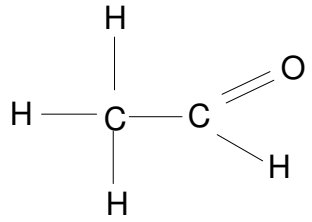
ACETALDEHYDE
(CAS Reg. No. 75-07-0)



INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommittee for AEGLS

2009

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicological and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels X AEGL-1, AEGL-2 and AEGL-3 X are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Acetaldehyde is a colorless, highly volatile liquid at ambient temperature and pressure. It has a pungent, suffocating odor that is fruity in dilute concentrations. Acetaldehyde is a metabolic intermediate in animals and humans as well as in plants. The compound is a natural constituent of a large number of fruits, vegetables, beverages and other foods. Release into air occurs during biomass combustion, such as forest and brush fires. The largest source of general population exposure to acetaldehyde is through the metabolism of ingested alcohol.

Acetaldehyde is produced since 1916, and its main industrial use is as a chemical intermediate in the production of other chemicals. The annual production in the US was estimated at 443,000 tonnes in 1989.

Available data for acetaldehyde included several recent human volunteer studies with very short exposure times, and two older volunteer studies with longer and more relevant exposure periods. Animal data were available for lethal and non-lethal endpoints in various species, and included also genotoxicity and carcinogenicity data. Adequate data for time scaling were not available. Therefore, where appropriate, default time scaling was performed.

The AEGL-1 values are based on the human volunteer study of Sim and Pattle 1957, where workers experienced only mild respiratory irritation and no eye irritation following chamber exposure to acetaldehyde at a measured concentration of 134 ppm for 30 minutes. This concentration was considered the no effect level for the eye irritation as observed in another study. An uncertainty factor of 3 was applied to account for variation among humans. The resulting 30-minute AEGL-1 value of 45 ppm was flatlined across time because mild irritant effects generally do not vary greatly over time.

The AEGL-2 values are based on histopathological changes observed in a study in rats (Cassee *et al*. 1996b). Mild pathological changes in the nasal epithelium were observed after 3 days of exposure to 750 and 1500 ppm (6h/day). Following a single exposure of 6 hours, these concentrations produced no histopathological changes in the nasal epithelium. Studies with a duration of 28 days or longer produced more severe histopathological changes at even lower doses. The data indicate that 1500 ppm for 6 hours is a no effect level, and that the exposure time is an important factor for the effects observed. The test concentration of 1500 ppm for 6 hours was the point of departure for AEGL-2. No interspecies uncertainty factor was used because the effect was well below the level that would be irreversible. An intraspecies uncertainty factor of 10 was used to protect susceptible humans.

The AEGL-3 values are based on 4-hour lethality data in rats published by Appelman *et al.* in 1982. In the same study, additional groups were exposed for 28 days (6 hours per day) at lower concentrations. All data from this study were taken into account to calculate the 4-hour $BMDL_{05}$ of 5295 ppm, which was used as the point of departure for AEGL-3. Uncertainty factors of 3 and 3 for inter- and intraspecies variation were applied. Default time scaling was performed.

The Level of Distinct Odor Awareness (LOA) is calculated to be 0.56 ppm.

The calculated AEGL values are listed in the table below.

Summary of AEGL Values for Acetaldehyde						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	No eye irritation in human volunteers, 30 minutes exposure (Sim and Pattle 1957)
AEGL-2 (Disabling)	340 ppm (620 mg/m^3)	340 ppm (620 mg/m^3)	270 ppm (490 mg/m^3)	170 ppm (310 mg/m^3)	110 ppm (200 mg/m^3)	No effect level for histopathological changes to the nasal epithelium in rats (Cassee et al. 1996b)
AEGL-3 (Lethal)	1100 ppm (1900 mg/m^3)	1100 ppm (1900 mg/m^3)	840 ppm (1500 mg/m^3)	530 ppm (950 mg/m^3)	260 ppm (480 mg/m^3)	$BMDL_{05}$ in acute and subacute rat lethality study (Appelman et al. 1982)

References

Appelman, L.M, R.A.Woutersen, V.J.Feron (1982) Inhalation Toxicity of Acetaldehyde in Rats (I. Acute and Subacute Studies). *Toxicology* **23**: 293-307.

Cassee, F., Groten, J., Feron, V. (1996b) Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. *Fundamental and Applied Toxicology* **29** (no. 2) 208-18

Sim, V.M., and R.E. Pattle (1957) Effect of Possible Smog Irritants on Human Subjects. *Journal of American Medical Association* **165** (15):1908-1913.

1. INTRODUCTION

Acetaldehyde is a colorless, highly volatile liquid at ambient temperature and pressure. It has a pungent, suffocating odor that is fruity in dilute concentrations. Nagata (2002) reports a threshold for odor perception at 0.0015 ppm (0.00275 mg/m^3), a value obtained using the Japanese triangle method (a method which is known to produce results that agree well with the standard method CEN13725). Acetaldehyde is highly flammable when exposed to heat or flame and in air it can be explosive. It is miscible with water and with most common organic solvents (IPCS 1995).

Acetaldehyde is a metabolic intermediate in animals and humans as well as in plants. The compound is a natural constituent of a large number of fruits, vegetables, beverages and other foods. Release into air occurs during biomass combustion, such as forest and brush fires. Acetaldehyde is present in tobacco smoke and in gasoline and diesel exhaust. It is also a by-product of fermentation. In the atmosphere acetaldehyde can be formed by oxidation of non-methane hydrocarbons, both in the background troposphere and in photochemical smog. In urban air, during periods of photochemical smog, secondary atmospheric formation often exceeds direct emissions (IPCS 1995; Health Canada 2000).

Acetaldehyde is a highly reactive compound. After environmental emission to air it primarily reacts with photochemically generated hydroxyl radicals, nitrate radicals, hydroperoxyl radicals and ozone. Direct photolysis also occurs. Small amounts are transferred into rain, fog and clouds or may be removed by dry deposition. Overall half-lives for acetaldehyde vary considerably, depending on the weather conditions. In US cities residence times under clear skies in summer during daylight were estimated at only 3 hours whereas under conditions typical for winter nights this was as much as 3000 hours (Health Canada 2000).

Acetaldehyde was first produced commercially in 1916. Its principal industrial use is as a chemical intermediate in the production of acetic acid, pyridine derivatives, pentaerythritol and several other compounds. For the year 1989 US production was estimated at 443,000 tonnes. Production levels in Western Europe and Japan are even higher, at least they were so in the year 1982 (706,000 tonnes in Western Europe, 323,000 tonnes in Japan, 281,000 tonnes in USA). A minor use is as a food flavoring agent, for which it has the status of being Generally Recognized as Safe (GRAS) by the US FDA (IARC 1985; IPCS 1995, IARC 1999).

The general population is exposed to acetaldehyde via air and via food and beverages. Levels in some fruit juices may be up to 100 mg/kg but by far the largest source of general population exposure to acetaldehyde is through the metabolism of ingested alcohol (IPCS 1995).

Workers may be exposed to acetaldehyde in some manufacturing industries and during alcohol fermentation but there is a paucity of quantitative data on these exposures (IPCS 1995).

Acetaldehyde's chemical structure is depicted below, and its physicochemical properties are presented in Table 1.

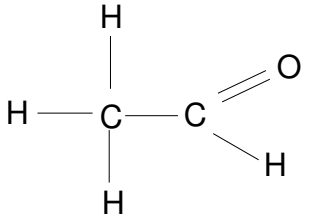

Table 1. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	Ethanal; acetic aldehyde; ethyl aldehyde	-
Chemical formula	C_2H_4O	-
Molecular weight	44.1	-
CAS Reg. No.	75-07-0	-
Physical state	Liquid or gas	IARC 1999
Color	Colorless	IARC 1999
Solubility in water	Miscible	IARC 1999
Vapor pressure	98 kPa at 20 °C	IARC 1999
Vapor density (air = 1)	1.52	IARC 1999
Liquid density (water = 1)	0.778	DECOS 1993
Melting point	-123 °C	IARC 1999
Boiling point	20.1 °C	IARC 1999
Flash point	-38 °C closed cup; -40 °C open cup	IARC 1999
Explosive limits	Upper 57%, lower 4% v/v in air	IARC 1999
Conversion factors (at 25 °C)	1 mg/m^3 = 0.56 ppm 1 ppm = 1.8 mg/m^3	IPCS 1995

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No acute lethality data are available for humans.

2.1.1. Case Reports

No cases are known of death due to exposure to acetaldehyde.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

No published case studies of acute acetaldehyde intoxications are available. According to information from poisoning-handbooks as presented in ACIGH (1991), irritation of eyes, skin, and respiratory tract are the primary effects of acute acetaldehyde inhalation. In addition, erythema, coughing, pulmonary edema and narcosis may develop. At high concentrations (not specified) paralysis leading to death may occur. The Poisindex ® from 1998 indicates acetaldehyde to be a skin and mucous irritant that causes a burning sensation of the nose, throat, and eyes. Prolonged exposure to high concentrations (unspecified) may injure the corneal epithelium, causing persistent lacrymation, photophobia, and foreign body sensation. Fatalities following inhalation are due to anesthesia when prompt, and to pulmonary edema when delayed.

2.2.2. Experimental Studies

A number of inhalation studies in human volunteers is available. These include several recent studies in asthmatics of which the value for AEGL derivation however is limited due to the extremely short exposure period of only 2-4 minutes that was used in these studies. Inhalation experiments in which exposure lasted longer are old and of limited design (only one test concentration). For non-inhalation routes a single study with intravenous exposure is available.

The earliest study known is that by Silverman et al. (1946) who examined the potential for the induction of sensory irritation by a number of industrial solvents, one of which was acetaldehyde. A group of 12 volunteers (of both sexes, numbers not specified) was exposed to increasing (nominal) concentrations of acetaldehyde for 15 minutes. A majority of the subjects (number not specified) experienced eye irritation at 50 ppm. Subjects that did not report eye irritation showed blood shot eyes and reddened eyelids at 200 ppm. The subjects did not report nose or throat irritation. The very brief report that is available on this study states that a majority of subjects was willing to work an 8-hour day in 200 ppm. Several subjects however "objected strenuously to" the compound even at an exposure concentration of 25 ppm but no details are given on the nature of their complaints.

Sim and Pattle (1957) investigated the irritant properties of a number of compounds present in acid smog. One of the aldehydes tested was acetaldehyde. A group of 14 healthy male volunteers inhaled a measured concentration of 134 ppm for 30 minutes while sitting in a 100 m^3 exposure chamber. According to the very brief summary of results presented, the test concentration was mildly irritating to the upper respiratory tract. No mention is made of the presence or absence of eye irritation. Because for similar chamber experiments with other aldehydes the report indicates that eye irritation did occur, it is concluded that acetaldehyde probably was not eye irritating in this study.

Within the Japanese population aldehyde dehydrogenase-2 polymorphism occurs, with about 50% of the individuals having inactive genotypes compared to almost zero percent in white European populations. Aldehyde dehydrogenase plays an important part in the metabolism of ethanol in making possible the conversion of acetaldehyde (previously formed from ethanol by alcohol dehydrogenase) to acetic acid. The lack of aldehyde dehydrogenase leads to elevated concentrations of acetaldehyde in the blood, which in asthmatic subjects may produce bronchoconstriction. The mechanism of the latter effect remains to be clarified but there are indications that enhanced release of histamine from pre-activated airway mast cells plays an important role. As a result of the polymorphism nearly half of the Japanese patients with asthma show bronchoconstriction after drinking alcohol, a phenomenon that is also known to occur in other Asian populations.

In several studies in asthmatic volunteers inhaled acetaldehyde has been tested for bronchoconstrictive effect, first in three studies in Japanese subjects (Myou et al. 1993, 1994; Fujimura et al. 1999) and subsequently in three studies in Caucasian subjects (Prieto et al 2000; 2002a and 2002b). In these studies, however, subjects inhaled aerosolized acetaldehyde for very short periods only (2-4 minutes), which reduces their value for AEGL derivation.

Myou et al. (1993) exposed a group of nine asthmatic volunteers (age 39.2±5.4 yr) and nine age- and sex-matched controls to aerosolized acetaldehyde for 2 minutes immediately followed by measurement of Force Expiratory Volume (FEV_1). The aerosol was produced using a DeVilbiss 646 nebulizer operated by compressed air at 5 liter/minute. Nebulizer output was not reported but probably this was the same as in later studies by this group, i.e. 0.14 ml/minute. Acetaldehyde solutions in saline of 4, 10, 20, and 40 mg acetaldehyde/ml were tested. The aerosol was inhaled by tidal mouth breathing while wearing a nose clip and this was immediately followed by measurement of FEV_1. Saline solution was inhaled first for 2 minutes and if the change in FEV_1 from baseline values was ≤10%, inhalation of

acetaldehyde was started. No measurements of acetaldehyde concentration in air were made. Several studies were carried out in the same groups of volunteers. In one study acetaldehyde solutions in saline of 4, 10, 20, and 40 mg acetaldehyde/ml were tested for effect on FEV_1 (determination of dose response curve). In another experiment increasing concentrations of acetaldehyde were given in order to determine the PC_{20}, the acetaldehyde concentration producing a 20% reduction in FEV_1. The result of the latter experiment, however, are not reported clearly. In further experiments the influence of oral terfenadine, a histamine H_1 blocker, was examined as was the bronchial responsiveness to metacholine (challenge with metacholine is a common asthma identification test). The dose response study showed significant reductions in FEV_1 at all acetaldehyde test concentrations in asthmatics whereas no effect was seen in normal subjects. A rough estimate from the dose response curve as presented in the paper, suggests a PC_{20} for acetaldehyde of about 20 mg/ml. The response seen after inhalation of acetaldehyde was completely suppressed by pretreatment with terfenadine, which indicates that the bronchoconstriction produced by acetaldehyde is histamine-mediated (Myou et al. 1993). The acetaldehyde aerosol concentration as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 5 liter air/minute for 2 minutes with a acetaldehyde solution output of 0.14 ml/minute. When given at this rate a 20 mg acetaldehyde/ml solution (the estimated PC_{20}) corresponds to a concentration in air of 560 mg/m^3 (about 314 ppm).

In a subsequent study Myou et al. (1994) studied the potentiating effect of aerosolized acetaldehyde on the bronchial responsiveness to metacholine in nine asthmatic subjects of Japanese origin (age 46.1±6.6 years). The subjects inhaled a solution of 0.8 mg acetaldehyde/ml that was nebulized at 0.14 ml/minute for 4 minutes followed by provocation with a range of increasing metacholine concentrations (challenge with metacholine is a common asthma identification test). Before and after treatment Forced Expiratory Volume (FEV_1) was measured. A control treatment, given on a separate day, consisted of inhalation of saline followed by provocation with metacholine. No measurements of acetaldehyde concentrations in air were made. For each treatment the PC_{20}-MCH, the metacholine concentration producing a 20% reduction in FEV_1, was determined. Acetaldehyde produced a marked reduction in PC_{20}-MCH (0.48 mg/ml versus 0.85 mg/ml after saline treatment) (Myou et al. 1994). The acetaldehyde aerosol concentration as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 5 liters air/minute for 4 minutes with a acetaldehyde solution output of 0.14 ml/minute. When given at this rate a 0.8 mg acetaldehyde/ml solution corresponds to a concentration in air of 22.4 mg/m^3 (about 12.5 ppm)

In a later study in asthmatics by the same Japanese research group (Fujimura et al. 1999), the hypothesis was tested that asthmatics who are sensitive to alcohol (showing bronchoconstriction after drinking alcohol) also have increased airway responsiveness to inhaled acetaldehyde when compared to asthmatics not sensitive to alcohol. The test groups consisted of ten alcohol-sensitive asthmatics and 16 alcohol-insensitive asthmatics, all adults (20-65 years). Acetaldehyde aerosol was inhaled for 2 minutes by tidal mouth breathing and followed immediately by measurements of FEV_1. Increasing concentrations were inhaled until FEV showed a fall of ≥20%. The aerosol was produced using a DeVilbiss 646 nebulizer operated by compressed air at 5 liter/minute with a nebulizer output of 0.14 ml/minute. Acetaldehyde solutions in saline of 0.04 to 80 mg acetaldehyde/ml were tested. PC_{20} (provocative concentration required to produce a 20% fall in FEV_1) were calculated by linear interpolation on the logarithmic concentration-response curve. In the alcohol-sensitive group the geometric mean PC_{20} was 21.0 mg/ml (range not reported) whereas in the alcohol-insensitive group this was 31.7 mg/ml (range not reported). The difference between the groups, however, was not statistically significant (Fujimura et al. 1999). The acetaldehyde aerosol concentration as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 5 liters air/minute for 2 minutes with a acetaldehyde solution output of 0.14 ml/minute. When given at this rate, inhaling of acetaldehyde solutions of 0.04 to 80 mg/ml amounts to concentrations in air of 1.12 to 2240 mg/m^3. Similarly, the geometric mean PC_{20} in the alcohol-sensitive

group corresponds to 588 mg/m^3 (about 330 ppm) and the geometric mean PC_{20} in the alcohol-insensitive group to 888 mg/m^3 (about 500 ppm).

Prieto et al. (2000) examined if the bronchoconstriction seen in Japanese asthmatics after inhalation of acetaldehyde also occurred in Caucasian subjects. They exposed 61 mildly asthmatic subjects and 20 healthy subjects (control group) to aerosolized acetaldehyde for two minutes using a two-minute tidal breathing-method. The subjects were adults aged 18-60 years. Aqueous solutions containing 5 to 40 mg acetaldehyde/ml were nebulized in a Hudson 1720 nebulizer operated by compressed air at 6 liter/minute with a nebulizer output of 0.18 ml/minute[1]. Concentration of acetaldehyde in air was not determined directly in this study. Forced Expiratory Volume (FEV_1) was measured at 60-90 seconds after inhalation. In the asthma group 56/61 subjects showed bronchoconstriction compared to 0/20 in the control group. PC_{20} (provocative concentration required to produce a 20% fall in FEV_1) was calculated by linear interpolation on the logarithmic concentration-response curve. In the asthma group the PC_{20}-values ranged from 1.96 to >40 mg/ml with a geometric mean value of 17.55 mg/ml (Prieto et al. 2000). The acetaldehyde aerosol concentrations as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 6 liter air/minute for 2 minutes with a acetaldehyde solution output of 0.18 ml/minute. When given at this rate, inhaling of acetaldehyde solutions of 5 to 40 mg/ml amounts to concentrations in air of 150 to 1200 mg/m^3. Similarly, the observed geometric mean PC_{20} of 17.55 mg/ml corresponds to 526 mg/m^3 (about 295 ppm).

In a follow-up study, Prieto et al. (2002a) exposed groups of 16 and 14 mildly asthmatic subjects (age 18-58 years) to acetaldehyde using the same exposure method as in the first study, this time with doubling concentrations of 2.5 to 80 mg acetaldehyde/ml. Nebulizer output in this study presumably was 5 liters/minute.[2] Again, concentration of acetaldehyde in air was not determined directly in this study. In the group of 16 subjects the response to acetaldehyde was compared to that to metacholine and adenosine-5'-monophosphate, two bronchoconstrictive agents of known potency. In the group of 14 subjects repeatability and side effects of acetaldehyde inhalation were examined. For acetaldehyde the PC_{20} ranged from 8.4 to 80 mg/ml with a geometric mean of 38.9 mg/ml (geometric mean values for metacholine and AMP were 0.6 and 17.4 mg/ml respectively). The response to acetaldehyde was found to be moderately repeatable. For the group in which repeatability was examined, it is stated that at acetaldehyde concentrations producing a >20% fall in FEV_1, most subjects had cough (64%), dyspnea (57%) or throat irritation (43%). Nausea was not reported; mostly no wheezing could be heard. Pulse rate was unchanged, as was blood pressure. The bronchoconstriction by acetaldehyde reversed rapidly (within 15 minutes with inhaled salbutamol) (Prieto et al 2002a). The acetaldehyde aerosol concentrations as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 5 liter air/minute for 2 minutes with a acetaldehyde solution output of 0.16 ml/minute. When given at this rate, inhaling of acetaldehyde solutions of 2.5 to 80 mg/ml amounts to concentrations in air of 80 to 2560 mg/m^3. The observed geometric mean PC_{20} of 38.9 mg/ml corresponds to 1245 mg/m^3 (about 700 ppm).

In a further volunteer study, Prieto et al. (2002b) studied comparative airway responsiveness to acetaldehyde in subjects with allergic rhinitis (n=43), asthmatics (n=16) and healthy subjects (n=19). All volunteers were adults. The test procedure was the same as used in the earlier studies. Nebulizer output in this study was 5 liters/minute.[3] The range of concentrations tested was from 2.5 mg acetaldehyde/ml to 80 mg/ml. As in earlier studies by this group, air concentrations of acetaldehyde were not measured. The proportion of subjects with a positive response (fall in FEV_1 >20%) was 8/43 in the group with allergic rhinitis, 13/16 in the asthmatics group and 0/19 in the healthy subjects group. PC_{20} values in the group

[1] Nebulizer airstream was not reported in original publication. In a personal communication, Dr. Prieto indicated that the nebulizer air stream was 6 liters/minute in this study.

[2] Personal communication Dr. Prieto, 23-03-2004.

[3] Personal communication Dr. Prieto, 23-03-2004.

with allergic rhinitis ranged from 15.5 to 80.0 mg/ml with a geometric mean of 67.7 mg/ml whereas in the asthmatics group PC_{20} ranged from 8.4 to 80.0 mg/ml with a geometric mean of 35.5 mg/ml (Prieto et al. 2002b). The acetaldehyde aerosol concentrations as mg/m^3 in this study can be estimated as follows. The nebulizer was operated at 5 liter air/minute for 2 minutes with a acetaldehyde solution output of 0.16 ml/minute. When given at this rate, inhaling of acetaldehyde solutions of 2.5 to 80 mg/ml amounts to concentrations in air of 80 to 2560 mg/m^3. The observed geometric mean of 67.7 mg/ml corresponds to 2166 mg/m^3 (about 1210 ppm) and the geometric mean of 35.5 mg/ml to 1136 mg/m^3 (about 640 ppm).

As stated above, for non-inhalation an intravenous study is available. Asmussen et al (1948) administered intravenous infusions to young male volunteers (number and age not reported) of solutions of 5% acetaldehyde for up to 36 minutes . At concentrations of 0.2 to 0.7% in the blood marked increases in heart rate, ventilation and calculated respiratory dead space were observed, as was a decrease in alveolar CO_2 levels.

2.2.3. Occupational / Epidemiological Studies

No studies on acute or chronic non-lethal effects in workers were identified.

2.3. Neurotoxicity

No human studies on neurotoxicity were identified.

2.4. Developmental / Reproductive toxicity

No inhalation studies for this endpoint were identified. Acetaldehyde may play a role in the development of the fetal alcohol syndrome, which is a specific pattern of congenital abnormalities found in children of mothers drinking heavily. Studies in humans in which the role of acetaldehyde is further explored, however, are lacking.

2.5. Genotoxicity

No studies for this endpoint were identified.

2.6. Carcinogenicity

In its review of acetaldehyde carcinogenicity, IARC identified only one single study with inhalation exposure. This was a limited survey in workers with exposure to several aldehydes. Nine cancers were observed in as many smokers in a group of workers (number unknown), an incidence that was reported as being higher than expected in the German Democratic Republic, the country where the study originated from (IARC, 1999). In addition IARC reported three case control studies in which the risk was assessed of several cancer types following heavy alcohol intake by populations showing genetic polymorphism of enzymes involved in the metabolism of alcohol to acetaldehyde and in the further metabolism of acetaldehyde. In these studies, IARC concluded, although they were limited in design and number of subjects, increased risks of alcohol-related cancers were consistently observed 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 (IARC, 1999).

Overall IARC concluded that there is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde (IARC, 1999).

Both US-EPA and Health Canada have developed quantitative cancer risk assessments based on the tumor incidences seen in the chronic rat bioassay by Woutersen et al. (1996). Using the Linearized

Multistage Model US-EPA (1991) derived an inhalation unit risk of $2.2.10^{-6}$ (risk per microgram/m^3 of lifetime exposure). See appendix C for calculation of the virtually safe doses for standard AEGL durations, based on the US-EPA unit risk.

2.7. Summary of human data

Human data are relatively scarce for acetaldehyde. No lethality data are available. Relevant volunteer studies are those by Silverman et al. (1946) and Sim and Pattle (1957). Both studies were limited in design (only one test group, limited number of test subjects). Recent studies in asthmatics are more elaborate but had a very short exposure time of 2 minutes only; the latter feature very much reduces the value of these studies for AEGL derivation.

In the study by Silverman et al. the majority of subjects reported eye irritation after exposure to a nominal concentration of 50 ppm for 15 minutes. The limited report states that some volunteers strenuously resisted to 25 ppm without however detailing what was the nature of the complaints these subjects experienced. Sim and Pattle (1957) reported mild irritation to the upper respiratory tract after exposure to a measured concentration of 134 ppm for 30 minutes (the only concentration tested). The recent volunteer studies in asthmatics showed significant bronchoconstriction (reduction of FEV_1 of 20%) at estimated concentrations of several hundred ppm to which the subjects were exposed for 2 minutes only. In these studies bronchoconstriction by inhaled acetaldehyde was seen not only in Oriental subjects but also in Caucasians. In all groups considerable inter-individual variation between asthmatics was noted. Geometric mean PC_{20}-values (acetaldehyde concentration in air that produced a 20% fall in FEV_1) as determined in these studies in asthmatics, ranged from 295 ppm to 700 ppm (estimated concentrations). Inter-individual variation in PC_{20}-values was in excess of this range. It should be noted that these studies were done using mouth breathing, which by-passes the scrubbing effect of the nose and delivers more acetaldehyde to the bronchioles.

For other toxicological endpoints the data are very limited. Acetaldehyde may play a role in the development of the fetal alcohol syndrome but further studies - let alone further inhalation studies - to explore this possible effect are lacking.

Human carcinogenicity data on acetaldehyde are very limited. IARC concluded that there is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde.

3. ANIMAL TOXICITY DATA

3.1. Acute lethality

3.1.1. Cats

In an early study Iwanoff (1911) exposed a single cat to increasing concentrations of acetaldehyde vapor. The first experiment involved exposure to a mean concentration of 460 mg/m^3 (258 ppm) (for 4.25 hours which led to transient lacrymation, transient salivation and closing of the eyes. Subsequent exposure to 1790 mg/m^3 (1002 ppm) for 3 hours produced sneezing, salivation, irregular breathing and sleepiness. In a further experiment the same cat was exposed to 3100 mg/m^3 (1736 ppm) for 4 hours. Agitation, salivation, dyspnea, sleepiness were noted. Next the cat was exposed to 3300 mg/m^3 (1848 ppm) for 3.5 hours which led to salivation, coughing, closed eyes and sleepiness. When exposed to 7400 mg/m^3 (4144 ppm) for 4 hours the cat showed salivation, sneezing, marked dyspnea, coughing, alternately agitation and sleepiness, vomiting of white liquid. Finally the cat received 24500

mg/m^3 (13720 ppm) for 15 minutes. This produced lacrymation, sneezing, marked salivation, agitation, convulsions, screaming, marked dyspnea, prostration, anesthetization and finally death.

3.1.2. Rabbits

In a multispecies inhalation study Salem and Cullumbine (1960) determined lethality in rabbits for a number of aldehydes, one of which was acetaldehyde. Groups of five animals were exposed to a single concentration of acetaldehyde, either as aerosol or as vapor. Exposures lasted up to 10 hours or until death intervened. The results of this study are reported very briefly only. The mean concentration to which the rabbits were exposed was 5887 mg/m^3 (3297 ppm) for vapor and 2151 mg/m^3 for aerosol. The mean fatal doses as mg-min/m^3 were 480,000 and 390,000 for acetaldehyde vapor and aerosol respectively. From this it can calculated that on average the rabbits died after 81.5 minutes in the vapor group and after 181 minutes in the aerosol group. The intoxication symptoms observed, were described in general only, for all aldehydes and all test species. Animals showed an initial increase in activity and signs indicating eye irritation (blinking, closing of eyes, rubbing of the face). After that respiration became slow and deep, which continued until the animals convulsed before death.

3.1.3. Guinea Pigs

In a multispecies inhalation study Salem and Cullumbine (1960) determined lethality in guinea pigs after exposure to a number of aldehydes, one of which was acetaldehyde. Groups of twenty animals were exposed to a single concentration, either as aerosol or as vapor. Exposures lasted up to 10 hours or until death intervened. The results of this study are reported very briefly only. The mean concentration to which the guinea pigs were exposed was 5887 mg/m^3 (3297 ppm) for vapor and 2151 mg/m^3 for aerosol. The mean fatal doses as mg-min/m^3 were 490,000 and 690,000 for acetaldehyde vapor and aerosol respectively. From this it can calculated that on average the guinea pigs died after 83 minutes in the vapor group and after 320 minutes in the aerosol group. Observed symptoms were described in general only, for all aldehydes and all test species taken together. The animals showed an initial increase in activity and signs indicating eye irritation (blinking, closing of eyes, rubbing of the face). After that respiration became slow and deep, which continued until the animals convulsed before death.

3.1.4. Hamster

In a 4-hour inhalation study Kruysse (1970) exposed groups of 10 (5m, 5f) Syrian Golden hamsters to acetaldehyde vapor at measured concentrations of 26, 28, 29, 30 and 32 grams/m^3 (14560, 15680, 16240, 16800 and 17920 ppm) (groups 1 through 5). The animals were observed for 14 days, at which time all survivors were autopsied. After 1-2 hours of exposure in all groups the animals showed severe dyspnea, lacrymation, and nasal secretion. Animals that died during exposure had convulsions. At all concentrations some animals survived after deep narcosis that was accompanied by apnea. The observed pattern of mortality was as follows: 1/10 in group 1, 2/10 in group 2, 3/10 in group 3, 4/10 in group 4 and 6/10 in group 5. The 4-hour LC_{50} was calculated to be 30.6 grams/m^3 (17000 ppm) with 32.1 and 29.1 grams/m^3 as 95% confidence limits (Kruysse et al. 1970).

3.1.5. Rats

Three inhalation mortality studies in rats are available. The earliest study is by Skog (1950) who studied the acute lethality of several aldehydes in rats. Groups of six rats (strain not reported) were placed in exposure chambers through which vaporized acetaldehyde was led for 30 minutes. Nominal test concentrations ranged from 14,000 to 57,000 mg/m^3 (7840 to 31920 ppm) (individual test concentrations not reported). Animals were observed for three weeks after treatment. Histological examinations were done on very few animals only (four rats per aldehyde). The pattern of mortality over the different dose groups was not reported, only a graphic curve depicting probits of mortality and doses. An LC_{50} of 37,000 mg/m^3 (20,720 ppm) was found. Symptomatology was reported as follows. The animals first passed through a stage of pronounced excitation followed by anesthetization after 10 to 15 minutes. All deaths occurred during exposure or a few minutes thereafter. The survivors recovered in about one hour. Histopathology revealed hyperemia, hemorrhages, intra-alveolar and perivascular edema in the lungs and focal perivascular edema in heart and liver (no changes in spleen, kidneys and brain) (Skog 1950).

Smyth et al. (1946) report the results of range-finding studies they carried out in rats (strain not reported) for a large number of chemicals one of which was acetaldehyde. Study results are reported as a summary table only. Six rats could inhale a saturated vapor concentration of acetaldehyde for 2 minutes before deaths started to occur. Concentrations 8,000 and 16,000 ppm for 8 hours resulted in 0/6 deaths (Smyth et al. 1946).

Appelman et al (1982) determined the 4-hour LC_{50} for acetaldehyde in rats. They exposed four groups of 10 rats (5 m, 5f) in glass exposure cylinders to measured concentrations of 10436, 12673, 15683 and 16801 ppm respectively for 4 hours (groups 1 through 4). After the exposure period the animals were returned to their cages and observed for 14 days during which period body weights were recorded. All survivors were then killed. No post mortem examinations were done. During the first half hour of the exposure restlessness, closed eyes and labored breathing were observed. After about 1 hour animals were lying with their eyes open and showing severe mouth breathing. Body weight loss occurred on the first day after exposure. The number of deaths were distributed as follows: 2/10 in group 1, 5/10 in group 2, 6/10 in group 3 and 8/10 in group 4. The LC_{50} was 13,300 ppm (24,000 mg/m^3) with 95% confidence limits of 11,200 and 15,400 ppm (Appelman et al 1982).

Appelman et al. (1982) also present the results of a 4-week inhalation study in rats they performed with acetaldehyde vapor. In the group exposed to the highest (measured) concentration of 4975 ppm (6 hours/day, 5 days week) 1/10 males and 1/10 females were found dead just before test end (i.e. in the fourth week of exposure). At the next lower concentration of 2217 ppm 1/10 males died (between day 7 and 14 of exposure). The cause of the deaths could not established. At the lower test concentrations (941 and 401 ppm) no deaths occurred (Appelman et al. 1982, Appelman and Woutersen 1981).

3.1.6. Mice

In a multispecies inhalation study Salem and Cullumbine (1960) determined lethality in mice after exposure to a number of aldehydes, one of which was acetaldehyde. Groups of fifty animals were exposed to a single concentration, either as aerosol or as vapor. Exposures lasted up to 10 hours or until death intervened. The results of this study are reported very briefly only. The mean concentration to which the mice were exposed was 5887 mg/m^3 (3297 ppm) for vapor and 2151 mg/m^3 for aerosol. The mean fatal doses as mg-min/m^3 were 480,000 and 330,000 for acetaldehyde vapor and aerosol respectively. From this it can calculated that on average the mice died after 81.5 minutes in the vapor group and after 153 minutes in the aerosol group. The test animals showed an initial increase in activity

and signs indicating eye irritation (blinking, closing of eyes, rubbing of the face). After that respiration became slow and deep, which continued until the animals convulsed before death. This is a general description of symptoms, referring to all aldehydes and all test species. Specifically for acetaldehyde in mice anesthetization after the initial irritation is additionally mentioned.

TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Cat	4,144	4 hours	Severe toxicity	Iwanoff (1911)
Cat	13720	15 min	Death	Iwanoff (1911)
Rabbit, guinea pig, mouse	3,296	81.5 min (mouse, rabbit), 83 min (guinea pig)	death	Salem and Cullumbine (1960)
Hamster	17,000	4 hours	LC50	Kruysse et al. (1970)
Rat	20,720	30 min	LC50	Skog (1950)
Rat	16,000	8 hours	No effect	Smyth et al. (1946)
Rat	13,300	4 hours	LC50	Appelman, et al. (1982)

3.2. Nonlethal toxicity

3.2.1. Guinea Pigs

As part of their research relating to alcohol-induced asthma, Myou et al. (2001) studied the involvement of tachykinins (sensory neuropeptides know to act on airway smooth muscles) in acetaldehyde-induced bronchoconstriction in guinea pigs. Anaesthetized males of the Hartley strain were cannulated from the trachea and then artificially ventilated with acetaldehyde aerosol for 20-second periods (aerosol concentration in air not reported). The failure of FK224, an agent known to produce tachykinin depletion, to reduce the bronchoconstrictive effect of acetaldehyde, indicates that tachykinins are not involved in the mechanism of acetaldehyde-induced bronchoconstriction.

3.2.2. Hamster

No acute inhalation studies for non lethal toxicity were identified. Kruysse et al. (1975) performed a semichronic inhalation toxicity study in which groups of 20 (10 m, 10 f) Syrian golden hamsters were exposed to acetaldehyde vapor concentrations of 0, 390, 1340 or 4560 ppm during 6 hours/day, 5 days/week for a 90 days period. At the highest concentration the following effects were observed: growth retardation, ocular and nasal irritation, increased numbers of erythrocytes, increased weights of heart and kidneys and severe degenerative hyperplastic and metaplastic changes in the respiratory tract epithelium, especially in the nasal cavity. The effect on the nasal epithelium was so severe that subepithelial glands and even turbinate bones were affected. Rhinitis was also observed with abundant nasal discharge and salivation. The epithelium of the larynx, trachea and lungs was damaged with some focal hyperplasia and metaplasia accompanied by inflammation in both trachea and bronchi.

Changes in tracheal epithelium were also observed at the next lower concentration of 1340 ppm. The NOAEL in this study was 390 ppm.

In a later experiment by the same research group (Feron et al. 1979) two groups of 210 male Syrian golden hamsters were exposed to 0 or 1500 ppm acetaldehyde vapor for 7 hours/day, 5 days week for 52 weeks. Subgroups of 35 animals received weekly intra-tracheal instillations of benzo(a)pyrene for 52 weeks. After 78 weeks all animals were killed and neoplastic and non-neoplastic changes were recorded. Effects noted included growth retardation, changes in hematological and urinalytic parameters. Non-neoplastic changes in the nasal cavity consisted of flattened epithelial cells with bizarrely formed nuclei, fewer subepithelial glands, submucosal thickening, and keratinizing stratified squamous metaplasia of olfactory and respiratory epithelium. Slight to moderate rhinitis was a frequent finding. In the trachea slight focal hyperplasia and metaplasia of the epithelium occurred. There was partial or complete recovery from these lesions in the animals killed at the end of the recovery period. In a follow-up experiment groups of 60 (30 m, 30 f) Syrian hamsters were exposed to 2500 ppm for 7 hours/day 4 days/week for 52 weeks followed by a 29-week recovery period. Because of marked growth retardation the exposure concentration was lowered to 1600 ppm. Again groups of animals were treated intra-tracheally with benzo(a)pyrene. Nasal changes observed in the acetaldehyde-only group consisted of rhinitis, thinning and degeneration of the olfactory epithelium, hyper- and metaplasia of the respiratory epithelium, and thickening of the submucosa in the dorso-medial part. Metaplastic stratified squamous epithelium with keratinization was observed in the maxillary turbinates and in the anterior part of the nasal septum. In both the larynx and the trachea slight to moderate focal hyperplasia and squamous metaplasia in the epithelium was found (Feron et al. 1982).

3.2.3. Rats

Egle (1972) studied the effects of acute inhalation of acetaldehyde on heart rate and blood pressure in male Wistar rats. He selected his test concentrations as being likely to occur in cigarette smoke. The animals were first anaesthetized by pentobarbital sorbitol (50 mg/kg bw) administered intraperitoneally, and subsequently exposed to acetaldehyde vapor for intervals of one minute by placing cylinders over the head which were attached to a bag containing the desired test concentration. Blood pressure and heart rate were allowed to return to normal between exposure periods. Control inhalations involved 1 minute exposures to air under the same conditions. The lowest (nominal) concentrations tested of 500 and 1000 mg/m^3 (278 and 556 ppm) produced no change in blood pressure. At ≥3000 mg/m^3 (≥1668 ppm) a dose-related increase in blood pressure was observed. Heart rate was increased significantly at 12,000 and 25,000 mg/m^3 only; the only higher concentrations that was tested, 30,000 mg/m^3, however, showed a slightly decreased heart rate.

Sensory irritants are known to induce a change in breathing-pattern in rodents characterized by a pause during expiration and decreased respiratory rate. This centrally mediated reflex response is thought to be mediated by stimulation of nasal sensory trigeminal nerves. The RD_{50} is the exposure concentration that results in 50% reduction in breathing-frequency. The acute sensory irritation response of acetaldehyde and several other aldehydes was studied by Babiuk et al. (1985) in male F-344 rats by measuring respiratory rate depression in a head-only inhalation chamber using a plethysmograph. The main focus of this study was to determine if pre-treatment with formaldehyde would cause sensory irritation cross tolerance to other inhaled aldehydes. Respiratory rates of groups of four simultaneously exposed rats were recorded during a 5-minute control period , a 10-minute exposure period and 5-minute recovery period. Concentration-effect curves were established and RD_{50}-values were calculated. The RD_{50} for acetaldehyde in naive rats was 2991 ppm (95% confidence limits: 2411-3825). In formaldehyde-pretreated rats this was 10601 ppm (95% confidence limits: 7902-15442), thus revealing that a marked cross tolerance towards acetaldehyde had developed.

Cassee et al. (1996a) studied the sensory irritation potential of three aldehydes (including acetaldehyde) by measuring respiratory rate depression in male Wistar rats. They exposed groups of 4 animals nose-only to various concentrations of acetaldehyde vapor for 10 minutes and measured respiratory rates using a plethysmograph before, during as well as after exposure. Concentration-effect curves were established and RD_{50}-values were calculated. The RD_{50} for acetaldehyde was 3046 ppm (95% confidence limits: 997-4036).

In another acute inhalation study in rats, Stanek et al. (2001) determined the acute nasal vasodilatory response to acetaldehyde and acetic acid in groups of 3-6 urethane-anesthetized male F-344 rats. The upper respiratory tract of the test animals was isolated by insertion of an endotracheal cannula, after which irritant-laden air was drawn continuously through that site at a rate of 100 ml/min for 50 minutes. Vascular function was monitored by measuring inert vapor (acetone) uptake throughout exposure. This uptake was measured as the difference in concentration between the air entering the upper respiratory system and that exiting it. The measured acetaldehyde exposure concentrations in this study were 6, 25, 49, 104, 164, 216, 379, 500, and 2950 ppm. A vasodilatory response (as measured by increased acetone uptake) was apparent within 3 minutes after the onset of exposure and was fully developed by the second half of the exposure period. Statistical analysis showed a significant effect at ≥25 ppm. Acetic acid showed a vasodilatory response at ≥130 ppm. The response to either compound was significantly diminished when rats were pretreated with the known nerve toxin capsaicin (50 mg/kg bw, 7 days prior to exposure), indicating that sensory nerves play a role in the vasodilatory response.

Cassee et al. (1996b) studied the mixture toxicology of three aldehydes by exposing groups of 5 male Wistar rats to various concentrations of the individual compounds in a one- and three-day inhalation study (6 hours/day), and comparing the observed nasal response to that seen after exposure to mixtures of these aldehydes. The test concentrations were selected as being either clearly non-toxic or toxic. For acetaldehyde concentrations of 750 and 1500 ppm were tested. After one-day exposure to acetaldehyde no nasal changes were noted. After three day exposure a few necrotic cells were detected in the nasal epithelium of 3/5 animals at 750 ppm whereas at 1500 a few necrotic cells were detectable in 1/5 animals and a moderate number of necrotic cells in 2/5 animals. The other aldehydes in this study were formaldehyde and acrolein, which also have the nose as target organ but probably affect different regions of nasal epithelium than does acetaldehyde. The observed mixture effects suggest that at non-toxic exposure levels combined exposure is not more hazardous than exposure to the individual compounds (no addition of effect). A mixture of individually-toxic concentrations produced markedly more severe effects than did the individual compounds (addition of effect).

In a subacute inhalation study Appelman et al. (1982) exposed groups of 20 (10m, 10f) Wistar rats to acetaldehyde vapor at 0, 401, 941, 2217 or 4975 ppm (measured concentrations) for 6 hours/day on 5 days/week for 4 weeks. Animals were observed for clinical signs daily; body weights were recorded weekly. Hematology, blood biochemistry and urinalysis were carried out at test end. The weights of kidneys, lungs, liver and spleen were determined. Microscopy was done in lungs, trachea and nose of all animals and in kidneys, liver and spleen of control and high-dose animals. At 4975 ppm rats showed severe dyspnea and marked excitation during the first 30 minutes of each exposure (during the remainder of the exposure these effects gradually subsided). By the end of the study the fur of the animals in this group was yellowish brown. In all other groups no clinical signs were noted. Growth was retarded significantly at ≥941 ppm. Histopathological changes were observed in the nose, trachea and lungs. The nose was most severely affected. At all exposure levels concentration-related degeneration of nasal epithelium was observed. Laryngeal and tracheal lesions were seen at 2217 and 4975 ppm only, and pulmonary changes of doubtful toxicological significance were present al 4975 ppm only.

The same authors carried out a further 4-week study with acetaldehyde in male Wistar rats using three different daily exposure regimens: 0, 110, 150 or 500 ppm for 6 hours, 0, 110, 150 or 500 ppm as two daily three-hour exposures separated by a 1.5 hour exposure-free interval and 0, 110, 150 or 500 ppm as two daily three-hour exposures separated by a 1.5 hour interval during which eight 5-minute peak exposures to a six-fold higher concentration were administered. No effects were observed at 110 or 150 ppm, not even when combined with the cytotoxic peak exposures to 660 or 850 ppm. At 500 ppm histological changes in the olfactory epithelium were noted (loss of microvilli and disarrangement of epithelial cells) as was a reduction of the phagocytic index of lung macrophages. The inclusion of the 1.5 hours exposure-free interval did not change the response significantly. The peak exposures of 3000 ppm did not change the nasal response but did lead to growth retardation, irritation of eyes and nose and a further decrease in the phagocytic index (Appelman et al. 1986).

Saldiva et al. (1985) exposed 12 male Wistar rats to acetaldehyde vapor at a concentration of 243 ppm during 8 hours/day, 5 days/week for 5 weeks. Pulmonary function tests were done one week before the first exposure and 1-6 hours after the last exposure. After pulmonary testing the animals were killed and the respiratory system was examined histologically. A group of 12 rats served as controls. Results showed that functional residual capacity was increased after exposure, as were residual volume, total lung capacity and respiratory frequency. In the nasal cavity an intense inflammatory reaction was observed, characterized by olfactory epithelium hyperplasia and polymorphonuclear and mononuclear infiltration of the mucosa.

In the only chronic rat inhalation study that is available, Woutersen et al. (1986) exposed groups of male and female rats to 0, 750, 1500 or 3000 ppm acetaldehyde vapor for 6 hours/day, 5 days/week for up to 27 months. Because of severe growth retardation and mortality the highest test concentration was gradually reduced from day 141 onwards and was held at 1000 ppm from day 313 onwards. Non-neoplastic effects noted consisted of growth retardation (all test concentrations), increased mortality (all test concentrations) and degenerative changes in the olfactory nasal epithelium (all test concentrations). In separate groups of rats that were maintained during recovery periods of 24 or 52 weeks after being exposed for 52 weeks, some regeneration of the nasal lesions was observed at 750 and 1500 ppm but not at 3000/1000 ppm. Neoplastic lesions detected consisted of nasal carcinomas and adenocarcinomas deriving from the respiratory or the olfactory epithelia at all test concentrations (Woutersen et al. 1986; Woutersen and Feron, 1987).

3.2.4. Mice

Acetaldehyde's potency for inducing sensory irritation was determined with the RD_{50}-test in mice by Kane et al. (1980) and by Steinhagen and Barrow (1984). In their study Kane et al. (1980) exposed groups of 4 male Swiss-Webster mice head-only to various concentrations of several industrial solvents, one of which was acetaldehyde. Respiration frequency was recorded for each mouse before, during and after the exposure period of 10 minutes and subsequently the concentration-response relationship was established. For acetaldehyde an RD_{50}-value of 4946 ppm was found with 95% confidence limits of 4579 ppm and 5381 ppm. Steinhagen and Barrow (1984) determined the RD_{50} for acetaldehyde in male B6C3F1 and Swiss-Webster mice as part of a structure-activity study of inhaled aldehydes. Groups of three or four mice were exposed head-only to five concentrations of acetaldehyde vapor for 10 minutes. Respiratory rates were determined pre-exposure, during exposure and post-exposure. The average maximum decrease for 1 minute was plotted against the logarithm of the concentration and concentration response curve was constructed. For acetaldehyde the RD_{50} was 2932 ppm (95% confidence interval: 2627-3364) for B6C3F1 mice and 2845 ppm (95% confidence interval: 1967-3954) for Swiss-Webster mice. The main finding as to structure-activity relation was that

unsaturated aldehydes like acrolein showed much lower RD_{50} values than did the saturated aldehydes like acetaldehyde.

In a subacute inhalation study Watanabe and Aviado (1974) exposed six male Swiss mice to 2500 mg/m^3 acetaldehyde for 30 minutes twice daily for a period of 5 weeks. Using a body plethysmograph tidal volume, pulmonary resistance and pulmonary compliance were measured, presumably at test end only. Of the parameters determined only the functional residual capacity was decreased.

TABLE 3. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
hamster	4560	90 days	severe degenerative hyperplastic and metaplastic changes in the respiratory tract epithelium, especially in the nasal cavity	Kruysse et al. 1975
hamster	1500	52 weeks	non-neoplastic changes in the nasal cavity with partial or complete recovery	Feron et al.1979
hamster	1600	52 week	metaplastic changes in respiratory tract	Feron et al. 1982
rat	2991 3046	10 minutes	RD50	Babiuk et al. 1985 Cassee et al. 1996a
rat	1500	6 hours	no nasal changes	Cassee et al. 1996b
rat	4975	30 minutes	severe dyspnea and marked excitation	Appelman et al. 1982
mouse	4946 2932	10 minutes	RD50	Kane et al. 1980 Steinhagen and Barrow 1984

3.3. Neurotoxicity

No acute studies were identified. Shiohara et al. (1985) exposed groups of 3 male Sprague-Dawley rats to acetaldehyde vapor at 0.3 mmol/liter (7.4 ppm) for 20 minutes, 4 times daily over a period of 2 to 21 weeks. Animals were killed 24 hours after the last exposure. The activity of $(Na^+ + K^+)$-ATP-ase was measured in subcellular fractions of the cerebral cortex. An increased activity was found both in synaptosomal plasma membrane fraction as in the microsomal fraction. The increase was greatest at 4 weeks. The authors consider this effect to indicate changes in neural membrane function of the brain.

3.4. Developmental / Reproductive toxicity

No acute inhalation studies are available for these endpoints. In fact the only information on reproductive toxicity of acetaldehyde comes for a 90-day hamster inhalation study by Kruysse et al. (1975) in which reduced gonad weights were observed in both sexes at ≥1340 ppm.

A number of studies on the developmental toxicity of acetaldehyde has been performed, aimed at clarifying the role of acetaldehyde in the induction the fetal alcohol syndrome. Exposure in these studies was via non-physiological routes (intraperitoneal, intravenous, intra-amniotic) and the relevance of the feto- and embryotoxicity, and teratogenicity observed, for the routes via which humans are normally exposed (inhalation, oral) is uncertain (IPCS 1995; Health Canada 2000).

3.5. Genotoxicity

IPCS (1995), IARC (1999) and Health Canada (2000) have reviewed acetaldehyde genotoxicity. A large number studies is available, both in vitro and in vivo. Tests for gene mutations in bacteria were negative, both without and with metabolic activation. Several in vitro tests for gene mutations in mammalian cells as well as tests for chromosomal aberrations, however, were positive in the absence of metabolic activation (not tested with activation). Also in mammalian cells in vitro, tests for sister chromatid exchanges have consistently shown positive results without activation (not tested with activation). Aneuploidy has been observed in vitro in non-mammalian eukaryotes and in one study in mammalian cells in vitro without activation (not tested with activation). Two tests for formation micronuclei in cultured mammalian cells without activation, were positive.

In vivo studies include a study for recessive lethal mutations in Drosophila melanogaster in which a positive result was observed after injection but not after feeding. Two tests for formation of micronuclei in erythrocytes and/or bone marrow in rat and mice respectively, both with intraperitoneal injection as the route of application, were positive, whereas a study for micronuclei in spermatocytes in mice using the same application route showed no effect. In the latter study sperm morphology was also evaluated, showing no effect of treatment. Three intraperitoneal studies for sister chromatid exchanges in bone marrow in mice and/or Chinese hamsters showed positive results.

DNA-DNA and DNA-protein cross-linking by acetaldehyde have been observed in several in vitro test systems. In vivo, evidence for DNA-protein cross-linking in the nasal epithelium after inhalation of acetaldehyde has been observed in rats. Lam et al. (1986) found reduced DNA extractability (as measure of DNA-protein cross-linking) in the respiratory epithelium of the nose after inhalation of 1000 or 3000 ppm acetaldehyde for 6 hours but not after inhalation of 100 or 300 ppm for the same time period. The olfactory epithelium of the nose proved to be somewhat less sensitive to this effect, showing no reduction in DNA extractability after single exposure to 1000 or 3000 ppm but such an effect did occur after exposure to 1000 ppm for 6 hours/day for 5 days (Lam et al. 1986). Formaldehyde is also known to produce DNA-protein cross-linking in rat nasal epithelium but is much more potent than acetaldehyde (for respiratory epithelium a single exposure to 1000 ppm of acetaldehyde produces the same level of reduction in DNA extractability as 5.6 ppm formaldehyde) (Morris, 1997).

In conclusion acetaldehyde has shown clear clastogenic, mutagenic and aneugenic effects in vitro. In vivo data are of a limited nature. No studies with inhalation or oral exposure are available. Nevertheless the in vivo evidence that is available indicates the compound to have genotoxic potential in vivo (DECOS 1993; Health Canada 2000). Acetaldehyde's ability to produce DNA-protein cross links resembles that of formaldehyde and the nasal tumors both of these aldehydes induce may well arise through a similar mechanism (Morris 1997).

3.6. Carcinogenicity

IARC (1985, 1999), US-EPA (1991), DECOS (1993), IPCS (1995) and Health Canada (2000) have reviewed the available animal bioassays.

All available studies were carried at the Central Institute for Nutrition and Food Research TNO in Zeist, the Netherlands. Feron (1979) exposed groups of 35 male Syrian hamsters to 0 or 1500 ppm acetaldehyde vapor for 7 hours/day, 5 days/week for 52 weeks and to weekly intratracheal instillations of five increasing doses of benzo(a)pyrene (range 0 to 1 mg). Further groups of hamsters received the B(a)P treatment only. At 52 weeks 5 animals/group were killed for pathological examination; the other animals were maintained for a further 26 weeks and then killed. In the group exposed to acetaldehyde only, no increase in tumor incidence was observed. In the groups treated with acetaldehyde and BaP the tumor incidences were the same as in the groups treated with BaP only (Feron, 1979). Feron (1982) reports a similar study in male and female Syrian hamsters, with slight increases in the number of respiratory tract tumors (8/29 in males, 5/30 in females, none in controls) after exposure to 2500-1650 ppm acetaldehyde (concentration reduced because of toxic reactions) for 52 weeks followed by a 29 week exposure-free period. In separate groups of animals the acetaldehyde exposure was combined with intratracheal injections of BaP or subcutaneous injections of diethylnitrosamine (DENA). Acetaldehyde markedly enhanced the tumorigenic response of BaP but showed no such effect vis à vis the development of DENA-induced tumors.

Woutersen et al. (1986) carried out the only lifetime study, i.e. in Wistar rats. Groups of 110 (55 m, 55 f) rats were exposed to 0, 750, 1500 of 3000 ppm for 6 hours/day, 5 days/week for up to 28 months. The 3000 ppm test concentration was reduced to 1000 ppm in week 52 and beyond. Dose-related histopathological changes in nasal epithelium were observed at all concentrations. Incidences of nasal tumors were increased as follows:

TABLE 4 Incidence of nasal tumors in Wistar rats (Woutersen et al. 1996)

Type of tumor	Controls	750 ppm	1500 ppm	3000/1000 ppm
Males				
Squamous cell carcinoma	1/49	1/52	10/53*	16/49***
Adenocarcinoma	0/49	16/52***	31/53***	21/49***
Carcinoma *in situ*	0/49	0/52	0/53	1/49
Females				
Squamous cell carcinoma	0/50	0/48	5/53	17/53***
Adenocarcinoma	0/50	6/48*	28/53***	23/53***
Carcinoma *in situ*	0/50	0/48	3/53	5/53

Significance: *P <0.05, **P <0.01, ***P<0.001

Based on all animal bioassay data, IARC concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1999).

3.7. Summary of animal data

Lethality studies were performed in rats, mice, guinea pigs, hamsters and rabbits. The intoxication symptoms after inhalation were similar in all test species. The first effect seen is increased activity, which is followed by eye irritation and lacrymation. After that slow and deep breathing or dyspnea occur. Finally the animals convulse and die. Most of the lethality data are old. The best studies are those by Kruysse et al. (1970) in hamsters and Appelman et al. (1982) in rats, who found 4 hour LC50-values of 17,000 ppm and 13,300 ppm respectively. In an old multispecies study in mice, guinea pigs and rabbits death was seen already at 3297 ppm for about 80 minutes, which suggests that these species are more sensitive. The limitations of this study qua design and reporting, however, preclude firm conclusions on this point. Overall the studies by Kruysse et al. (1970) and by Appelman et al. (1982) provide the best available dose-response information on acetaldehyde lethality. Benchmark modeling based on the results of these studies indicates an LC_{05}-value of 14,466 ppm in hamsters with a corresponding lower 95% confidence limit of 10,640 ppm. In rats the LC_{05}-value was 7,925 ppm with a corresponding lower 95% confidence limit of 5,295 ppm. From other studies no reliable acute NOAEL for lethality is available but in a subacute inhalation study by Appelman et al. (1982) rats survived exposure to 2217 ppm for 6 hours per day for four weeks.

The data base on acute non-lethal inhalation toxicity is limited. The potential of acetaldehyde for inducing acute sensory irritation was studied in rats and mice with the RD_{50} test (determination of the concentration producing a 50% decrease in breathing-frequency), providing individual RD_{50}s ranging from 2932 to 4946 ppm (Cf. formaldehyde 3.3-31.7 ppm). For the use of RD_{50} studies see paragraph 4.2. An acute rat inhalation study by Stanek et al (2001) showed vasodilatation already at concentrations of ≥25 ppm but the toxicological significance of this effect is doubtful (it may represent a physiological protective response). The only other acute inhalation study is that by Cassee et al. (1996b) who observed no histological changes in the nasal epithelium after exposure or male rats to 750 or 1500 ppm for 6 hours. When exposure was for three days at the same concentrations slight histological changes were discernible in the nasal epithelium. In the subacute inhalation study in rats by Appelman et al. (1982) at the highest test concentration of 4975 ppm severe dyspnea and marked excitation occurred during the first 30 minutes of exposure; these effects subsided during the remainder of the exposure period (rats were exposed 6 hours/day). At the next lower test concentration of 2217 ppm these effects were not seen.

Histological damage of the nasal and respiratory epithelia was the most sensitive effect in inhalation studies of longer duration. Appelman et al (1982) observed concentration-related degeneration of nasal epithelium at all test concentrations in their subacute inhalation study in rats (lowest test concentration 401 ppm for 6 hours/day, 5 days week for 4 weeks) whereas in a semichronic inhalation study in hamsters (Kruysse et al. 1975) histological effects in nasal and respiratory epithelium were noted at 1340 and 4560 ppm, but not at 390 ppm. Degenerative changes in the olfactory nasal epithelium were the most sensitive effect in a chronic inhalation study with a LOAEL of 750 ppm (Woutersen et al 1986).

In genotoxicity assays acetaldehyde has shown clear clastogenic, mutagenic and aneugenic effects in vitro. In vivo data are of a limited nature. No studies with inhalation or oral exposure are available. Nevertheless the in vivo evidence that is available indicates the compound to have genotoxic potential in vivo (DECOS 1993; Health Canada 2000). Acetaldehyde's ability to produce DNA-protein cross links resembles that of formaldehyde and the nasal tumors both of these aldehydes induce, may well arise through a similar mechanism (Morris, 1997).

Acetaldehyde's carcinogenic potential was studied in hamsters and rats. In hamsters with a limited protocol a slight increase in respiratory tract tumors was observed whereas in rats a clearly positive response was seen in nasal tumors in both males and females after chronic inhalation. IARC

concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

IPCS (1995) and Health Canada (2000) have reviewed acetaldehyde toxicokinetics.

Acetaldehyde is an intermediary in the normal catabolism of deoxyribose phosphate and various amino acids. A quantitatively much more important source of acetaldehyde in the body, however, is its formation through the action of alcohol dehydrogenase on ingested ethanol.

Upon inhalation acetaldehyde is absorbed well. Egle (1970) determined acetaldehyde retention in eight volunteers after mouth and nose inhalation of low concentrations of 100 to 800 mg/m^3 for 1 to 4 minutes from a recording respirometer. Total retention varied between 45 and 70% independently of whether inhalation was through the nose or the mouth.

The greatest portion of inhaled acetaldehyde is retained at the site of contact, so the data indicate. Inhaled acetaldehyde is rapidly oxidized to acetate by aldehyde dehydrogenase in human nasal and lung epithelia. Alternatively the compound rapidly and irreversibly binds to free protein and non-protein sulfhydryl groups (cystein, glutathione) present in these epithelia. In the latter pathway hemimercaptal or thiazolidine intermediates are formed which end up eliminated in urine as thioethers and disulfides.

According to IPCS (1995) the conversion to acetic acid by aldehyde dehydrogenase constitutes the major biotransformation route for acetaldehyde. The acetate may enter into normal metabolism by the formation of acetyl-CoA, as is shown in the figure below.

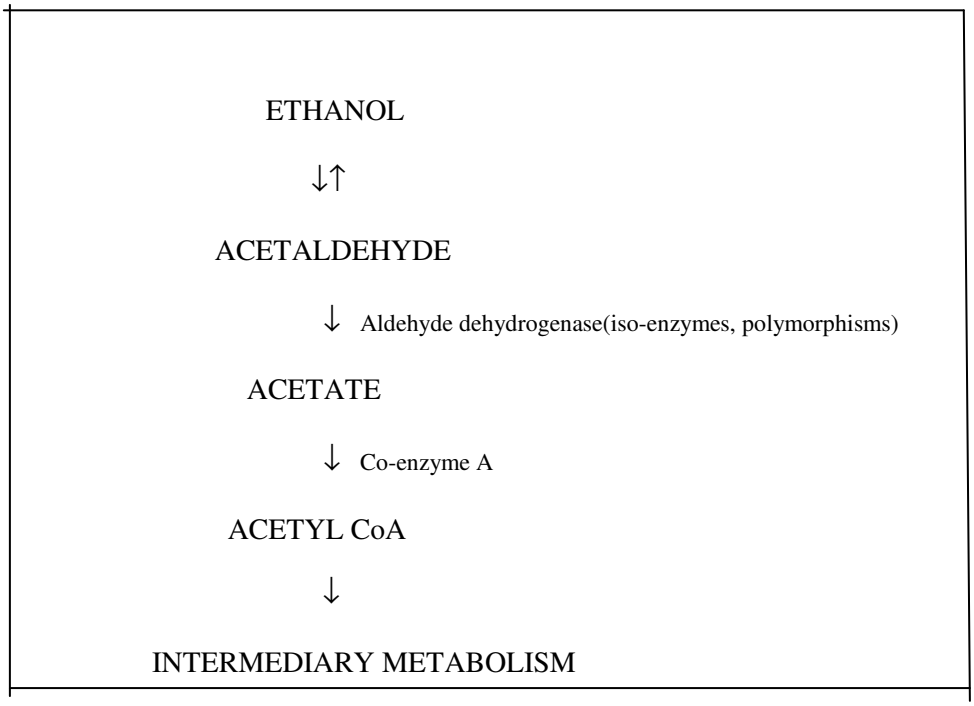

Figure: Major biotransformation route for acetaldehyde (From: IPCS, 1995)

4.2. Mechanism of Toxicity

Bronchoconstriction

The bronchoconstriction observed in aldehyde dehydrogenase-inactive asthmatics of oriental descent after inhalation exposure to acetaldehyde, was completely suppressed by treatment with histamine-blocker, which indicates that this effect is histamine-mediated (Myou et al. (1993). The same research group studied the involvement of tachykinins (airway sensory neuropeptides known to be linked to at least some asthmatic responses) in acetaldehyde-induced bronchoconstriction in guinea pigs. The results of this study suggest no role for tachykinins.

RD_{50} studies

The suitability of the sensory irritation test as proposed in the past by Alarie for AEGL-setting is questionable. Bos et al. (1992) evaluated this test for the assessment of Occupational Exposure Limits. Among others, the reproducibility, reliability and interpretation were discussed. It was concluded that there was an insufficient basis for the use in standard setting. As to the possible use of the RD_{50} in setting AEGL-values the main point of concern is that no relationship is found between the RD_{50} and other toxic effects like respiratory tract irritation, systemic effects, and mortality. These effects may occur at or below RD_{50} concentrations, e.g. the RD_{50}s for epichlorohydrin and chlorine are even lethal concentrations (Bos *et al* 1992, 2002). Therefore, the outcome of the sensory irritation test cannot be placed on a toxicity scale with increasing severity, and can thus for the moment not be directly linked with toxicity endpoints defined for AEGL-1, AEGL-2, or AEGL-3.

Nasal vasodilatation as the first sign of sensory irritation?

The known sensory irritant aldehyde acrolein produces an immediate nasal vasodilatory response not accompanied by a change in nasal airflow. This response, which for acrolein was seen at about 30% of the RD50, probably is triggered via the sensory nerves in the nose. Stanek et al. (2001) observed a similar response for acetaldehyde at concentrations of ≥25 ppm and for acetic acid at ≥130 ppm (which is at ≥0.7 and ≥12% of their RD_{50}s respectively). Vasodilatation, so the authors state, appears to be a common response to inspired irritants and may serve as useful biomarker for sensory nerve activation in rats. The physiological significance of the vasodilatory response however, is unknown. They point out that it may reflect a protective response because increased blood flow may serve to remove irritating vapors from the nasal mucosa. As to the mechanism of the action of inhaled acetaldehyde on nasal sensory nerves, the partial inhibition of the response after treatment with cyanamide (inhibitor of aldehyde dehydrogenase) at 200 ppm acetaldehyde, indicates the response in part is mediated by acetic acid formation. Thus, for this effect the conversion of acetaldehyde to acetic acid is not detoxifying.

Nasal cytotoxicity

A consistent finding in the animal toxicity studies is that the nasal cavity is the most sensitive target for acetaldehyde toxicity after inhalation. Toxic responses were observed in both of the principal tissue types of the nose, the respiratory and the olfactory mucosa. The latter tissue type is the most sensitive. A full explanation of this heightened sensitivity is not available but there is evidence that it is linked to the lower aldehyde dehydrogenase activity in the olfactory epithelium (compared to the respiratory epithelium). Acetaldehyde dehydrogenase converts acetaldehyde to acetic acid, which is of lower cytotoxic and DNA-reactive potential, so the reasoning goes. However, as Morris (1997) points out, the olfactory epithelium is more sensitive to acids than is the respiratory epithelium and the production of acetic acid by aldehyde dehydrogenase may play a pivotal role in the induction of acetaldehyde-induced olfactory damage, despite the fact that in the respiratory epithelium aldehyde dehydrogenase activity is higher and more acetic acid is produced.

Stanek and Morris (1999) studied the dose dependence of acetaldehyde detoxification by aldehyde dehydrogenase in nasal tissues in rats, observing that at concentrations of 300 ppm or higher

(single exposure for 6 hours) the dose delivered to the nasal tissue equals or exceeds the capacity of the enzyme. This capacity limitation they regard as the explanation of their previously observed higher efficiency of acetaldehyde uptake in rat nasal tissue at 10 ppm compared to 300 or 1500 ppm. Stanek and Morris (1999) also determined DNA-protein cross links in the nasal respiratory after a single exposure to 1500 ppm for 6 hours, a concentration clearly in excess of the aldehyde dehydrogenase metabolic capacity in this tissue, but failed to find an increase. Thus they could not reproduce the finding by Lam et al. (1986) who detected increased crosslink formation in the same tissue after exposure to 1000 ppm for 6 hours.

Nasal tumor formation

The mechanism of tumor formation by acetaldehyde is discussed in Health Canada (2000). The pattern of observed nasal tissue cytotoxicity for acetaldehyde and its potency to form stable adducts with DNA and proteins resembles that for other aldehydes such as formaldehyde, which are also carcinogenic in the respiratory system. Although the exact mechanism is unknown, the tumor formation by these aldehydes is considered to be a function of both regenerative cell proliferation and DNA-protein cross-linking at the site of contact. However, the limited data for acetaldehyde indicate that the pattern of DNA-protein cross-linking and proliferative response for this compound is different from that for other carcinogenic aldehydes. Health Canada cites Cassee et al. (1996b) who failed to find proliferation at concentrations in excess of those at which tumors are known to develop, while at these concentrations they did observe increased formation of DNA-protein cross-links. This is in contrast to formaldehyde for which the two endpoints were always increased simultaneously. The conclusion was that for acetaldehyde it cannot be ruled out that genotoxicity plays a role in tumor development. DECOS (1993) and Morris (1997) had previously drawn a similar conclusion.

4.3. Structure Activity Relationships

Acetaldehyde shares its irritative properties with other aldehydes including formaldehyde and acrolein. Compared to the latter two however, acetaldehyde has a much lower potency for this effect. Bos et al. (1992) in their comprehensive review of the sensory irritation test that determines the 50% decrease in respiratory rate in rodents (RD_{50}), present mouse RD_{50} values for formaldehyde of 3.2-5.3 ppm, for acrolein of 1.7-2.9 ppm and for acetaldehyde of 2845-4946 ppm.

Also in its ability to form DNA-DNA and DNA-protein cross links in the respiratory tract acetaldehyde resembles other aldehydes. However, as explained in paragraph 4.2, acetaldehyde may differ from other aldehydes in the pattern of cross linking that it induces and/or in the concomitant proliferative response that is also needed for tumor development.

4.4. Other relevant information

4.4.1. Species variability

No relevant data were identified.

4.4.2. Susceptible populations

As discussed in paragraph 2.2.2, populations of Oriental descent exhibit aldehyde dehydrogenase-2 polymorphisms, with about 50% of the individuals having inactive genotypes compared to almost zero percent in white European populations. Consumption of ethanol by those who lack aldehyde dehydrogenase leads to elevated concentrations of acetaldehyde in the blood, which in asthmatic subjects in this group, may lead to bronchoconstriction. Asthmatics who lack aldehyde dehydrogenase are a susceptible subgroup for the toxic action of *inhaled* acetaldehyde also, as was

shown by Myou et al. (1993) and Fujimura et al. (1999) in their volunteer studies in Japanese volunteers. Later studies in Caucasian subjects by Prieto et al. (2000; 2002b) however provide evidence that all asthmatics, even those who do possess normal aldehyde dehydrogenase activity, are a susceptible subgroup for bronchoconstriction produced by inhaled acetaldehyde. The Prieto et al. (2002b) study also showed higher airway responsiveness (compared to normal subjects) of persons suffering from allergic rhinitis. The picture that emerges is that asthmatics are a sensitive subgroup for the bronchoconstrictive effect of inhaled acetaldehyde with the highest susceptibility within this group for those asthmatics that are lacking in aldehyde dehydrogenase activity. Patients suffering from allergic rhinitis are also more sensitive than healthy people but are probably less than are asthmatics are.

4.4.3. Irritation and Sensitization

Industrial experience shows acetaldehyde to be a irritant of skin, eyes and respiratory tract (ACGIH, 1991). The effect on the respiratory tract has been studied extensively in animals. For skin and eyes, however, only a few unpublished rabbit studies are available, the results of which reportedly show a low potential for induction of skin irritation and a high potential for induction of eye irritation (IUCLID, 2000).

Information on sensitization is very limited. In two human patch studies cross-sensitization to acetaldehyde was found in subjects with demonstrated allergy towards ethanol (applied dermally or orally) (Stotts et al. 1977; Wilkin and Fortner, 1985). Shmunes and Kempton (1980) report the case of a female textile worker who developed allergic contact dermatitis towards dimethoxane and showed sensitization when patch tested with acetaldehyde (a hydrolysis product of dimethoxane). No animal studies are available for this endpoint.

4.4.4. Concentration-Exposure Duration Relationship

The results of the animal lethality studies by Kruysse et al. (1970) and Appelman et al. (1982) in hamsters and rats respectively, demonstrate a steep dose response curve for this endpoint in hamsters with LC_{05} and LC_{95}- values of 14,466 ppm and 21,122 ppm respectively (derived using US-EPA Benchmark Dose Software version 1.3.1). For rats the curve was less steep with LC_{05} and LC_{95}- values of 7,925 ppm and 22,682 ppm respectively (again derived using US-EPA Benchmark Dose Software version 1.3.1).

For sensory irritation the dose response relation seems to be less steep. Babiuk et al (1985) determined the decrease of respiratory rate in rats as a measure of sensory irritation. Based on their dose response curve the RD95 was 2,1130 ppm and the RD05 was 424 ppm, thus showing a considerably wider margin between these effect levels for this endpoint that for lethality.

4.4.5. Concurrent Exposure Issues

Pretreatment with formaldehyde can induce remarkable tolerance to sensory irritation by acetaldehyde, so Babiuk et al. (1985) showed in their RD50 experiment in rats.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of human data relevant to AEGL-1

The relevant human data for acetaldehyde are limited to two old volunteer studies by Silverman et al. (1946) and Sim and Pattle (1957) respectively. In the Silverman study eye irritation was observed at a nominal concentration of 50 ppm for 15 minutes in the majority of the twelve volunteers. The very brief report of this study states that several subjects objected strenuously to working in 25 ppm but it does not make clear the nature of the effects they experienced. In the other study (Sim and Pattle, 1957) mild irritation of the respiratory tract was the only effect reported after inhalation by fourteen subjects of acetaldehyde at a measured concentration of 134 ppm for 30 minutes. Whether or not eye irritation occurred with acetaldehyde was not reported, but eye irritation was reported for a number of other chemicals tested in this reference. More recent volunteer studies carried out to examine bronchoconstriction after inhalation of acetaldehyde aerosols by asthmatics, had exposure duration of only two minutes. In all groups considerable interindividual variation between asthmatics was noted. Geometric mean PC_{20}-values (acetaldehyde concentration in air that produced a 20% fall in FEV_1) as determined in these studies in asthmatics, ranged from 295 ppm to 700 ppm (estimated concentrations). Interindividual variation in PC_{20}-values was in excess of this range. It should be noted that these studies were done using mouth breathing, which by-passes the scrubbing effect of the nose and delivers more acetaldehyde to the bronchioles. As stated above, the exposure period in the recent asthmatics studies was only 2-4 minutes which makes them unsuited for AEGL derivation. Besides, the exposure to aerosols of acetaldehyde is considered not appropriate for AEGL development.

The lowest effect level for acetaldehyde is 50 ppm for 15 minutes from the study by Silverman et al. (1946). At this level significant eye irritation occurred in the majority of test subjects. However, the exposure methods were poorly described and actual concentrations were not determined. In the other volunteer study by Sim and Pattle the actual exposure concentration was determined, and so the quality of this study is considered superior to that of Silverman et al.. Sim and Pattle noted no eye irritation after 134 ppm for 30 minutes, but they did observe mild respiratory tract irritation at their only test concentration of 134 ppm.

5.2. Summary of animal data relevant to AEGL-1

In animal studies acetaldehyde has been shown to be a sensory irritant. Its potency, as expressed in the RD_{50} (the concentration producing a 50% decrease in breathing-frequency), however is considerably lower than that for aldehydes such as formaldehyde or acrolein. The RD_{50}s reported for acetaldehyde are about two orders of magnitude higher than those for formaldehyde. An acute animal NOAEL or LOAEL for sensory irritation by acetaldehyde is lacking. In the subacute rat inhalation study by Appelman et al. (1982) no clinical signs were noted at test concentrations at or below 2217 ppm (exposure for 6 hours/day).

In many studies it has been shown that acetaldehyde adversely affects the nasal and respiratory epithelium. Cassee et al. (1996b) found no effect on nasal epithelium histology of male rats after single inhalation of 750 or 1500 ppm acetaldehyde for 6 hours. The same treatment given for three days produced only slight effects at both test concentrations. In an earlier subacute study by Appelman et al. (1982) concentration-related degeneration of nasal epithelium was observed at test concentration of ≥401 ppm administered for 6 hours/day, 5 days week for 4 weeks. In a semichronic inhalation study in hamsters (Kruysse et al. 1975) severe histological effects in nasal and respiratory epithelium were noted at 4560 ppm with a slight effect at 1340 ppm, the next lower concentration, and none at 390 ppm, the lowest test concentration.

5.3. Derivation of AEGL-1

In the study by Sim and Pattle (1957) mild respiratory irritation was observed at a measured concentration of 134 ppm for 30 minutes. Subjects did not report eye irritation, like in the study of Silverman et al (1946), but in the latter study only nominal concentrations were given. The concentrations of 134 ppm for 30 minutes is chosen as the point of departure for AEGL-1 derivation.

An uncertainty factor of 3 is applied to this concentration to account for intraspecies variability. A higher factor is not needed because little variation is expected for direct eye irritation effects. In addition, such effects generally do not vary greatly over time. Therefore no time scaling is applied and the resulting value of 45 ppm is flatlined across the AEGL time points.

This leads to the following proposed AEGL-1 values:

TABLE 5. AEGL-1 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of human data relevant to AEGL-2

Handbooks indicate that inhalation of acetaldehyde by humans may lead to coughing, irritation of nose, throat and eyes, persistent lacrymation, corneal epithelial damage, photophobia, foreign body sensation, pulmonary edema and anesthesia. The dose-response for these effects however is unknown. Thus no usable human data for AEGL-2 derivation are available.

Silverman et al. (1946) and Sim and Pattle (1957) observed sub AEGL-2 effects in the two volunteer studies respectively. The first research group report eye irritation at nominal 50 ppm for 15 minutes and bloodshot eyes and reddened eyelids at nominal 200 ppm for 15 minutes. Actual concentrations were not determined in this study. The second research group observed mild irritation of the upper respiratory tract but no eye irritation at a measured concentrations of 134 ppm for 30 minutes.

6.2. Summary of animal data relevant to AEGL-2

There is a paucity of relevant data. Histological damage to nasal and respiratory epithelia is an effect that was consistently seen after acetaldehyde inhalation in many experiments. Upon single inhalation for 6 hours Cassee et al (1996b) observed no effects in male rats for this endpoint at 750 and 1500 ppm. Repeating this treatment for three days led to slight epithelial damage. When rats were exposed for several weeks, concentration-related degeneration of nasal epithelium at all test concentrations (lowest test concentration 401 ppm for 6 hours/day, 5 days week for 4 weeks; Appelman et al. 1982). This effect, particularly in its mild form, is reversible, and should therefore be considered as a sub-AEGL-2 effect.

The RD_{50} studies in animals are considered not useful for AEGL-development (see paragraph 4.2).

6.3. Derivation of AEGL-2

In absence of usable human data animal data must be used for deriving the AEGL-2. In the subacute rat study by Appelman et al. (1982) degeneration of the nasal epithelium was observed after exposure to 410 ppm, 6 hours/day, 5 days/week for 4 weeks. This effect was not observed after a single exposure to 750 or 1500 ppm for 6 hours, although some nasal changes were observed following exposure to 750 and 1500 ppm on 3 consecutive days (6-h/day; Cassee et al. 1996b). The concentration of 1500 ppm for 6 hours is taken as the point of departure for AEGL-2, this being the no effect level for sub-AEGL-2 damage to the nasal epithelium. The different studies used different exposure durations, and the results indicate that time is an important factor for this effect. Default time-scaling was applied using $C^n xt = k$ with default values n=1 for extrapolation to longer time periods and n=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-2 10-minute value is the same as the AEGL-2 30-minute value.

A total uncertainty factor of 10 is applied, consisting of an interspecies factor of 1 and an intraspecies factor of 10. The interspecies factor of 1 was chosen because the AEGL-2 was based on the no effect level for a sub-AEGL-2 effect. The intraspecies factor of 10 was chosen to account for variability in human susceptibility to acetaldehyde. This variability is illustrated in the 2-minute exposure studies in healthy and asthmatic human volunteers, where the bronchoconstrictive response in asthmatics was measured (see e.g. Prieto et al. 2002b).

Thus the following AEGL-2 values were derived:

TABLE 6. AEGL-2 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
340 ppm (620 mg/m^3)	340 ppm (620 mg/m^3)	270 ppm (490 mg/m^3)	170 ppm (310 mg/m^3)	110 ppm (200 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of human data relevant to AEGL-3

No relevant human data are available.

7.2. Summary of animal data relevant to AEGL-3

Most of the animal lethality data are old. The 4-hour LC_{50}-studies by Kruysse et al. (1970) and Appelman et al. (1982), in hamsters and rats, respectively, provide the most reliable dose-response information. LC_{50}-values found by these investigators were 17,000 ppm (hamster) and 13,300 ppm (rat). In a limited and poorly reported multispecies study by Salem and Cullumbine (1960) a lower concentration of 3296 ppm was lethal to mice, guinea pigs and rabbits after an average exposure time of about 80 minutes which indicates that these species may be more sensitive to acetaldehyde lethality than are rats and hamsters. Nevertheless the rat and hamster studies are used because they provide superior dose-response information, obtained in a validated standard assay of reasonably recent date and from reputable test laboratories. This dose-response information is suited for modeling, the result of which can

then be extrapolated across species using an appropriate uncertainty factor (thus taking into account the possible higher sensitivity of other species).

Benchmark log-probit modeling based on the results of the Kruysse et al. (1970) study indicated a BMD_{05} of 14,466 ppm and a $BMDL_{05}$ of 10,640 ppm for hamsters.

Benchmark log-probit modeling was also performed on the results of the Appelman et al. (1982) study in rats. The analysis was performed with all available data, which included the 4-hour lethality data and the sub-acute non-lethal doses as provided in the same reference. This was considered appropriate because the combined data give better information on the dose-response curve compared to the 4-hour data alone, in particular in the lower concentration range, thus providing for a better estimate of the $BMDL_{05}$. The combination of data was also considered justified because the same rat strain was used by the same group of investigators in the same study under similar conditions. Using benchmark log-probit modeling on the combined data, the calculated BMD_{05} is 7,925 ppm and the $BMDL_{05}$ is 5,295 ppm. From these values the most appropriate point of departure for deriving the AEGL-3 was selected.

7.3. Derivation of AEGL-3

In absence of usable human data, AEGL-3 derivation is based on animal data. As explained in the previous paragraph, the studies by Kruysse et al. (1970) and Appelman et al. (1982) in hamsters and rats respectively, provide the most reliable basis for the AEGL-3. Rats being the more sensitive species in these studies, they are the preferred species. Using the Benchmark software of the US-EPA log-probit modeling was done on the results from the Appelman et al. (1982) acute and subacute rat studies. This led to a $BMDL_{05}$ of 5,295 ppm for a 4-hour exposure. To this level a total uncertainty factor of 10 is applied, consisting of a factor of 3 for interspecies extrapolation and a factor of 3 for sensitive human subpopulations. Larger factors are considered not necessary given the typical irritative aldehyde toxic action by acetaldehyde.

The value of 5,295 ppm for 4 hours was extrapolated across time periods using $C^n xt = k$ with default values n=1 for extrapolation to longer time periods and n=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is the same as the AEGL-3 30-minute value. The following AEGL-3 values were derived:

TABLE 7. AEGL-3 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
1100 ppm (1900 mg/m^3)	1100 ppm (1900 mg/m^3)	840 ppm (1500 mg/m^3)	530 ppm (950 mg/m^3)	260 ppm (480 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL values and toxicity endpoints

TABLE 8. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)
AEGL-2 (Disabling)	340 ppm (620 mg/m^3)	340 ppm (620 mg/m^3)	270 ppm (490 mg/m^3)	170 ppm (310 mg/m^3)	110 ppm (200 mg/m^3)
AEGL-3 (Lethal)	1100 ppm (1900 mg/m^3)	1100 ppm (1900 mg/m^3)	840 ppm (1500 mg/m^3)	530 ppm (950 mg/m^3)	260 ppm (480 mg/m^3)

8.2. Comparison with other standards and guidelines

TABLE 9. Extant Standards and Guidelines for Acetaldehyde

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)
AEGL-2	340 ppm (620 mg/m^3)	340 ppm (620 mg/m^3)	270 ppm (490 mg/m^3)	170 ppm (310 mg/m^3)	110 ppm (200 mg/m^3)
AEGL-3	1100 ppm (1900 mg/m^3)	1100 ppm (1900 mg/m^3)	840 ppm (1500 mg/m^3)	530 ppm (950 mg/m^3)	260 ppm (480 mg/m^3)
ERPG-1 (AIHA)[a]			10 ppm		
ERPG-2 (AIHA)			200 ppm		
ERPG-3 (AIHA)			1000 ppm		
EEGL (NRC)[b]	None established				
SMAC[c]			10 ppm		6 ppm (24 hours)
PEL-TWA (OSHA)[d]					200 ppm
PEL-STEL (OSHA)e	None established ?				

IDLH (NIOSH)[f]	2000 ppm				
REL-TWA (NIOSH)[g]	None established because of carcinogenicity				
REL-STEL (NIOSH)[h]	None established				
TLV-TWA (ACGIH)[i]	None established				100 ppm
TLV-STEL (ACGIH)[j]	25 ppm (15 minutes ceiling value)				
MAK (Germany)[k]					50 ppm
MAK Peak Limit (Germany)[l]	50 ppm (15 minutes)				
MAC (The Netherlands)[m]					100 ppm

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association**
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual=s ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b] **EEGL (Emergency Exposure Guidance Levels, National Research Council**
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[C] **SMAC (Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants)** provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The one-hour SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposure may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies. SMACs are derived for exposure periods of 1 hour, 24 hours, 7 days and 180 days.

[d] **OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[e] **OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** is defined analogously to the ACGIH-TLV-STEL.

[f] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[g] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** is defined analogously to the ACGIH-TLV-TWA.

[h] **NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** is defined analogous to the ACGIH TLV-STEL.

[i] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[h] **ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[k] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** is defined analogously to the ACGIH-TLV-TWA.

[l] **MAK Spitzenbegrenzung (Peak Limit [give category])** constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[m] **MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** is defined analogously to the ACGIH-TLV-TWA.

8.3. Data quality and research needs

The data for AEGL-3 are sufficient and of good quality. The data for AEGL-1 and AEGL-2 are scarce and limitedly reported (AEGL-1). Nevertheless, the whole database was considered to give sufficient information to have confidence in the proposed AEGL values.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key study:	Sim and Pattle 1957
Toxicity Endpoint:	mild respiratory irritation and no eye irritation in humans when exposed to 134 ppm for 30 minutes
Time scaling:	no
Uncertainty factors:	3 for intraspecies
Calculations:	134 ppm / 3 = 45 ppm
10-minute AEGL-1	45 ppm (81 mg/m^3)
30-minute AEGL-1	45 ppm (81 mg/m^3)
1-hour AEGL-1	45 ppm (81 mg/m^3)
4-hour AEGL-1	45 ppm (81 mg/m^3)
8-hour AEGL-1	45 ppm (81 mg/m^3)

Derivation of AEGL-2

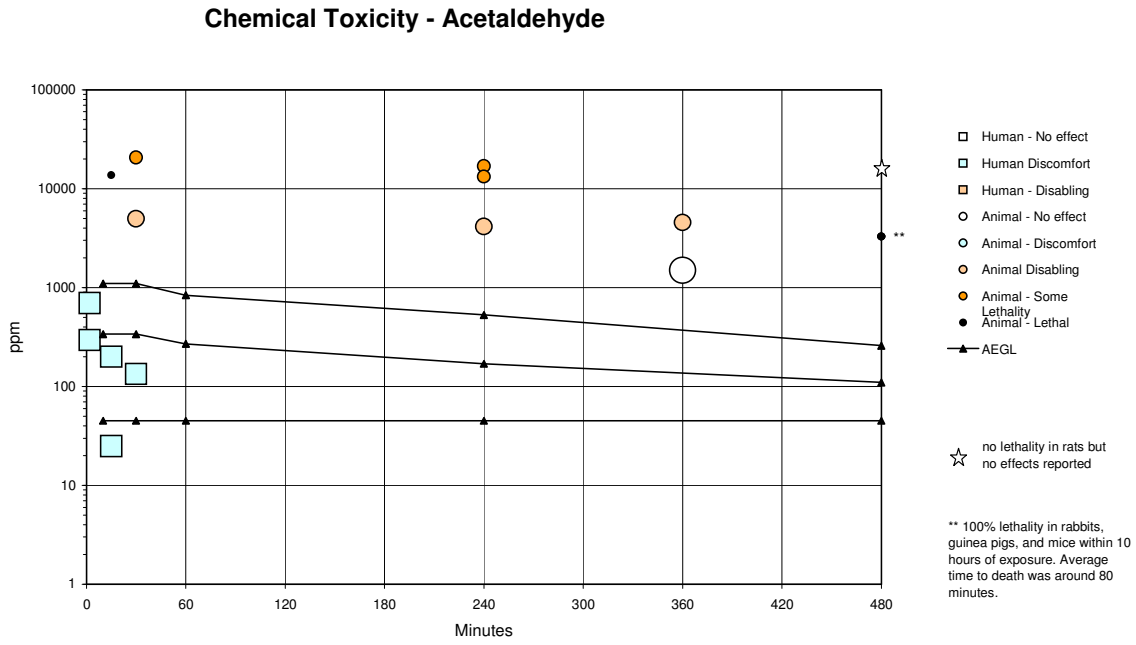
Key study:	Cassee et al. 1996b
Toxicity Endpoint:	Slight histopathological changes to the nasal epithelium in rats. 1500 ppm for 6 hours was the no effect level for this sub-AEGL effect.
Time scaling:	$C^n * t = k$ with n=1 for longer time points and n=3 for shorter time points (flatlined from 30-min to 10-min)
Uncertainty factors:	1 for interspecies and 10 for intraspecies
Calculations:	1500 / 10 = 150 ppm (6 hours)
10-minute AEGL-2	340 ppm (620 mg/m^3)
30-minute AEGL-2	340 ppm (620 mg/m^3)
1-hour AEGL-2	270 ppm (490 mg/m^3)
4-hour AEGL-2	170 ppm (310 mg/m^3)
8-hour AEGL-2	110 ppm (200 mg/m^3)

Derivation of AEGL-3

Key study:	Appelman *et al.* 1982
Toxicity Endpoint:	lethality in rats observed following acute and subacute exposure, revealing a 4-h $BMDL_{05}$ of 5,295 ppm
Time scaling:	$C^n * t = k$ with n=1 for longer time points and n=3 for shorter time points (flatlined from 30-min to 10-min)
Uncertainty factors:	3 for interspecies and 3 for intraspecies (total UF 10)
Calculations:	5,295/10=529.5 ppm for 4 hours
10-minute AEGL-3	1100 ppm (1900 mg/m^3)
30-minute AEGL-3	1100 ppm (1900 mg/m^3)
1-hour AEGL-3	840 ppm (1500 mg/m^3)
4-hour AEGL-3	530 ppm (950 mg/m^3)
8-hour AEGL-3	260 ppm (480 mg/m^3)

APPENDIX B: Category plot

1


Chemical Toxicity - Acetaldehyde
100000
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
Minutes
**
Human - No effect
Human Discomfort
Human - Disabling
Animal - No effect
Animal - Discomfort
Animal Disabling
Animal - Some Lethality
Animal - Lethal
AEGL
no lethality in rats but no effects reported
** 100% lethality in rabbits, guinea pigs, and mice within 10 hours of exposure. Average time to death was around 80 minutes.

2

APPENDIX C: Carcinogenicity Assessment

US-EPA (1991) provided a quantitative cancer risk estimation for inhalation of acetaldehyde based on incidences of nasal tumors as observed in the chronic rat study of Woutersen et al. (1986). Using the Linearized Multistage model a unit risk was derived of $2.2x10^{-6}$ per microgram/m^3 of lifetime exposure.

To convert the unit risk to a level of acetaldehyde that would cause a theoretical excess cancer risk of 10^{-4}:

Risk of $1 \times 10^{-4} = (1 \times 10^{-4}) / 2.2 \times 10^{-6} = 0.045$ mg/m^3 (virtually safe dose)

To convert a 70-years exposure to an 8-hours exposure:

8-h exposure = virtually safe dose x 25,600 days x (24h/8h)
= (0.045 mg/m^3) x 25,600 x (24h/8h)
= 3491 mg/m^3 (rounded value)

To account for the uncertainty regarding the variability in the stage of the cancer process at which acetaldehyde or its metabolites may act, a multistage factor of 6 is applied according to the procedure described in the AEGL Standing Operating Procedures.

(3491 mg/m^3)/6 = 581 mg/m^3 (326 ppm)

Therefore, based on the potential carcinogenicity of acetaldehyde, a conservative acceptable 8-hours exposure would be 581 mg/m^3 (326 ppm). For shorter exposures the acceptable exposures increase proportionally in a linear fashion:

8-h exposure : 581 mg/m^3 (326 ppm)
4-h : 1162 mg/m^3 (654 ppm)
1-h : 4648 mg/m^3 (2616 ppm)
0.5 h : 9296 mg/m^3 (5232 ppm)

For deriving the corresponding 10^{-5} and 10^{-6} cancer risks the above figures must be divided by 10 and 100 respectively. This gives the following set of cancer risk values:

Exposure (hours)	**10^{-4} cancer risk**	**10^{-5} cancer risk**	**10^{-6} cancer risk**
8	581 mg/m^3 (326 ppm)	58.1 mg/m^3 (32.6 ppm)	5.81 mg/m^3 (3.26 ppm)
4	1162 mg/m^3 (654 ppm)	116.2 mg/m^3 (65.4 ppm)	11.62 mg/m^3 (6.54 ppm)
1	4648 mg/m^3 (2616 ppm)	464.8 mg/m^3 (261.6 ppm)	46.48 mg/m^3 (26.16 ppm)
0.5	9296 mg/m^3 (5232 ppm)	929.6 mg/m^3 (523.2 ppm)	92.96 mg/m^3 (52.32 ppm)

Comparing these values with the AEGL-2 and AEGL-3 values shows that all the calculated acceptable exposures that would result in a $1:10^{-4}$ cancer risk are above the AEGL-2 and –3 values.

APPENDIX D: Derivation Summary for Acetaldehyde AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR ACETALDEHYDE (CAS Reg. No. 75-07-0) DERIVATION SUMMARY

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)	45 ppm (81 mg/m^3)

Key Reference: Sim and Pattle 1957

Test Species/Strain/Number: human, 14 males

Exposure Route/Concentrations/Durations: inhalation of 134 ppm for 30 minutes

Effects: Slight respiratory irritation, no eye irritation

Endpoint/Concentration/Rationale: 134 ppm gave only slight respiratory irritation. It was also the no effect level for eye irritation (which was observed in another study).

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 (study in humans)
Intraspecies: 3 (not much variation expected for direct irritating effects)

Modifying Factor: n.a.

Animal to Human Dosimetric Adjustment: n.a.

Time Scaling: no time scaling: irritation effects generally do not vary greatly over time.

Data Adequacy: not optimal. Recent studies were of too short duration. Studies with relevant exposure duration were old and poorly reported.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
340 ppm (620 mg/m^3)	340 ppm (620 mg/m^3)	270 ppm (490 mg/m^3)	170 ppm (310 mg/m^3)	110 ppm (200 mg/m^3)
Key Reference: Cassee 1996b				
Test Species/Strain/Number: Rat, Wistar, 5 males per group				
Exposure Route/Concentrations/Durations: inhalation, 750 or 1500 ppm, 6-h/day, for 1 or 3 days				
Effects: 750-1500 ppm for 3 days: few (750 ppm) to moderate (1500 ppm) number of necrotic cells in nasal epithelium 750-1500 ppm for 1 day: no histopathological changes to nasal epithelium				
Endpoint/Concentration/Rationale: no effect level for changes of nasal epithelium at 1500 ppm for 6 hours				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 1 (considering the no effect level for a sub-AEGL effect) Intraspecies: 10 (considering the variation within humans, in particular the sensitivity to bronchoconstriction observed in healthy and asthmatic people)				
Modifying Factor: n.a.				
Animal to Human Dosimetric Adjustment: n.a.				
Time Scaling: $C^n * t = k$ with n=1 for longer time points and n=3 for shorter time points (flatlined from 30-min to 10-min)				
Data Adequacy: poor: acute AEGL-2 effects were not observed in humans and animals.				

1

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1100 ppm (1900 mg/m^3)	1100 ppm (1900 mg/m^3)	840 ppm (1500 mg/m^3)	530 ppm (950 mg/m^3)	260 ppm (480 mg/m^3)

Key Reference: Appelman *et al.* 1982

Test Species/Strain/Number: Rat, Wistar, 5-10 males and 5-10 females per group

Exposure Route/Concentrations/Durations: inhalation, 0, 401, 941, 2217, or 4975 ppm, 6-h/day, 28 days (n=20/group), and 10436, 12673, 15683, or 16801 ppm, 4-h (n=10/group). Acute and subacute data were combined.

Effects:

	lethality
0 ppm	0/20
401 ppm	0/20
941 ppm	0/20
2217 ppm	0/20
4975 ppm	0/20
10436 ppm	2/10
12637 ppm	5/10
15683 ppm	6/10
16801 ppm	8/10

Endpoint/Concentration/Rationale: lethality, $BMDL_{05}$=5295 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Larger factors are considered not necessary given the typical irritative aldehyde toxic action by acetaldehyde and because larger factors would lead to AEGL-3 values equal to AEGL-2 values.

Modifying Factor: n.a.

Animal to Human Dosimetric Adjustment: n.a.

Time Scaling: $C^n * t = k$ with n=1 for longer time points and n=3 for shorter time points (flatlined from 30-min to 10-min)

Data Adequacy: good

2

APPENDIX E: Derivation of level of distinct odor awareness

For acetaldehyde Nagata (2002) reports an odor threshold of 0.0015 ppm (0.00275 mg/m^3). This value was obtained using the Japanese Triangle Method which has been shown to produce results that agree very well with the standard method CEN13725. The same Japanese source reports an odor threshold of 0.038 ppm for n-butanol. The latter value is very close to the European Reference Odor Mass for n-butanol of 0.040 ppm.

The value reported by Nagata (2002) represents a Level 1 odor threshold as defined in the AEGL document "Guidance for the Use of Odor in the Derivation of AEGL-1".

The standardized odor threshold for acetaldehyde ($C_{0, stand}$) is equal to:

0.0015 * 0.040/0.038 = 0.0018 ppm

For acetaldehyde a Fechner-Weber coefficient for odor intensity (K_w) is known of 1.01 (Van Doorn et al., 2001). The default peak-to-mean-ratio is $10^{0.48}$.

The Level of Distinct Odor Awareness (LOA) for acetaldehyde can now be calculated according to:

LOA = 0.0018 ppm x $10^{(3 / 1.01)}$ / $10^{0.48}$ = 0.0018 ppm x $10^{2.49}$ = 0.56 ppm