (CLP regulation)) under the EU chemicals legislation. The substance is not regulated in an Annex to the Cosmetics Directive.

The Scientific Committee on Cosmetic Products and non-food products intended for consumers expressed its opinion (SCCNFP/0821/04) with the following conclusions:

- Based on the information on the amount of fragrance compound present in the finished cosmetic products provided, the SCCNFP is of the opinion that acetaldehyde can be safely used as a fragrance/flavour ingredient at a maximum concentration of 0.0025% in the fragrance compound.
- SCCNFP does not recommend any further restrictions to the use of Acetaldehyde as a fragrance/flavour ingredient in cosmetic products.

This assessment was based on the presence of acetaldehyde in the fragrance compound of cosmetic products. This exposure was estimated to pose no increased life time cancer risk. However, the exposure to acetaldehyde from other uses of ethanol and/or acetaldehyde in cosmetics was not considered.

Moreover, concentration limits proposed on the basis of above opinion were considered so low that they might cause analytical problems when applied in practice.

Consequently, Industry was requested to prepare an exposure and safety assessment taking into account all possible sources of acetaldehyde exposure from cosmetic products.

This information was submitted by COLIPA in July 2011. This submission contains the requested safety assessment of acetaldehyde in all cosmetic products at concentration of 100 ppm, regardless whether deliberately added or from incidental presence.

2. TERMS OF REFERENCE

The SCCS is requested to answer the following questions:

1. *Is acetaldehyde safe when present up to 100 ppm in cosmetic products taking into account the new data provided?*

2. *And/or does the SCCS recommend any other concentration limit with regard to the use of Acetaldehyde as an ingredient in cosmetic products?*

3. *Does the SCCS have any further scientific concerns regarding the use of Acetaldehyde in mouth-washing products?*

3. OPINION

3.1 Chemical and Physical Specifications

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Acetaldehyde (INCI name)

3.1.1.2 Chemical names

IUPAC Name: Acetaldehyde
Synonyms: Acetic aldehyde, acetic ethanol, acetylaldehyde, ethanal, ethyl aldehyde

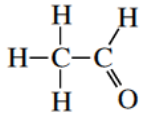
3.1.1.3 Trade names and abbreviations

/

3.1.1.4 CAS / EC number

CAS: 75-07-0
EC: 200-836-6

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

Formula: C_2H_4O

3.1.2 Physical form

Colourless liquid or gas with a characteristic pungent odour

3.1.3 Molecular weight

Molecular weight: 44.05 g/mol

3.1.4 Purity, composition and substance codes

/

3.1.5 Impurities / accompanying contaminants

Acetic acid

3.1.6 Solubility

Miscible with water, benzene, diethyl ether and ethanol

3.1.7 Partition coefficient (Log Pow)

Log P_{ow}: 0.5 (measured)

Ref.: 31

3.1.8 Additional physical and chemical specifications

Melting point:	-123 °C
Boiling point:	20.1 °C
Flash point:	-38 °C
Vapour pressure:	98 kPa at 20 °C
Density:	0.78 g/cm³
Viscosity:	0.2456 mPa x sec at 15 °C
pKa:	13.57
Refractive index:	/
UV_Vis spectrum (200-800 nm):	/
Conversion factor:	mg/m³ = 1.80 × ppm

3.1.9 Homogeneity and Stability

Pure acetaldehyde is flammable; it polymerizes violently in the presence of trace amounts of metals or acids. Acetaldehyde may undergo auto-polymerisation upon contact with air or moisture. Upon prolonged storage, it may form unstable peroxides.

Solutions of acetaldehyde in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal laboratory conditions.

3.2 Function and uses

Acetaldehyde is 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. Other uses of acetaldehyde include silvering of mirrors; leather tanning; denaturant for alcohol; fuel mixtures; hardener for gelatine fibres; glue and casein products; preservative for fish and fruit; synthetic flavouring agent; paper industry; and manufacture of cosmetics, aniline dyes, plastics and synthetic rubber.

The concentration of acetaldehyde in alcoholic beverages is generally below 500 mg/l. Low levels of acetaldehyde are also reported to occur in several essential oils.

Acetaldehyde is an intermediate product in the metabolism of ethanol and sugars and also occurs as a natural metabolite in small quantities in human blood.

In cosmetic products, two possibilities of occurrence of acetaldehyde can be distinguished:

1) Acetaldehyde is used as a **fragrance/flavour ingredient** in fragrance compounds used in cosmetic products. The SCCNFP concluded in its opinion of 25th May 2004 that acetaldehyde can be safely used as a fragrance/flavour ingredient at a maximum concentration of 0.0025% (25 ppm) in the fragrance compound.

2) In addition, acetaldehyde can also be found in cosmetic products in the form of unavoidable **traces** originating mainly through:

- Plant extracts and botanical ingredients
- Ethanol.

3.3 Toxicological Evaluation

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

In rats oral LD_{50} values ranged from >600 to 1 930 mg/kg bw

In mice the oral LD_{50} is reported to be 1 230 mg/kg bw

Oral LD_{50} in dogs is >600 mg/kg bw

Ref.:1

3.3.1.2 Acute dermal toxicity

In rabbit a dermal LD_{50} of 3 540 mg/kg bw has been reported.

Ref.: 1

3.3.1.3 Acute inhalation toxicity

Rats: LC_{50}, 20 500mg/m³ for 30 min, 13 000 mg/m³ for 4 hours
Mice: LC_{50}, 1 500 ppm (2 700 mg/m³) for 4 hours
Hamster: LC_{50}, 17 000 – 24 000 ppm (30 600 – 43 200 mg/m³) for 4 hours

Ref.: 1, 31

3.3.2 Irritation and corrosivity

3.3.2.1 Skin irritation

On the basis of a number of short- and long-term studies, acetaldehyde liquid and vapour has been shown to be acutely irritating to the skin.

Ref.: 2, 3

In a test with rabbits carried out according to OECD Test Guideline 404, acetaldehyde was not found to be irritating to the skin. In another test not conducted in accordance with test guidelines, in the same species 500 mg acetaldehyde produced slight irritation of the skin.

In a test with human volunteers, all 13 subjects showed erythema in a non-occlusive patch test with a 10% acetaldehyde preparation (vehicle not specified, probably water).

Ref.: 3

Concentrations greater than 1% in solution are likely to be irritating to the human skin.

Ref.: 4

Comment
Acetaldehyde is a skin irritant.

3.3.2.2 Mucous membrane irritation

In the rabbit eye, 40 mg acetaldehyde produced marked irritation. Long-term inhalative exposure of experimental animals to acetaldehyde vapour causes irritation of the mucous membranes of the eye, nose and upper respiratory tract.

Ref.: 3

All of the 14 humans exposed in controlled studies to acetaldehyde vapour at 135 ppm (240 mg/m^3) for 30 minutes reported mild irritation to the upper respiratory tract.

Ref.: 1

In another human study, inhalative exposure for 15 minutes to acetaldehyde in concentrations of ≥91 mg/m^3 resulted primarily in eye irritation in the majority of 24 volunteers. Sensitive persons showed eye symptoms even at concentrations as low as 45 mg/m^3. Irritation of the upper respiratory tract seems to be less sensitive and is not described up to 246 mg/m^3.

Ref.: 3

Twenty volunteers were exposed in a cross over design for 4 hours to 0 or 91 mg/m^3 acetaldehyde. No subjective irritative symptoms were reported (assessed by questionnaire). Before and after exposure the olfactory threshold for n-butanol and the mucociliary transport time was determined and did not show any change. Concentrations of interleukin-1ß and interleukin-8 in nasal secretion were not increased after exposure to acetaldehyde. mRNA levels of inflammatory factors (interleukin-1ß, -6 and -8, TNFα, granulocyte-macrophage colony stimulating factor, monocyte chemotactic protein 1, and cyclooxygenases 1 and 2) were determined in nasal epithelial samples and did not show any increase after exposure. The authors concluded that test persons were not adversely affected by acute exposure to 91 mg /m³.

Ref.: 5

Comment
The SCCS considers that acetaldehyde is an eye and respiratory tract irritant.

3.3.3 Skin sensitisation

The skin sensitisation potential of acetaldehyde was tested in a modified Cumulative Contact Enhancement Tests (CCET). Fifteen female albino Dunkin-Hartley guinea pigs were tested. A 0.2 ml aliquot of acetaldehyde was applied to a 2x4 cm lint cloth and then applied to shaved skin on the upper back for 24 hours under occlusion. Induction applications (15% acetaldehyde in saline) were administered on days 0, 2, 7 and 9. The animals also received two intradermal injections of 0.1 ml FCA in the same region on day 7. Animals were challenged 14 days after the final induction at doses of 2.5%, 5.0% and 10.0% acetaldehyde in saline. At challenge, a 0.015 ml aliquot of Acetaldehyde in saline was applied to a Finn Chamber and then applied to a shaved site on the lateral back for 24 hours under occlusion. Reactions were read 48 and 72 hours after start of exposure. Acetaldehyde showed significant sensitising capacity and a clear dose-response relationship was observed. Specifically, at the 48-hour reading, challenge at 2.5% produced 4/15 sensitisation reactions; challenge at 5.0% produced 7/15 sensitisation reactions; challenge at 10.0% produced 13/15 sensitisation reactions. At the 72-hour reading, challenge at 2.5% produced 5/15 sensitisation reactions; challenge at 5.0% produced 9/15 sensitisation reactions; challenge at 10.0% produced 13/15 sensitisation reactions. The animals were rechallenged 78 days after the start of the experiment with acetaldehyde at concentrations of 0.035 and 2.5%, and no significant reactions were observed.

Ref.: 6

Comment

This was a non-guideline method and it is unknown whether the reactions observed were irritant (false positive) in nature.

In a study of intolerance reactions to air-oxidized and non-oxidized surface-active ethoxylated (fatty) alcohols, six of 528 consecutive patients tested also with a 1% preparation of acetaldehyde in water produced reactions (erythema plus oedema, papules or vesicles). In ten further patients, only erythematous reactions occurred. In the follow-up test, only one of the six patients still reacted to 1% and 0.33% acetaldehyde in water. The relevance of these reactions has not been clarified, although the authors consider the presence of slight quantities of acetaldehyde in the oxidized surfactants to be possible.

Ref.: 3

A maximization test was carried out with 2% acetaldehyde in petrolatum on 28 healthy, male and female volunteers. Application was under occlusion to the same site on the volar forearms of all subjects for five alternate-day 48-hour periods. The initial patch site was pretreated with 2% aqueous sodium lauryl sulphate (SLS) under occlusion for 24 hours. Following a 10- to 14-day rest period, challenge patches were applied under occlusion to fresh sites for 48 hours. Challenge applications were preceded by 30-minute applications of 2% aqueous SLS under occlusion on the left side of the back whereas the test materials were applied with SLS treatment on the left and petrolatum on the right. Reactions were read at patch removal and again 24 hours after patch removal. No sensitisation reactions were produced.

Ref.: 7

The skin sensitisation potential of acetaldehyde was assessed in 4 female patients with eczematous reactions to lower aliphatic alcohols. The individuals were patch tested with 2% acetaldehyde in water. The study consisted of 48-hour patch tests using A1-test units conducted on the upper backs of the patients. Reactions were read at removal and 24 and 48 hours post-removal. No evidence of skin sensitisation reactions to acetaldehyde was observed at any time interval.

Ref.: 8

Following participation in a human repeated insult patch test with ethanol, one subject became strongly sensitised and was further tested for cross-reactivity. A 0.15 ml 1% aqueous acetaldehyde was applied to a 12 mm Webril patch and reactivity to acetaldehyde was observed. In the same study the author inadvertently sensitised himself to acetaldehyde during a test to determine a non-irritant concentration of acetaldehyde. The exposure consisted of single applications of 5% and 10% acetaldehyde for a 3-hour period followed by single sequential applications of 0.5% and 1% for 24 hours, all within an 8-day period. A subsequent application of 2% acetaldehyde produced a strong allergic response and prompted a flare at the 10% application site that was made 20 days earlier.

Ref.: 9

Comment
There is limited evidence for skin sensitisation. The SCCS considers the HRIPT tests as unethical. Respiratory sensitisation has not been investigated to date.

3.3.4 Dermal / percutaneous absorption

No *in vitro* studies of dermal absorption have been found.

Comment
Some studies are available concerning increase in blood acetaldehyde after dermal exposure to ethanol (see Section 3.3.12 Special investigations). However, no quantitative conclusions can be drawn from these studies regarding skin absorption of acetaldehyde.

In the safety evaluation 100% skin absorption is used as no experimental data is available.

3.3.5 Repeated dose toxicity

3.3.5.1 Repeated Dose (28 days) oral toxicity

Guideline:	/
Species/strain:	SPF-bred (Cpb:WU) Wistar rats
Group size:	Control groups 20 males and 20 females, treated groups 10 males and 10 females
Test substance:	Acetaldehyde
Batch:	/
Purity:	99.8%
Vehicle:	Water
Dose levels:	0 (control), 5, 25, 125, 675 mg/kg bw/d
Dose volume:	/
Route:	Oral
Administration:	Drinking water
GLP:	/
Study period:	Before 1988

In a 4 weeks study, acetaldehyde was added to drinking water of rats (5 weeks old at start of experiment), providing daily intake levels of 0, 25, 125, or 675 mg/kg bw/d. The rats were weighed at weekly intervals and observed daily. Food and liquid intakes were measured over weekly periods. Early in week 5, the rats were killed.

There were no deaths and the rats appeared to be healthy throughout the study. The only clearly compound-related effect reported was moderate or slight focal hyperkeratosis of the forestomach in the high-dose group (8/10 males and 8/10 females). In the control group, very slight or slight focal hyperkeratosis of the forestomach was noted in 6/20 females and 4/20 males. In the high-dose group, the relative kidney weights were slightly increased in males, and urinary production was decreased. The effects and reported variations in serum biochemistry, were generally attributed to reduced water intake. Acetaldehyde exposure did not affect indices of liver function and produced no evidence of histological change in this organ.

Ref.: 10

Comment
A NOAEL of 125 mg/kg bw/d can be derived from the study.

3.3.5.2 Repeated Dose (28 days) inhalation toxicity

Several studies investigating toxicity of acetaldehyde by inhalation have been published but most of them are not recent ones and did not followed standardized procedures. Two short-term studies conducted by the same research group are considered as the most reliable and informative and then are the principal studies used for risk assessment of acetaldehyde by inhalation.

In a first 28 days study, Appelman et al (1982) have exposed groups of 10 male and 10 female Wistar rats to 0, 400, 1000, 2200 or 5000 ppm acetaldehyde for 6 h/day, 5 days/week. Treatment-related changes observed at the 5000 ppm level included dyspnoea and excitation during the first 30 min of each exposure, yellow-brown fur, severe growth retardation, more neutrophils and less lymphocytes in the blood, a reduced production of urine with a high density, increased lung weights, and severe degenerative, hyperplastic and metaplastic changes of the nasal, laryngeal and tracheal epithelium. Major lesions seen at 1000 and 2200 ppm included growth retardation and an increased production of urine in males, slight to moderate degeneration with or without hyper- and metaplasia of the nasal

epithelium, and only at 2200 ppm, minimal epithelial changes in the larynx and trachea. The only change observed at the 400 ppm level that could be attributed to acetaldehyde was slight degeneration of the nasal olfactory epithelium seen as loss of microvilli and thinning and disarrangement of the layer of epithelial cells.

Ref: 40

Comment
This study does not follow OECD/GLP guidelines. No NOAEL can be derived from this study and, based on the slight degeneration of the nasal olfactory epithelium, 400 ppm could be considered as a LOAEL.

In a second 28 days study, Appelman et al (1986) have studied the effect of short-term increases and interruption in exposure on the inhalation toxicity of acetaldehyde during 28 days in male Wistar rats. Male rats were exposed to 110, 150 and 500 ppm for 6 h per day/5 days per week. One group of animals was exposed without interruption, the exposure of a second group was interrupted for 1.5 h between the first and second 3-h periods, the exposure of a third group was similarly interrupted and for six 5 min periods exposure was increased six fold. Peak exposures of up to 3000 ppm superimposed on 500 ppm acetaldehyde caused irritation and excitation, and reduced body weight gain. No such effects occurred after interrupted or uninterrupted exposure to 500 ppm acetaldehyde without peak loads. A reduced phagocytotic index of lung macrophages was found in each of the groups exposed to 500 ppm acetaldehyde, the effect being most marked in the group with superimposed peaks of 3000 ppm. Degeneration of the nasal olfactory epithelium was observed in rats uninterruptedly exposed to 500 ppm acetaldehyde. Interruption of the exposure or interruption combined with peak exposure did not visibly influence this adverse effect on the nose. No compound-related effects were seen in rats interruptedly or uninterruptedly exposed to 150 ppm acetaldehyde or interruptedly exposed to 110 ppm with peak loads of 660 ppm. As a consequence 150 ppm acetaldehyde can be considered a 'no-toxic-effect level' in male rats exposed for 6 h/day, 5 days/week, during a 4-week period.

Ref: 41

Comment
This study does not follow OECD/GLP guidelines. Based on the degeneration of the nasal olfactory epithelium observed at 500 ppm, which could be considered as a LOAEL and 150 ppm (273 mg/m³) as a NOAEL. The NOAEL, based on continuous exposure, would then be (273 x 5/7 x 6/24) 49 mg/m³.
This value will be used in the safety assessment for non-cancer effects by inhalation.

3.3.5.3 Sub-chronic (90 days) oral toxicity

In a group of rats exposed to 0.05% acetaldehyde in the drinking water (estimated to be about 40 mg/kg bw for 6 months, an increase in collagen synthesis in the liver was reported. Since no other indices of toxicity were reported, the significance of this finding is unknown.

Ref.: 11

Guideline:	/
Species/strain:	Male Wistar rats
Group size:	Control groups 10 males, low dose group 4 males, high dose group 10 males
Test substance:	Acetaldehyde
Batch:	/
Purity:	/
Vehicle:	Water
Dose levels:	0 (control), 120, 500 mg/kg bw/d
Dose volume:	/

Route: Oral
Administration: Drinking water for 11 weeks
GLP: /
Study period: Before 1996

24 male rats, 10 weeks old, where divided into 3 groups, a control group (10 males), a low dose group (4 males) and a high dose group (10 males). The low and high dose groups received drinking water containing 20 mM (corresponding to 120 mg/kg bw/day) and 120 mM acetaldehyde (corresponding to 500 mg/kg bw/day), respectively for 11 weeks. The control group received drinking water without acetaldehyde. The general health of the rats was good and no signs of illness could be observed throughout the experiment. No differences in the body weights or in the liquid intakes of the rats were detected between different groups during the study. Among the high dosed rats microvesicular fatty degeneration was found. On morphometric analysis, a significantly greater accumulation of fat could be detected both in the periportal and in the pericentral areas of the hepatic acinus in the livers of rats receiving the high dose acetaldehyde. In rats receiving a high dose of acetaldehyde, some foci of inflammatory cells were found in the liver specimens of seven out of ten rats. No inflammatory changes were found either in the rats receiving a low dose of acetaldehyde or in the controls.

Ref.: 37

Comment
Based on the accumulation of fat and inflammatory changes in the liver of the male rats receiving 500 mg/kg bw/day, a NOAEL of 120 mg/kg bw/day for acetaldehyde can be derived.

The potential toxicity of acetaldehyde administered perorally in aqueous solution to white rats and guinea pigs at dose levels of 0.5, 10, or 100 mg/kg bw/d for periods of 5-6 months was studied. In guinea pigs, indices monitored at every dose level, with the exception of the high-dose level, included peripheral blood cholinesterase and leukocyte phagocytic activity, as well as the ratio of protein fractions in blood serum. In rats, conditional reflex activity and blood pressure levels were evaluated at every dose level.

Rats in the high-dose group were reported to exhibit inhibition of reflex activity, increases in blood pressure, as well as unspecified histological variations in the internal organs. A transient disruption of the conditioned reflex activity also was reported in rats receiving 10 mg acetaldehyde/kg bw/d at the 2 and 3 month of treatment. Compound-related effects reported in guinea pigs were limited to a statistically significant reduction in eosinophil count in groups treated at 10 mg/kg bw/d. No apparent adverse effects were reported in groups of animals administered 0.5 mg/kg bw/d.

Ref.: 12

Comment
No documentation for the above study was available to SCCS for evaluation. The study is not suitable for the estimation of the NOAEL/LOAEL.

No dermal study with acetaldehyde has been found.

3.3.5.4 Chronic (> 12 months) toxicity

See Section 3.3.7 Carcinogenicity

3.3.6 Mutagenicity / Genotoxicity

This section is based on IARC, 1999, 2011, 2012 (Ref.: 13, 14, and 15)

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.

Numerous *in vitro* studies have consistently shown that acetaldehyde causes DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells *in vitro* (ref.: 16, 17). In comparison with other assays, the Comet assay requires relatively high concentrations of acetaldehyde to show a positive result, probably reflecting the formation of crosslinks (ref.: 16). Acetaldehyde induced also DNA protein crosslinks, sister chromatid exchanges and chromosomal aberrations in rodents *in vivo* (ref.: 14)

Table 1: *Genetic and related effects of acetaldehyde in vitro (See IARC (Ref 13) for references)*

Test system	Results -S9	Results +S9	Dose (LEDorHID	References
Escherichia coli K-12 uvrB/recA, differential toxicity	–	–	78200	Hellmér & Bolcsfoldi (1992)
Salmonella typhimurium TA100, TA104, TA1535, TA98, TA97, reverse mutation	–	–	10 mg/plate	Zeiger et al. (1992)
Salmonella typhimurium TA100, TA1535, TA1537, TA97, TA98, reverse mutation	–	–	5–10 mg/ plate	Phillips & Jenkinson (2001)
Saccaromyces cerevisiae, (repair-deficient) strand breaks	+	NT	39100	Ristow et al. (1995)
Aspergillus nidulans, chromosome malsegregation	+	NT	35500	Crebelli et al. (1989)
Vicia faba, sister chromatid exchange	+	NT	16000	Zhang et al. (1991)
Hordeum species, sister chromatid exchange	+	NT	16000	Zhang et al. (1991)
Plant (other), sister chromatid exchange	+	NT	16000	Zhang et al. (1991)
Drosophila melanogaster, somatic mutation (and recombination)	–	NT	120000	Graf et al. (1994)
Gene mutation, mouse lymphoma L5178Y cells, Tk locus in vitro	(+)	(+)	4200	Wangenheim & Bolcsfoldi (1988)
Gene mutation, mouse lymphoma L5178Y cells, Tk locus in vitro	–	–	35900	Phillips & Jenkinson (2001)
Sister chromatid exchange, mouse embryos in vitro	+	NT	300	Lau et al. (1991)
Chromosomal aberrations, Chinese hamster lung cells in vitro	–	–	8000	Phillips & Jenkinson (2001)
Chromosomal aberrations, Chinese hamster ovary cells in vitro	–	NT	32000	Lin et al. (1989)
Chromosomal aberrations, mouse embryos in vitro	+	NT	800	Lau et al. (1991)
DNA strand breaks, human lymphocytes in vitro	+	NT	1380	Blasiak et al. (2000)
DNA strand breaks, human colonic mucosa in vitro	+	NT	460	Blasiak et al. (2000)
DNA strand breaks, human gastric mucosa in vitro	+	NT	46000	Blasiak et al. (2000)
Sister chromatid exchange, human lymphocytes in vitro	–	NT	40000	Zhang et al. (1991)
Chromosomal aberrations, human lymphocytes in vitro	–	–	8000	Phillips & Jenkinson (2001)
Chromosomal aberrations, human lymphoid cell lines in vitro	–	NT	32000	Hsu et al. (1991)
Chromosomal aberrations, human lymphoblast cell lines in vitro	–	NT	8000	Brown et al. (1991)

[a]+, positive; (+), weak positive; –, negative; NT, not tested [b]LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/ml.

Table 2: *Genetic and related effects of acetaldehyde in vivo (See IARC (Ref 13) for references)*

Test system	Results[a]	Dose

(LED or HID)[b]			References
DNA adducts, BD6 rat tissues in vivo	–	4300	Izzotti et al. (1998)
DNA strand breaks, rat brain cells in vivo	+	4000	Singh et al. (1995)
DNA strand breaks, Wistar rat liver cells in vivo	+	5000	Navasumrit et al. (2000)
Sister chromatid exchange, mouse cells in vivo	+	1600	Zhang et al. (1991)
Sister chromatid exchange, mouse bone marrow in vivo	+	600	Piña Calva & Madrigal-Bujaidar (1993)
Micronucleus formation, B6C3F1 mouse spermatids in vivo	–	28500	Pylkkänen & Salonen (1987)
Micronucleus formation, BD6 rat bone-marrow cells and pulmonary alveolar macrophages in vivo	–	50 g/l in drinking water	Balansky et al. (1993)
Micronucleus formation, CD-1 mouse polychromatic erythrocytes in *vivo*	–	3500	Choy et al. (1995)
Micronucleus formation, CD-1 mouse polychromatic erythrocytes in *vivo*	–	2500	Choy et al. (1996)
Micronucleus formation, mouse in vivo	–	2000	Phillips & Jenkinson (2001)
Chromosomal aberrations, Wistar rat bone marrow in vivo	–	200 g/l in drinking-water	Tavares et al. (2001)
Aneuploidy, Chinese hamster spermatogonia in vivo	–	6250	Daniel & Roane (1987)
Aneuploidy, (C57BL x CBA) F1 Mouse oocytes in vivo	+	4800	O'Neill & Kaufman (1987)
Dominant lethal test, mice	(+)	1260 × 3	Rao et al. (1994)
Dominant lethal test, mice	+	25000	Berryman et al. (1992)

[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

Table 3: *Genetic and related effects of acetaldehyde in vivo (See IARC (Ref 13) for references)*

Test system	Results[a]	References
Studies on alcoholics		
Gene mutation, human lymphocytes, HPRT locus in vivo	–	Cole & Green (1995)
Sister chromatid exchange, human lymphocytes in vivo	+	Butler et al. (1981)
Sister chromatid exchange, human lymphocytes in vivo	(+)	Seshadri et al. (1982)
Sister chromatid exchange, human lymphocytes in vivo	+	Kucheria et al. (1986)
Sister chromatid exchange, human lymphocytes in vivo	+	Rajah & Ahuja (1996)
Sister chromatid exchange, human lymphocytes in vivo	+c	Karaoğuz et al. (2005)
Micronucleus formation, human buccal mucosa cells in vivo	–	Stich & Rosin (1983)
Micronucleus formation, human buccal epithelium in vivo	+	Ramirez & Saldanha (2002)
Micronucleus formation, human lymphocytes in vivo	+ c	Castelli et al. (1999)
Micronucleus formation, human lymphocytes in vivo	+	Maffei et al. (2000)
Micronucleus formation, human lymphocytes in vivo	+	Maffei et al. (2002)
Micronucleus formation, human lymphocytes in vivo	(+)	Ishikawa et al. (2006)
Chromosomal aberrations, human lymphocytes in vivo	+	De Torok (1972)
Chromosomal aberrations, human lymphocytes in vivo	+	Lilly (1975)
Chromosomal aberrations, human lymphocytes in vivo	+	Mitelman & Wadstein (1978)
Chromosomal aberrations, human lymphocytes in vivo	+	Obe et al. (1980)
Chromosomal aberrations, human lymphocytes in vivo	+	Badr & Hussain (1982)
Chromosomal aberrations, human lymphocytes in vivo	+	Kucheria et al. (1986)
Chromosomal aberrations, human lymphocytes in vivo	–	Rajah & Ahuja (1996)
Chromosomal aberrations, human lymphocytes in vivo	+	Gattás & Saldanha (1997)
Chromosomal aberrations, human lymphocytes in vivo	+ c	Castelli et al. (1999)
Chromosomal aberrations, human lymphocytes in vivo	+	Hüttner et al. (1999)
Chromosomal aberrations, human lymphocytes in vivo	+	Maffei et al. (2002)
Chromosomal aberrations, human lymphocytes in vivo	+	Burim et al. (2004)
Aneuploidy, human sperm in vivo	+	Robbins et al. (1997)

[a]+, positive; (+), weak positive; –, negative; NT, not tested bw/day [c] In these studies, people who consumed alcohol were also heavy smokers.

The most abundant DNA adduct that results from the reaction of acetaldehyde is *N*2-ethylidenedeoxyguanosine (*N*2EtidG). This adduct is too unstable to be purified and isolated, but can be converted into the stable adduct *N*2EtdG by treatment with a reducing

agent (sodium cyanoborohydride). The reduction step can also be carried out by a mixture of GSH and ascorbic acid, which may occur *in vivo.*

Ref.: 18, 19

Fang and Vaca examined the levels of the *N*2EtdG adduct in a group of Swedish alcohol abusers compared to controls. They found that chronic alcoholics had higher levels of the *N*2EtdG adduct in both lymphocytes and granulocytes compared with controls. Balbo *et al.* measured later the level of *N*2-EtdG in blood leukocyte DNA of two groups of subjects, one consisting of alcohol drinkers and abstainers and the other of heavy drinkers. A significant trend between *N*2-EtdG level and daily alcohol dose was found.

Ref.: 18, 20

In addition to the major adduct *N*2EtidG, three acetaldehyde-derived DNA adducts have been identified. These are: *N*2-(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine (*N*2-Dio-dG); an interstrand crosslink, and two diastereoisomers (R and S) of α-methyl-γ-hydroxy-1,*N*2-propanodeoxyguanosine (α-Me-γ-OH-PdG).

Ref.: 21

Comment
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. Acetaldehyde induced also DNA protein cross links, sister chromatid exchanges and chromosomal aberrations in rodents *in vivo.* Increased frequency of acetaldehyde DNA adducts in humans has been found in relation to alcohol use.

3.3.7 Carcinogenicity

Animal studies

Oral administration
Rat

Guideline:	/
Species/strain:	Sprague-Dawley rats
Group size:	Control group: 100 male and 100 female rats. Dosed groups: 50 male and 50 female rats.
Test substance:	Acetaldehyde
Batch:	/
Purity:	> 99.0%
Vehicle:	Water
Dose levels:	0 (control), 50, 250, 500, 1500, and 2500 mg/l
Dose volume:	Drinking water supplied *ad libitum*
Route:	Oral
Administration:	Drinking water
Positive control:	/
GLP statement:	Yes
Study period:	Before 2002

Groups of 50 male and 50 female Sprague-Dawley rats, 6 weeks of age, were exposed to 0, 50, 250, 500, 1500 or 2500 mg/l acetaldehyde in the drinking-water for 104 weeks. The experiment was terminated when the last animal died at 161 weeks of age.

No significant differences in the daily consumption of beverages and feed, behaviour, body weight, or survival were observed between treated and control animals, nor were any treatment-related non-oncological pathological changes detected by gross inspection or histopathological examination.

Complete histopathology was performed on all animals. In female rats administered 0, 50, 250, 500, 1500 and 2500 mg/l acetaldehyde, respectively, the incidence of malignant mammary tumours (adenocarcinomas) was 6% (3/50), 18% (9/50), 6% (3/50), 20% (10/50) [*P* = 0.04 compared with controls; one-sided Fisher's exact test, but not significant in two-sided test], 16% (8/50) and 12% (6/50). Slight treatment-related increases were observed in the incidence of Zymbal gland carcinomas, ear duct carcinomas and oral cavity carcinomas in both sexes [not statistically significant]. Nasal cavity carcinomas (4%, 2/50) were only observed in male rats administered 2500 mg/l acetaldehyde. Sporadic incidences of lung adenomas and adenocarcinomas, forestomach acanthomas and squamous-cell carcinomas and intestinal fibromas and adenocarcinomas were observed in male and/or female rats administered acetaldehyde [no statistically significant difference]. Testicular interstitial-cell tumours were observed in all groups [not statistically significant]. The incidence of uterine adenocarcinomas was increased in rats administered 250 mg/l acetaldehyde (10% (5/50) versus 0/50 controls) [*P* = 0.03, one-sided, P = 0.056 two-sided]. The incidence of cranial osteosarcomas was increased in male rats administered 50 mg/L (10% (5/50) versus 0/50 controls) [*P* = 0.03 one-sided, P = 0.056 two-sided] and 2500 mg/L acetaldehyde (14% (7/50) versus 0/50 controls) [*P* = 0.01 two-sided]. Lymphomas and leukaemias combined were observed in all groups; compared with the controls (12% (6/50) males and 4% (2/50) females), the incidences were increased in male rats administered 50 mg/L (28%, 14/50) [*P* = 0.04 one-sided, P = 0.08 two-sided and 1500 mg/l acetaldehyde (30%, 15/50) [*P* = 0.02 one-sited, 0.05 two-sided].

Ref.: 22

Comment

The IARC working group (ref.: 13) evaluating the study noted "that a variety of tumours were observed in male and female rats administered acetaldehyde in the drinking-water. In some instances, the incidence in the treated groups was significantly greater than that in the respective control groups; nevertheless, these increases may be due to chance because no obvious dose–response relationship was observed in any of the tissues. The Working Group expressed concerns whether the doses were accurate due to the volatility of acetaldehyde." A similar criticism has been raised by BfR-Kommission für kosmetische Mittel (ref. 39).

Despite some uncertainties in the dose-response relationship and other criticisms of the study, as stated by IARC and BfR, the SCCS calculated a T25 value from the study.

In Table 4 the frequencies of tumour sites with significant increase and the corresponding T25 are shown.

Table 4: Tumour types with significant increased frequencies (two-sided Fisher's exact test compared to control, P ≤ 0.05, bold) after exposure to acetaldehyde in drinking water

Tumour	***Control***	***50 mg/l***	***250 mg/l***	***500 mg/l***	***1500 mg/l***	***2500 mg/l***	***T25 mg/kg bw/d***
Male		*5* mg/kg bw/d*	*25 mg/kg bw/d*	*49 mg/kg bw/d*	*147 mg/kg bw/d*	*246 mg/kg bw/d*	
Cranial osteosarcomas	0 (0%)	5 (10%)	1 (2%)	2 (4%)	0 (0%)	**7 (14%)**	283
Lymphomas and leukaemias	6 (12%)	14 (28%)	10 (20%)	9 (18%)	**15 (30%)**	8 (16%)	116

Tumour	***Control***	***50 mg/l***	***250 mg/l***	***500 mg/l***	***1500 mg/l***	***2500 mg/l***	***T25 mg/kg bw/d***
Female		*5 mg/kg bw/d*	*27 mg/kg bw/d*	*53 mg/kg bw/d*	*155 mg/kg bw/d*	*260 mg/kg bw/d*	
Uterine adenocarcinomas	0 (0%)	0 (0%)	5 (10%)**	1 (2%)	2 (4%)	1 (2%)	44

* *Recalculated using data about body weight and drinking volume (average for each group up to week 104) provided by M. Soffritti (2008, personal communication).From Lachenmeier et al., 2009a; Ref.: 27)*

** P= *0.056*

T25 calculated on the basis of significant increased tumour frequencies for cranial osteosarcomas and lymphomas and leukaemias combined in male rats were 283 and 116 mg/kg bw/d respectively and 44 mg/kg bw/d for uterine adenocarcinomas in female. Lachenmeier *et al*. (2009a) (Ref.: 27) derived and used a T25 value of 127 mg/kg bw/day based on the total number of malignant tumours in male rats.

Inhalation

Rats

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 28 months. Each group comprised five subgroups, three of which were used for interim kills at weeks 13 (5 males and 5 females), 26 (5 males and 5 females) and 52 (10 males and 10 females), respectively. One group was exposed for 12 months and killed after a recovery period of 12 months (30 males and 30 females). The remaining animals (55 males and 55 females) were killed after maximum 28 months.

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 (2%), 17/52 (33%), 41/53 (77%) and 37/49 (76%) in the control, low-, mid- and high-dose groups, respectively; and in females: 0/50 (0%), 6/48 (13%), 34/53 (64%), and 43/53 (81%) 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.

Ref.: 23

Comment

SCCS notes that the experiment lasted for 28 month and not 24 months as stipulated by modern guidelines. A T25 of 121 mg/kg bw/day based on nasal carcinomas in males was calculated in the previous SCCNFP Opinion on Acetaldehyde (ref.: 28).

Hamster

Groups of 35 male Syrian golden hamsters were exposed to 0 or 1500 ppm [2700 mg/m^3] acetaldehyde vapour for seven hours per day on five days per week for 52 weeks, and

received weekly intratracheal instillations of 0, 0.0625, 0.125, 0.25, 0.5 or 1 mg benzo[*a*]pyrene suspended in saline for the same period.

Groups of five animals were killed at the 52nd week and the remainder allowed surviving untreated for an additional 26 weeks.

There was no significant difference in mortality between the animals exposed to acetaldehyde and those exposed to air, except for the subgroup treated with the highest dose of benzo[*a*]pyrene, for which the mortality in the acetaldehyde-exposed animals was increased more rapidly than the mortality in the corresponding benzo[*a*]pyrene group exposed to air ($p < 0.001$ in both groups).

No tumour was found in hamsters exposed to acetaldehyde only; but 3/30, 4/30, 9/30, 25/29 and 26/28 hamsters exposed to benzo[*a*]pyrene alone developed respiratory-tract tumours and 1/28, 5/29, 8/29, 16/29 and 29/30 hamsters exposed to benzo[*a*]pyrene and acetaldehyde vapour developed the same type of tumour.

Ref.: 24

Comment
Acetaldehyde alone did not induce tumours under the experimental conditions used, nor did acetaldehyde affect the carcinogenic effect of benzo[*a*]pyrene.

Groups of 36 male and 36 female Syrian golden hamsters, six weeks of age, were exposed for seven hours per day on five days per week to room air (chamber controls) or to decreasing concentrations of acetaldehyde (distilled and analysed by gas chromatography) (initial concentration, 2500 ppm [4500 mg/m^3]; final concentration, 1650 ppm [2970 mg/m^3]) for 52 weeks. Six animals killed and examined from each group had no tumour. The remaining animals were observed until 81 weeks and killed. The incidences of respiratory-tract tumours were 0/30 (0%), 8/29 (29%), 0/28 (0%) and 5/29 (17%) in control males, exposed males, control females and exposed females, respectively ($p < 0.05$). The acetaldehyde-induced tumours were predominantly laryngeal carcinomas with a few laryngeal polyps, and nasal polyps and carcinomas.

Ref.: 25

Human studies

Several case-control studies have been carried out in chemical plants. In the former 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 and other higher, condensed aldehydes, as well as to traces of acrolein. 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 IARC Working Group (Ref.: 13) noted the mixed exposure, the small number of cases and the poorly defined exposed population.

IARC concluded in 1999 (Ref.: 13) that “There is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde.

In 2012 IARC (Ref.: 15) has concluded: “Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1).”*

In reaching the above conclusion the IARC made the following considerations:

- Upon ingestion of alcoholic beverages, ethanol is converted into acetaldehyde, which is then oxidized to acetate.

- Ethanol and acetaldehyde are both carcinogenic in experimental animals.
- There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, in particular of the oesophagus and the upper aero-digestive tract.

Comment
The term upper aero-digestive tract include oral cavity, pharynx, larynx and oesophagus.

On the basis of the calculated T25-values, acetaldehyde should be considered a “low potency” carcinogen (ref.: 38).

3.3.8 Reproductive toxicity

Several studies on the developmental effects of acetaldehyde have been conducted, primarily to investigate its role in ethanol-induced teratogenicity. In these studies, reviewed by IARC, acetaldehyde was given by amniotic or intraperitoneal injection, not by ingestion or inhalation. Dose-related embryotoxic, fetotoxic and teratogenic effects were seen in most of these studies, particularly in rats, but maternal toxicity was often not assessed adequately or reported in any of these investigations. Dose-related embryotoxic effects were observed in *in vitro* studies on rat embryos exposed to acetaldehyde. Effects on the placenta have been observed following intraperitoneal injection of acetaldehyde into pregnant rats. Foetal malformations and resorptions were found in mice and rats treated with acetaldehyde.

Ref.: 14

Ethanol
It is widely accepted that ethanol has profound effects on the female as well as the male reproductive system. Moreover, ethanol is a well-documented human teratogen that can cause a spectrum of physical and mental dysfunctions following prenatal exposure. Multiple terms are used to describe the continuum of effects that result from prenatal exposure to ethanol, the most commonly known of which is foetal alcohol syndrome

Ref.: 14

Comment
SCCS notes that it is not known whether acetaldehyde, the primary metabolite of ethanol, is involved in the aetiology of the human foetal alcohol syndrome.

3.3.8.1 Two generation reproduction toxicity

No data submitted

3.3.8.2 Teratogenicity

No data submitted

3.3.9 Toxicokinetics

The main part of this section is taken from IARC (2012) (Ref.: 15).

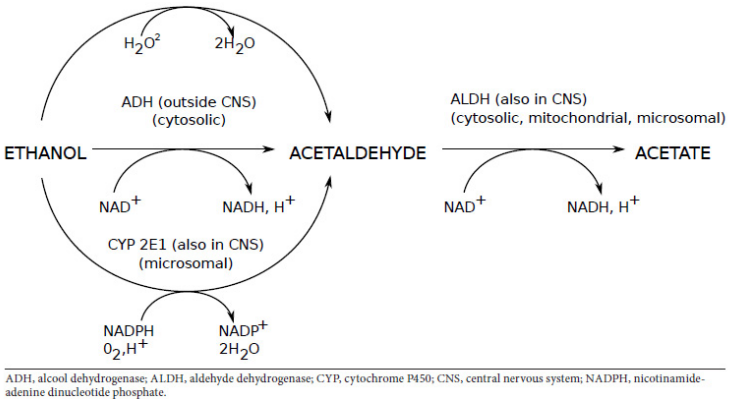


Figure 1: Ethanol and acetaldehyde metabolism (taken from ref. 15)

Acetaldehyde is the first metabolite in the oxidation of ethanol. Ethanol is metabolized to acetaldehyde by three major pathways (see Fig. 1) the alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing cytochrome P450 (CYP) pathway, and the catalase-H_2O_2 system. Acetaldehyde, to which many deleterious effects of ethanol can be attributed, is oxidized to acetate primarily by acetaldehyde dehydrogenases (ALDHs).

Interindividual variations of the acetaldehyde-mediated effects will depend on the genetic polymorphisms and other factors affecting the metabolism and levels of acetaldehyde, and its effects on the target organs.

Several degradation reactions are known to form endogenous acetaldehyde in the human body. Without external alcohol ingestion, acetaldehyde concentrations are below the level of detection, except in the gastrointestinal tract.

Aldehyde dehydrogenase pathway

Acetaldehyde is metabolized by ALDHs, which are widely expressed in the mitochrondria (low-Km enzyme) and cytosol (high-Km enzyme) of most tissues. Oxidation of acetaldehyde is regulated by the rate of acetaldehyde formation, ALDH activity and the cytosolic and mitochondrial redox states. Ethanol consumption is not known to induce *ALDH* expression. Chronic alcohol abuse is reported to reduce the ALDH activity. The high-Km ALDH1A1 (Km = 50 µM) accounts for most of the acetaldehyde oxidizing capacity in the cytosolic compartment of the liver and other tissues. This enzyme is also abundant in the erythrocytes. The low-Km (about 5 µM) ALDH2 is located in the mitochondria and is believed to be responsible for the bulk of the oxidation of the ethanol-derived acetaldehyde. This enzyme is not significantly expressed in the erythrocytes. Of all the polymorphisms in genes encoding enzymes that metabolize alcohol and acetaldehyde, the *ALDH2*2* allele has the greatest functional impact on the human phenotype. This allele is common in East-Asian populations, about 5–10% are homozygotes and 30–40% are heterozygotes. In both groups the acetaldehyde levels are elevated, which creates several toxic effects and also euphoric reinforcing reactions. The relevance of the elevated acetaldehyde for the development of cancers is briefly mentioned in section 3.3.7. Carcinogenicity.

Other pathways in the metabolism and reactions of acetaldehyde

In addition to the ALDH-catalysed reactions, acetaldehyde may also be oxidized to a minor extent by CYP2E1 and by different oxidases. Due to its chemical reactivity, most, if not all, of the ethanol-derived acetaldehyde that is not further oxidized binds to a variety of constituents. These interactions vary between easily reversible and firm covalent bonds. Different kinds of Schiff's bases, which are formed by acetaldehyde and the free amino groups of amino acids, peptides and proteins, are the most common products. Some of these unstable products become stable under reducing conditions, such as during alcohol intoxication. Although only a small fraction of all acetaldehyde formed during ethanol

oxidation produces these adducts, they are important in some of the chronic toxic actions of alcohol. The acetaldehyde adducts may play a role in the carcinogenic effects of ethanol.

Levels of acetaldehyde in tissues
From the liver, where most of the ethanol derived acetaldehyde is formed and oxidized, the remaining acetaldehyde, free and/or loosely bound, escapes into the *vena hepatica*, reaching concentrations of approximately 70 µM (3 µg/ml) under normal conditions. Thereafter, the concentration of acetaldehyde in the blood will be diluted by the *vena cava* blood and further reduced by the circulation in the heart and the lungs before reaching peripheral tissues. Human data show that acetaldehyde levels in pulmonary arterial blood are in the range of 0–4.4 µM (0 – 0.2 µg/ml), 30 and 60 minutes after ethanol consumption. Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 µM; <0.04 µg/ml), during ethanol intoxication in Caucasian male populations. However, in Caucasian women, acetaldehyde levels of 1–8 µM (0.04 – 0.3 µg/ml) have been detected during the use of oral contraceptives and during the high-estradiol phase of the normal cycle. Except for the blood and the liver, in which acetaldehyde concentration should be approximately the same as in the *vena hepatica*, little is known about acetaldehyde levels in other tissues during ethanol oxidation in humans. In Asian subjects carrying the ALDH*2 allele, blood acetaldehyde levels above 200 µM (8 µg/ml) have been reported.

Increased levels of acetaldehyde in the saliva are also reported in after alcohol intake. The acetaldehyde in the saliva is almost exclusively derived from microbiological alcohol oxidation and correlate positively with the blood alcohol concentration. Levels varying between 15 to 25 µM (0.7 – 1.1 µg/ml and 20 to 40 µM (0.9 – 1.8 µg/ml) at blood ethanol concentrations of 10 to 20 mM (0.5 – 0.9 ^{0}/oo), respectively.

Ref.: 15

Levels of acetaldehyde in blood
Acetaldehyde has been measured in blood from 225 teetotallers (people that do not drink alcohol). A mean acetaldehyde level of 7.7 $\pm$ 0.7 µM (0.3 $\pm$ 0.03 µg/ml) (range 6.1 – 10.1 µM) was found. The authors reported that in an alcoholic population the mean acetaldehyde level was 25.3 + 15.6 µM (1.1 $\pm$ 0.7 µg/ml). In a subsequent study among students (645 women and 332 men), blood samples were drawn for clinical indications over a two year period. The mean blood acetaldehyde level in this group was 9.7 $\pm$ 2.1 µM (0.4 $\pm$ 0.1 µg/ml). The levels were a little higher among men than among women. The higher acetaldehyde levels among the students than the teetotallers were explained by the alcohol intake by the students.

Ref.: 44, 45

Comment
The results concerning acetaldehyde levels in blood in the two articles above (ref. 44, 45) are in contrast to that reported in the paragraph above *"Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 µM; <0.04 µg/ml), during ethanol intoxication in Caucasian male populations."* (ref. 15). The text give the impression that *"free and/or loosely bound"* acetaldehyde was measured. The analytical procedure used in the two experiments cited above (ref. 44, 45) involve heating the samples to 70^{o}C and it is claimed that they measure whole blood-associated acetaldehyde (both free and bound acetaldehyde). Other authors claim that the heating introduces artefacts.

3.3.10 Photo-induced toxicity

No data submitted

3.3.11 Human data

No data submitted

3.3.12 Special investigations

Acetaldehyde from food intake
Acetaldehyde has been analysed in a wide variety of food matrices. The analysis was conducted using headspace gas chromatography. The samples were digested in full automation with simulated gastric fluid. 140 authentic samples were analyzed. The authors estimated that the average exposure from food (without alcoholic beverages) would be around 40 µg/kg bw/day for the German population. The median intake was calculated to be 24 – 28 µg/kg bw/day.

Ref.: 42

Food flavouring substance
The use of acetaldehyde as a flavouring substance was evaluated by JECFA in 1997. The Committee estimated that the intake of acetaldehyde at the estimated level of 11 mg per person per day in Europe (183 µg/kg bw/d) would not present safety concern.

Ref.: 32

Tobacco products
All tobacco products contain acetaldehyde. Cigarette mainstream smoke typically contains 800–900 µg acetaldehyde/cigarette. This implies that a smoker will inhale of the order 10 - 20 mg (170 – 330 µg/kg bw/d) acetaldehyde per day. In rooms where cigarettes are smoked the acetaldehyde level may be in the order of 200–300 µg/m^3 (4 µg/kg bw/d). Levels of acetaldehyde in ambient air generally average 5 µg/m^3.

During the last years the levels of acetaldehyde in snuff have been reduced from about 36 to 6 µg/g dry weight.

Ref.: 15

Exposure to acetaldehyde from different uses of ethanol

Acetaldehyde formation by oxidation of exogenous ethanol
The major part of the total acetaldehyde to which the body is exposed during alcohol ingestion originates from ethanol oxidation. The liver and the gut are the primary sites of acetaldehyde formation to such an extent that the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, which consequently leads to diffusion of the surplus acetaldehyde into the bloodstream. Under normal conditions, the acetaldehyde produced at other sites is usually directly oxidized within the tissue. The exception is the aerodigestive tract, where acetaldehyde is produced at least partly by microbial alcohol oxidation. Consequently, acetaldehyde can be detected both in breath and saliva during alcohol intoxication.

As discussed above acetaldehyde levels in pulmonary arterial blood are in the range of 0–4.4 µM (0 – 0.2 µg/ml), 30 and 60 minutes after ethanol consumption. Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 µM; <0.04 µg/ml), during ethanol intoxication. The acetaldehyde in the saliva correlates positively with the blood alcohol concentration. Levels varying between 15 to 25 µM (0.7 – 1.1 µg/ml and 20 to 40 µM (0.9 – 1.8 µg/ml) at blood ethanol concentrations of 10 to 20 mM (0.5 – 0.9 ^{0}/oo), respectively, have been reported.

Acetaldehyde in alcoholic beverages
All alcoholic beverages contain acetaldehyde in variable amounts: average levels in different types vary between 60 to > 7000 µM (2.5 - > 300 µg/ml). Lachenmeier and co-workers have estimated the average exposure to acetaldehyde from its content in alcoholic beverages to 112 µg/kg bw/day. The life-time cancer risk was calculated to 7.6 x 10^{-4}. The authors pointed out that alcohol consumption is a direct source of acetaldehyde exposure,

which in conjunction with other sources (food flavourings, tobacco) results in a magnitude of risk requiring intervention. An initial public health measure could be to reduce the acetaldehyde content in alcoholic beverages as low as technologically possible, and to restrict its use as a food flavour additive.

Ref.: 27

Mouthwashes

La Vecchia (2009) reviewed 10 epidemiological studies on the link between mouthwash use and oral cancer risk. Information on alcohol in the mouthwashes was only available in two of the studies. One of these showed an increased risk of oral cancer among those using alcohol containing mouthwashes while no increased risk was found among those using mouthwashes without alcohol. The other showed no increase in relation the use of alcohol containing mouthwashes.

Ref.: 29

Gandini *et al* (2012) reviewed and performed a meta-analysis of 18 epidemiological studies including the 10 studies reviewed by La Vecchia on the use of mouthwashes and cancer. The authors concluded that there was no statistically significant associations found between regular use of mouthwash and risk of oral cancer (RR=1.13 [0.95-1.35]). There was no association between reported use of mouthwash specifically containing alcohol and risk of oral cancer (RR=1.16 [0.44-3.08]).

Ref.: 43

Comment
SCCS notes that in the Abstract it is written: "*There was no association between reported use of mouthwash specifically containing alcohol and risk of oral cancer (RR=1.16 [0.44-3.08])"* while in the text of the article the same RR was given as *(RR=1.0 [0.39-2.60]).*

Ethanol is contained in a number of ready to-use mouthwashes typically between 5 and 27% vol. The acetaldehyde levels in saliva after use of alcohol-containing mouthwashes have been measured. Ready to-use mouthwashes and mouth rinses (n = 13) were rinsed in the mouth by healthy, non-smoking volunteers (n = 4) as intended by the manufacturers (20 ml for 30 sec). Saliva was collected at 0.5, 2, 5 and 10 min after mouthwash use. The acetaldehyde content in the saliva was 41 ± 15 µM, (range 9–85 µM) after 0.5 min, 52 ± 14 µM, (range 11–105 µM) after 2 min, 32 ± 7 µM, (range 9–67 µM) after 5 min and 15 ± 7 µM, (range 0–37 µM) after 10 min. The contents were significantly above endogenous levels and corresponding to concentrations normally found after alcoholic beverage consumption. A twice-daily use of alcohol-containing mouthwashes leads to a systemic acetaldehyde exposure of 0.26 µg/kg bw/d on average, which corresponds to a lifetime cancer risk of 3 x 10^{-6}. However, the local acetaldehyde-contents in the saliva are reaching concentrations associated with DNA adduct formation and sister chromatid exchange *in vitro*, so that concerns for local carcinogenic effects in the oral cavity remain.

Ref.: 30

Comment
The results from measurements of acetaldehyde in the saliva indicate the levels are similar after ingestion of alcoholic beverages and the use of mouthwashes containing ethanol. Since most of the acetaldehyde in the saliva is formed by microbiological alcohol oxidation this may also be anticipated.

Exposure of skin to ethanol
Sixteen adults sprayed an aerosol containing 44% ethanol over the body for approximately 10 sec (mean amount used per treatment: 9.72 g). Blood samples were taken after a 15

min period and analysed by gas chromatography. Subsequent samples were taken 5, 10, 30 and 60 min after that. Ten of the panelists produced at least one blood sample with a detectable alcohol content (detection limit: 5 mg/l). The maximum value recorded was 13 mg/l. However, there remained some uncertainty in the analytical method, as other alcohols may co-elute. Using another gas chromatographic column (detection limit: 9 mg/l), none of the blood samples exhibited detectable levels of ethanol. The application as a spray also includes a potential pulmonary uptake. Despite the high concentration of ethanol (44%) and the high exposure to large surfaces, the maximum blood levels were only slightly elevated above physiological blood levels.

Ref.: 33

Miller and coworkers reported the blood alcohol level after using an alcohol-based instant hand sanitizer (62% (v/v) ethanol) under most extreme conditions (applying 5 ml, 25 times over the course of 2 hours). The blood alcohol level measured immediately following the final application was below the detection limit (< 5 mg/dl). In a subsequent study of 5 subjects using 5 ml of the product with a repetition of 50 times over 4 hours, the result was confirmed as all participants had blood ethanol levels less than 5 mg/dl.

Ref.: 34

Twelve volunteers applied three hand-rubs containing 95% (hand-rub A), 85% (hand-rub B) and 55% ethanol (hand-rub C; all w/w). For hygienic hand disinfection, 4 ml were applied 20 times for 30 s, with 1 minute break between applications. For surgical hand disinfection, 20 ml of each hand rub was applied to hands and arms up to the level of the elbow 10 times for 3 minutes, with a break of 5 minutes between applications. Blood concentrations of ethanol and acetaldehyde were determined immediately prior and up to 90 minutes after application using head space gas chromatography. The median of absorbed ethanol after hygienic hand disinfection was 1365 mg (A), 630 mg (B), and 358 mg (C). The proportion of absorbed ethanol was 2.3% (A), 1.1% (B), and 0.9% (C). After surgical hand disinfection, the median of absorbed ethanol was 1067 mg (A), 1542 mg (B), and 477 mg (C). The proportion of absorbed ethanol was 0.7% (A), 1.1% (B), and 0.5% (C). The highest median acetaldehyde concentration after 20 hygienic hand disinfections was 0.57 mg/l (hand-rub C, after 30 min), after 10 surgical hand disinfections 3.99 mg/l (hand-rub A, after 20 minutes). The authors concluded that the overall dermal and pulmonary absorption of ethanol was below toxic levels in humans and allows the conclusion that the use of the evaluated ethanol-based hand-rubs is safe.

Ref.: 35

Inhalation of ethanol

An occupational physician reported to the French Health Products Safety Agency (Afssaps) a case of adverse effect of acute pancreatitis (AP) in a teaching nurse, after multiple demonstrations with ethanol-based hand sanitizers (EBHSs) used in a classroom with defective mechanical ventilation. It was suggested by the occupational physician that the exposure to ethanol may have produced a significant blood ethanol concentration and subsequently the AP. In order to verify if the confinement situation due to defective mechanical ventilation could increase the systemic exposure to ethanol *via* inhalation route, a physiologically based pharmacokinetic (PBPK) modelling was used to predict ethanol blood levels. Under the worst case scenario, the simulation by PBPK modelling showed that the maximum blood ethanol concentration which can be predicted of 5.9 mg/l is of the same order of magnitude to endogenous ethanol concentration (mean = 1.1mg/l; median = 0.4 mg/l; range = 0–35 mg/l) in non-drinker humans. The present study does not support the likelihood that EBHS leads to an increase in systemic ethanol concentration high enough to provoke an acute pancreatitis.

Ref.: 36

General comment

The blood level of acetaldehyde depends on the rate of formation from ethanol, the intake of acetaldehyde from different sources and on the rate of oxidation of acetaldehyde to acetic acid.

All alcoholic beverages contain acetaldehyde in variable amounts. Lachenmeier and co-workers (ref. 27) have estimated the average exposure to acetaldehyde from its content in alcoholic beverages to 112 µg/kg bw/d. This may, however, be a small amount compared to that formed from alcohol by oxidation. On the other hand it will add to the amount formed by microbiological alcohol oxidation in the upper aerodigestive tract were there are considerable evidence that acetaldehyde is involved in tumour formation in humans.

JECFA estimated in 1997 the intake of acetaldehyde from food flavouring substances to 183 µg/kg bw/d, while Uebelacker and Lachenmeier estimated the mean intake of acetaldehyde in the German population from food to 40 µg/kg bw/d (median intake 24 – 28 µg/kg bw/d) in 2011 (ref. 42) after having measured acetaldehyde in 140 authentic food samples. Another important source of acetaldehyde is cigarettes. A smoker will inhale of the order 10 - 20 mg (170 – 330 µg/kg bw/d) acetaldehyde per day.

Measurements of the blood levels have given widely different results. In the recent IARC evaluation it was stated that *"Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 µM; <0.04 µg/ml), during ethanol intoxication in Caucasian male populations."* (ref. 15). On the other hand the group of Halvorson (ref. 44, 45) measured mean values of 7.7 µM acetaldehyde in teetotallers, 9.7 µM in students and 25.3 µM in alcoholics. The reason for the apparent divergence is not clear. It should be noted that while in the first case it is stated that *"free and/or loosely bound"* acetaldehyde was measured while in the latter case "*whole blood-associated acetaldehyde (both free and bound acetaldehyde)"* was measured.

A blood level of 7.7 µM acetaldehyde will correspond to 0.3 µg/ml. Assuming a blood volume of 5 liter and a bodyweight of 60 kg, this will correspond to 25 µg/kg bw. The size of the intake that give rise to 0.3 µg/ml blood is not known as the "steady state" concentration will depend not only on the intake but also on how fast acetaldehyde is removed.

3.3.13 Safety evaluation

For some health endpoints it is not possible to establish a threshold. This is especially the case for mutagens and genotoxic carcinogens. The decision on a threshold and a non-threshold mode of action for carcinogens may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If this is not clear, *the assumption of a non-threshold mode of action would be the prudent choice for risk characterisation of carcinogens* (46).

Derivation of T25 for calculation of lifetime cancer risk
Although, the long-term experiments with acetaldehyde and especially the oral study is criticised, a quantitative lifetime cancer risk (LCR) may be calculated in order to obtain an indication of the potential cancer risk.

In the present Opinion the same T25 = 121 mg/kg bw/d will be used as in the previous SCCNFP Opinion on Acetaldehyde (Ref.: 28). The T25 of 121 mg/kg bw/d is based on nasal carcinomas in male rats from the inhalation study of Woutersen *et al*. (1986) (Ref.: 23). These tumours occurred at the site of contact. However, since acetaldehyde is considered to be a genotoxic carcinogen it is expected that it may induce cancer by all routes of exposure and the site of tumour formation in humans may be different from that found in carcinogenicity studies with rodents. In this respect it should be noted that formaldehyde which also induced tumours primarily at the site of contact in experimental carcinogenicity studies has recently been found also induce leukaemia in humans (ref. 15). An oral study where acetaldehyde was added to the drinking water of rats was published by Soffritti *et al*.

in 2002 (ref.: 22). A T25 = 116 mg/kg bw/d based on lymphomas and leukaemias combined in male rats was calculated. Moreover, Lachenmeier *et al*. (2009a) (Ref.: 27) have derived and used a T25 = 127 mg/kg bw/d based on the total number of malignant tumours in male rats. Although, this oral study has several shortcomings, the finding that the average of the two calculated T25 values is the same ([116 + 127]/2 = 121.5) as the T25 from the inhalation study gives confidence in the T25 value used.

Derivation of systemic exposure dose (SED).
Dose calculations: According to the Notes of Guidance, an aggregate value of **17.4 g/day** will be used in the calculation of the MoS.

The applicant considers a concentration of acetaldehyde up to 100 ppm.

100 ppm corresponds to 1.74 mg/day.

In the absence of dermal absorption data, it is assumed that 100% is absorbed (see the previous Opinion; Ref: 28)

SED 1.74/60 0.029 mg/kg bw/d

Calculation of lifetime cancer risk

T25 = 121 mg/kg bw/d

$$HT_{25} = \frac{T_{25}}{(\text{body weight}_{human}/\text{body weight}_{animal})^{0.25}}$$

$$HT25 = T25 / (bw_h / bw_r)^{0.25} = 121 / (60/0.5)^{0.25} = 121/3.3 = 37 \text{ mg/kg bw/d}$$

$$\text{Lifetime cancer risk} = \frac{SED}{HT_{25} / 0.25}$$

$$= 0.029 / (37/0.25) = 2 \times 10^{-4}$$

The calculation is based on several worst case considerations. 100% skin absorption is used in the calculation. Moreover, since acetaldehyde is highly volatile, a significant fraction may evaporate and not be dermally available. Since 100% dermal absorption is used, the calculation will actually cover absorption by all routes.

The only permitted use of acetaldehyde in cosmetics is up to 25 ppm acetaldehyde in fragrance compounds. Acetaldehyde should otherwise only be found in cosmetic products in the form of unavoidable traces originating mainly through plant extracts and botanical ingredients and ethanol. The probability of cancer risk for a lifetime exposure to 100 ppm from all cosmetic products is 2×10^{-4}. It can be derived from the above calculation that a safe concentration with a LCR of 10^{-5} would be 5 ppm in all cosmetic products.

In the case of non-cancer effects, a NOAEL of 49 mg/m³ has been derived from a 28 day inhalation study in rats. As a worse case approach, complete evaporation of acetaldehyde present in all cosmetic products (total exposure of 1.74 mg/d) in a small room (10 m³) without ventilation would result in a concentration of 0.174 mg/m³. In this worst case scenario, the Margin of Exposure would be much higher than 100.

It should be noted that the estimated intake of acetaldehyde used as flavouring substances in food was estimated to 11 mg/person per day in Europe (183 µg/kg bw/d) by JECFA in 1993. More recently, Uebelacker and Lachenmeier estimated the mean intake of acetaldehyde in the German population from food to 40 µg/kg bw/d (median intake 24 – 28 µg/kg bw/d) (ref. 42). These values should be compared with the maximum estimated intake from cosmetics (29 µg/kg bw/d).

Based on the recent IARC evaluations (ref. 15) that "*there is sufficient epidemiological evidence that acetaldehyde has increased the risk of alcohol related cancer in particular of the oesophagus and the upper aero-digestive tract*" including oral cavity. SCCS is of the opinion that acetaldehyde should not be intentionally used in mouth-washing products.

3.3.14 Discussion

This evaluation considers potential exposures from acetaldehyde in cosmetic products alone. Other relevant exposures from food and alcoholic beverages and smoking, for example, have not been assessed and are likely to be considerably higher compared to cosmetic exposure.

Acetaldehyde is a naturally occurring substance, also in human metabolic pathways. It is the main metabolite of ethanol. It is metabolised to acetic acid.

Physico-chemical properties
Pure acetaldehyde is flammable; it polymerizes violently in the presence of trace amounts of metals or acids. Acetaldehyde may undergo auto-polymerisation upon contact with air or moisture. Upon prolonged storage, it may form unstable peroxides. Solutions of acetaldehyde in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal laboratory conditions.

Irritation, sensitisation
Acetaldehyde is a skin, eye and respiratory tract irritant. There is limited evidence for skin sensitisation. Respiratory sensitisation has not been investigated to date.

Dermal absorption
Some studies are available concerning increase in blood acetaldehyde after dermal exposure to ethanol. However, no quantitative conclusions can be drawn from these studies regarding skin absorption of acetaldehyde. A dermal absorption of 100% is used in the risk characterization.

General toxicity
No toxicity studies have been performed according to present day requirements. A NOAEL of 125 mg/kg bw/d was found in a 4 week study based on relative increase in kidney weight and focal hyperkeratosis of the forestomach.

In a 28-day inhalation study with rats, a NOAEL of 49 mg/m³ based on the degeneration of the nasal olfactory epithelium was established.

Mutagenicity
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. Increased frequency of acetaldehyde DNA adducts in humans has been found in relation to alcohol use.

Carcinogenicity
Acetaldehyde has been found to induce tumours in rats after oral and inhalation exposure and in hamster after inhalation exposure. IARC conclude that there is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Acetaldehyde is a carcinogen classified as Carc Cat 2 according to Annex VI of regulation 1272/2008 (CLP). IARC concludes that "Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1).*" In reaching this conclusion the IARC made the following considerations: Upon ingestion of alcoholic beverages, ethanol is converted into acetaldehyde, which is then oxidized to acetate. Ethanol and acetaldehyde are both carcinogenic in experimental animals. There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, in particular of the oesophagus and the upper aero-digestive tract.

In the present Opinion the same T25 = 121 mg/kg bw/d will be used as in the previous SCCNFP Opinion on Acetaldehyde (Ref.: 28). The T25 of 121 mg/kg bw/d is based on nasal carcinomas in male rats from the inhalation study of Woutersen *et al*. (1986) (Ref.: 23). These tumours occurred at the site of contact. However, since acetaldehyde is considered to be a genotoxic carcinogen it is expected that it may induce cancer by all routes of exposure and the site of tumour formation in humans may be different from that found in carcinogenicity studies with rodents. In this respect it should be noted that formaldehyde which also induced tumours primarily at the site of contact in experimental carcinogenicity studies has recently been found also induce leukaemia in humans (ref. 15). An oral study where acetaldehyde was added to the drinking water of rats was published by Soffritti *et al*. in 2002 (ref.: 22). A T25 = 116 mg/kg be/d based on lymphomas and leukaemias combined in male rats was calculated. Moreover, Lachenmeier *et al*. (2009a) (Ref.: 27) have derived and used a T25 = 127 mg/kg bw/d based on the total number of malignant tumours in male rats. Although, this oral study has several shortcomings, the finding that the average of the two calculated T25 values is the same ([116 + 127]/2 = 121.5) as the T25 from the inhalation study gives confidence in the T25 value used. On the basis of the calculated T25-values, acetaldehyde should be considered a "low potency" carcinogen (ref.: 38).

Reproductive toxicity
No reproductive toxicity studies have been performed according to present day requirements. SCCS notes that it is not known whether acetaldehyde, the primary metabolite of ethanol, is involved in the aetiology of the human foetal alcohol syndrome.

Toxicokinetics
Acetaldehyde is the first metabolite in the oxidation of ethanol. Ethanol is metabolized to acetaldehyde by three major pathways: the alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing cytochrome P450 (CYP) pathway, and the catalase-H_2O_2 system. Acetaldehyde, to which many deleterious effects of ethanol can be attributed, is oxidized to acetate primarily by acetaldehyde dehydrogenases (ALDHs). Inter-individual variations of the acetaldehyde-mediated effects will depend on the genetic polymorphisms and other factors affecting the metabolism and levels of acetaldehyde, and its effects on the target organs.

The major part of the total acetaldehyde to which the body is exposed during alcohol ingestion originates from ethanol oxidation. The liver and the gut are the primary sites of acetaldehyde formation to such an extent that the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, which consequently leads to diffusion of the surplus acetaldehyde into the bloodstream. Under normal conditions, the acetaldehyde produced at other sites is usually directly oxidized within the tissue.

Acetaldehyde is metabolized by ALDHs, which are widely expressed in the mitochrondria (low-Km enzyme) and cytosol (high-Km enzyme) of most tissues. The high-Km ALDH1A1 (Km = 50 µM) accounts for most of the acetaldehyde oxidizing capacity in the cytosolic compartment of the liver and other tissues. The low-Km (about 5 µM) ALDH2 is located in the mitochondria and is believed to be responsible for the bulk of the oxidation of the ethanol-derived acetaldehyde. Of all the polymorphisms in genes encoding enzymes that metabolize alcohol and acetaldehyde, the *ALDH2*2* allele has the greatest functional impact on the human phenotype. This allele is common in East-Asian populations, about 5–10% are homozygotes and 30–40% are heterozygotes. In both groups the acetaldehyde levels are elevated, which creates several toxic effects and also euphoric reinforcing reactions.

4. CONCLUSION

1. *Is Acetaldehyde safe when present up to 100 ppm in cosmetic products taking into account the new data provided?*

The SCCS is of the opinion that acetaldehyde, present up to 100 ppm in cosmetic products, is not safe based on life-time cancer risk. However, the calculations are based on a number of worse case considerations which will lead to an overestimation of the risk.

Exposure from the dermal, inhalation and oral route cannot be properly assessed. In addition, there are no data available on metabolism of acetaldehyde in the skin.

2. *And/or does the SCCS recommend any other concentration limit with regard to the use of Acetaldehyde as an ingredient in cosmetic products?*

The SCCS is of the opinion that acetaldehyde should not be used as an intended ingredient in cosmetic products except used as a fragrance/flavour ingredient at a maximum concentration of 0.0025% (25 ppm) in the fragrance compound (ref previous opinion on acetaldehyde), resulting in approximately 5 ppm in the final finished product.

3. *Does the SCCS have any further scientific concerns regarding the use of Acetaldehyde in mouth-washing products?*

Based on the recent IARC evaluations (ref. 15), there is sufficient epidemiological evidence that acetaldehyde has increased the risk of alcohol related cancer in particular of the upper aero-digestive tract, assumed to be caused by the formation of acetaldehyde, SCCS is of the opinion that acetaldehyde should not be intentionally used in mouth-washing products.

5. MINORITY OPINION

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