

Acetaldehyde

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Citation for most recent IARC review:

IARC Monograph 71, 1999

Current evaluation

Conclusion from the previous Monograph:

Acetaldehyde is *possibly carcinogenic to humans (Group 2B)* because there is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde, and there is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Exposure and biomonitoring

Acetaldehyde is primarily used as an intermediate in the manufacturing of acetic acid, flavorings, aniline dyes, plastics and synthetic rubber, in some fuel compounds and in the manufacture of numerous other products (Muttray et al., 2009). Acetaldehyde is also a ubiquitous indoor and outdoor air pollutant. Sources of acetaldehyde are industrial burning processes, traffic emissions or emissions emerging from the combustion of wood. It is also a component of tobacco smoke. Acetaldehyde is also an endogenous metabolite produced from ethanol. During alcohol consumption, acetaldehyde is formed in the digestive system by microbes in normal gut and flora. Ethanol oxidation also occurs, to a limited extent, in nearby tissues. As ethanol is distributed to the aqueous phase of the human body, it is metabolized continuously to acetaldehyde as long as it remains in the blood and saliva, leading to its accumulation in the saliva and intestinal contents during and after the consumption of alcohol (Lachenmeier et al., 2009a).

Lachenmeier and Sohnius (2008) analyzed and evaluated a large sample of different alcoholic beverages. Beer (9 ± 7 mg/l, range 0–63 mg/l) had significantly lower acetaldehyde contents than wine (34 ± 34 mg/l, range 0–211 mg/l), or spirits (66 ± 101 mg/l, range 0–1159 mg/l). The highest acetaldehyde concentrations were generally found in fortified wines (118 ± 120 mg/l, range 12–800 mg/l). Foods and beverages produced or preserved by fermentation may contain small amounts of ethanol and mutagenic (>100 μ M) concentrations of acetaldehyde. These include dairy products (i.e. yogurts), fermented soy products (e.g., soy sauces), tofu products, fermented vegetables (e.g., Chinese pickles and kimchi), vinegar and homemade beers. Many fruits, such as apples, may have their own metabolic pathways for acetaldehyde production. In addition, acetaldehyde is used widely as a food additive and aroma agent (Salaspuro 2009a).

Occupational exposure

Occupational exposure to acetaldehyde may occur by inhalation and skin exposure at workplaces where this compound is produced or used. Acetaldehyde has also been detected in cutting fluids. It is also one of the major aldehyde components in tobacco smoke (Muttray et al., 2009). The OSHA Permissible Exposure Limit

In an investigation to evaluate environmental tobacco smoke exposure among casino dealers in three U.S. casinos, NIOSH (2009a) found that the levels of acetaldehyde in full-shift personal breathing zone ranged from 4.8 to 17.0 $\mu\text{g}/\text{m}^3$. For all three casinos combined, the geometric mean for personal breathing zone was 10.2 $\mu\text{g}/\text{m}^3$. The area air samples ranged in concentration from below the minimum detectable concentration to 20 $\mu\text{g}/\text{m}^3$. For all three casinos, the geometric mean for area acetaldehyde was 11.0 $\mu\text{g}/\text{m}^3$.

Three recent studies have reported acetaldehyde air concentrations in facilities that produce and use flavorings. In a facility that manufactures flavorings, modified dairy products and bacterial additives, NIOSH (2007) reported mean, full-shift time-weighted average (TWA) acetaldehyde air concentrations of 0.14 ppm in the powder production room, 0.07 ppm in the liquid production room, and 0.07 ppm in the pre-production corridor. A task-based acetaldehyde air concentration of 0.19 ppm was measured during pouring and mixing of ingredients for a fruit flavor in the liquid production room. In a follow-up visit, mean full-shift TWA acetaldehyde air concentrations were 0.44 ppm in the spray-drying room, 0.343 ppm in the powder production room, 0.273 ppm in the liquid production room, and 0.029 ppm in the pre-production corridor. The highest task-based acetaldehyde air concentration (4.02 ppm) was measured during packaging of a powdered dairy-flavored product in the powder production room.

In a small popcorn popping plant, NIOSH (2009b) reported that acetaldehyde concentrations in air were less than the detectable (0.09 ppm) or quantifiable (0.15 ppm) concentrations.

In a flavoring manufacturing plant in The Netherlands, control measures taken to enclose the process, led to a reduction in air concentrations from 7.6 to 0.7 mg/m^3 (geometric mean). Personal task-based sampling among process operators ranged from 0.2 to 14 mg/m^3 acetaldehyde (van Rooy et al., 2007).

Environmental exposures

Lachenmeier et al. (2009a) estimated exposure to acetaldehyde due to alcoholic beverage consumption, based on products from the EU. According to these estimates, a 60-kg person with mean alcoholic beverage consumption in Europe and a mean content of acetaldehyde would be exposed to 0.112 mg/kg body weight/day of acetaldehyde. A heavy drinker (99th percentile) exposed to a mean content of acetaldehyde would be exposed to 0.305 $\text{mg}/\text{kg}/\text{day}$. An average drinker consuming beverages with high content of acetaldehyde (99th percentile) would be exposed to 0.56 $\text{mg}/\text{kg}/\text{day}$. Lastly, a heavy drinker of beverages with high acetaldehyde content would be exposed to 1.639 $\text{mg}/\text{kg}/\text{day}$ of acetaldehyde.

Furthermore, Lachenmeier et al. (2009b) have estimated that twice-daily use of alcohol-containing mouthwashes leads to a systemic acetaldehyde exposure of 0.26 $\mu\text{g}/\text{kg}/\text{day}$ on average.

Acetaldehyde levels in drinking water were measured through a U.S. EPA Information Collection Rule (ICR) effort to gather water quality and treatment information in 500 treatment plants over an 18 month period. Acetaldehyde was observed at sub- to low- $\mu\text{g/L}$ levels; the maximum level of 11 mg/L was measured in ozonated drinking water, but levels were generally below the detection limit (<5 mg/L) in chlorine dioxide-treated waters (Richardson, 2007).

In a recently published study, McCarthy et al. (2009) compiled 3-year averages for ambient measurement of air toxics collected at monitoring locations in the United States from 2003 through 2005. They used national distributions of risk-weighted concentrations to identify the air toxics of most concern. The authors found that concentrations of acetaldehyde were above the 10^{-6} cancer risk at 99% of 163 sites nationally with a high degree of confidence.

A recent investigation of indoor airborne aldehyde levels in the bedrooms of 196 French infants, showed the presence of acetaldehyde in most dwellings, with geometric mean levels (geometric standard deviation) of 8.9 (1.8) $\mu\text{g/m}^3$ (Dassonville et al., 2009).

Cancer in humans: (*inadequate*, Vol 71, 1999)

IARC Monograph 71 (1999) included a case series of nine cancers (five bronchial tumors and two carcinomas of the oral cavity) among workers in an acetaldehyde dimerization plant in the German Democratic Republic. All cases were smokers. Main exposures included acetaldo (3-hydroxybutanal), acetaldehyde, butyraldehyde, crotonaldehyde, and other aldehydes, as well as traces of acrolein. The relative frequencies of these tumors were reported to be higher than those expected in the GDR, but the Working Group noted the mixed exposures, the small number of cases and the poorly defined exposed population. Other epidemiologic studies of cancer in populations occupationally-exposed to acetaldehyde were not identified.

The most compelling evidence of the carcinogenicity of acetaldehyde is provided by studies of alcohol drinkers. Acetaldehyde is the first metabolite of ethanol oxidation. The conversion from ethanol to acetaldehyde is catalyzed by the enzyme alcohol dehydrogenase (ADH), and the subsequent oxidation from acetaldehyde to acetate is catalyzed by the enzyme aldehyde dehydrogenase (ALDH).



The ALDH2 gene is polymorphic. The variant allele *ALDH2*2* encodes an enzyme with a deficient ability to detoxify acetaldehyde. After consumption of alcohol, homozygous carriers of the allele (*ALDH2*2-2*) ($<5\%$ of Asians) develop a severe flushing reaction, physical discomfort and other toxic responses. Most of them rarely consume alcohol. The heterozygous carriers (*ALDH2*1-2*) have about 10% residual ALDH activity (30-50% of Asians), and therefore less severe adverse effects. They may become heavy drinkers and alcoholics, and studies have shown that they have markedly elevated concentrations of acetaldehyde in their saliva after consumption of ethanol (Yokohama et al., 2008). Several studies conducted in Japan, China and Taiwan have shown increased risk of cancer of the esophagus associated with ALDH2 deficiency and alcohol consumption (Salaspuro 2009b). A study from Taiwan, published after the Monograph 96 meeting that evaluated the carcinogenicity of alcoholic beverages, included 406 cases with esophageal squamous cell carcinoma (ESCC) and 656 matched controls. Compared to non-drinkers, the odds ratio for

*ALDH2*1-2* carriers drinking at a low to moderate rate (0.1-30 g/day) was 14.5 (95% CI 7.1-29.6), and for *ALDH2*2-2* carriers was 17.3 (95% CI 1.4-213.7), whereas the risk for those with the active isoform (*ALDH2*1-1*) was 2.2 (95% CI 1.1-4.5). The risk for the *ALDH2* heterozygous drinkers of over 30 g/day was 102.5 (95% CI 38.3-274.8) (Lee et al., 2008).

Increased risks for gastric cancer, alcohol consumption and *ALDH2* deficiency have also been reported in Asian populations. The association with colorectal cancer has not been consistently demonstrated (Salaspuro, 2009b).

Another polymorphic *ALDH2* variant has been identified in Poland, and the encoded enzyme may be functionally deficient in eliminating acetaldehyde. A case-control study reported a stomach cancer risk of 2.6 (95% CI 1.0-6.9) among heterozygous carriers that drank alcohol daily, and of 3.7 (95% CI 1.2-11.2) among those with 40 or more drink-years (Zhang, 2007).

The 2 *ADH* enzymes responsible for most of ethanol metabolism are *ADH1B* and *ADH1C*. The *ADH1B*2* and the *ADH1C*1* alleles encode enzymes that result in fast metabolism of ethanol. *ADH1B*2* is highly prevalent in Asians. Studies of alcohol drinkers in Japan, China, Thailand and Central Europe have shown that the *ADH1B*1-1* genotype (enzyme with 1/40 activity of the normal) is a strong risk factor for esophageal and oropharyngolaryngeal cancers (Salaspuro, 2009b). It appears that after these individuals consume alcoholic beverages, ethanol remains elevated in blood and saliva for a longer time than in those with the normal enzyme, resulting in a longer exposure.

Among Caucasians, *ADH1C* is the main enzyme involved in alcohol metabolism. The *ADH1C*1* allele has been shown to increase the risk of esophageal, hepatocellular and head and neck cancers in some studies but not in others (Boffetta and Hashibe, 2006). This lack of consistency has been explained by differences in the geographic distribution of *ADH1C* genotypes in Europe and by the fact that negative studies have generally included controls and patients with little or moderate alcohol consumption (Homann et al., 2006).

Several studies have shown that the risk for upper digestive tract cancer is highest among *ALDH2*-deficient Asian drinkers who simultaneously have the low-activity *ADH1B*1-1* genotype (Salaspuro, 2009b). In a recent case-control study by Lee et al. (2008) in Taiwan, moderate alcohol users with the *ADH1B*1-1* genotype and the *ALDH2*2* allele had an increased risk of esophageal cancer (OR 37.5, 95% CI 10.4-134.7), and the risk was stronger for those drinking >30g/day (OR 382.3, 95% CI 47.4-3084.9). Furthermore, smoking had an independent and interactive effect on esophageal cancer risk among *ADH1B*1* and *ALDH2*2* carriers.

The evidence suggests that an increased risk for upper digestive tract cancer is associated with both a deficient ability to detoxify acetaldehyde and an enhanced or even deficient ability to produce it.

Cancer in experimental animals: (*sufficient*, Vol 71, 1999)

Oral administration of acetaldehyde has resulted in the development of tumors in experimental animals. After Monograph 71, a lifetime study was conducted in female and male rats given drinking water containing acetaldehyde at concentrations of 0, 50, 250, 500, 15000 or 2500 mg/L. The study showed an increase in total malignant tumors and specific carcinogenic effects on various organs and tissues (Soffritti et al., 2002).

Acetaldehyde, when inhaled, causes nasopharyngeal and laryngeal carcinoma in rats and hamsters (Woutersen et al., 1984; 1986).

Mechanisms of carcinogenicity:

Acetaldehyde interferes with DNA synthesis and repair, and *in vitro* studies have shown that acetaldehyde causes cytogenetic abnormalities in eukaryotic cells. Acetaldehyde causes point mutations in the hypoxanthine phosphoribosyltransferase 1 (*HPRT1*) locus in human lymphocytes, and induces sister chromatid exchanges and gross chromosomal aberrations. Acetaldehyde also binds to proteins, resulting in structural and functional alterations, such as enzymes involved in DNA repair (O6 methyl guanine methyltransferase) and DNA cytosine methylation, as well as glutathione, an important anti-oxidative peptide (Seitz and Stickel 2007).

Acetaldehyde binds to DNA, forming stable DNA adducts, and acetaldehyde DNA adducts have been found in alcohol consumers. The steady state level of DNA adducts, which can also be produced by reactive oxygen species (ROS), is influenced by various factors, including the activity of the anti-oxidative defense system, glutathione-S-transferase, the DNA repair system and apoptosis. Chronic ethanol ingestion may affect all of these mechanisms either directly or indirectly (Seitz and Stickel 2007).

A recent study showed that cells deficient in homologous recombination repair and Fanconi anemia like (KO40) cells were more sensitive to acetaldehyde, suggesting that these pathways are very important for the repair of acetaldehyde-induced lesions, confirming the evidence that this agent may induce DNA crosslinks (Mechilli, 2008).

Biomarkers of exposure:

No biomarkers of occupational exposure to acetaldehyde have been described in the literature.

Acetaldehyde has been measured in human saliva after ethanol consumption to demonstrate endogenous production of acetaldehyde after ingestion of ethanol (Homann, 1997). Acetaldehyde concentrations of 50–100 μM , which are known to be mutagenic, can be detected following the intake of 0.5 g alcohol per kg of body weight, equaling approximately half a bottle of wine. Salivary acetaldehyde concentrations are decreased after an antiseptic mouthwash by approximately 30–50%, underlining the importance of oral bacteria and poor oral hygiene in acetaldehyde generation (Seitz and Stickel 2007). It has also been used to demonstrate that use of alcohol-containing mouthwash increase salivary acetaldehyde levels to concentrations normally found after alcoholic beverage consumption (Lachenmeier, 2009b). Breath acetaldehyde has been used to investigate the production of acetaldehyde after ethanol ingestion. Additional research is necessary to standardize the technique used for breath sampling and to control the influence of the factors that are known to affect breath acetaldehyde determination (Tardif, 2007). Levels of acetaldehyde have been measured in blood and urine samples of alcohol consumers. The results showed an increase over time of free acetaldehyde, followed by a subsequent decrease. Acetaldehyde bound to biological components increased over time, suggesting that this is the mechanism by which acetaldehyde accumulates in the body as a result of chronic alcohol consumption (Tominaga, 2009).

The most abundant DNA adduct resulting from the reaction of acetaldehyde is N^2 -ethylidene-2'-deoxyguanosine (N^2 -EtidG). N^2 -EtidG needs a reduction step to become a stable adduct,

N²-ethyl-2'-deoxyguanosine (N²-EtdG). Fang and Vaca (1995) reported levels of N²-EtdG in Swedish drinkers and controls, and found higher adduct levels in lymphocytes of alcohol consumers compared with controls. They also found an increase of the same adducts in mice exposed to 10% alcohol in their drinking water.

α -Methyl- γ -OH-propano-deoxyguanosine is another DNA adduct with acetaldehyde that has been identified. As this adduct has been observed previously in DNA treated with crotonaldehyde, it is referred to as Cr-PdG. The formation of Cr-PdG adducts can be facilitated in the presence of basic amino acids, histones or polyamines. Relevant polyamine concentrations are present in tissues with hyper-regeneration. Chronic alcohol consumption results in mucosal hyperproliferation of the upper digestive tract, as well of the large intestine, probably due to the local toxic effect of highly concentrated acetaldehyde. In addition, high acetaldehyde concentrations are found in the saliva and colonic content following moderate alcohol consumption due to the bacterial oxidation of ethanol. As a consequence of high acetaldehyde concentrations in a hyper-regenerative environment, the generation of the highly-mutagenic Cr-PdG may be facilitated in these tissues (Seitz and Stickel 2007). Matsuda et al. (2006) reported that the level of acetaldehyde-derived DNA adducts in Japanese alcoholics with the *ALDH2*1-2* genotype is much higher than that in alcoholics with the *ALDH2*1-1* genotype, indicating that the ALDH2 genotype plays a crucial role in the formation of acetaldehyde DNA adducts.

Biomarkers of effect

Two genetic markers, chromosome aberrations and micronuclei, were used to evaluate genetic damage in peripheral lymphocytes from alcoholics, abstinent alcoholics, and controls. A statistically significant increase was observed in the frequencies of chromosomal aberrations and micronuclei in lymphocytes of alcoholics as compared both with controls and abstinent alcoholics. However, no correlation was found between the length of alcohol abuse and the frequencies of either biomarkers in alcoholics. Chromosomal aberrations and micronuclei frequencies in abstinent alcoholics were similar than those in controls (Maffei et al., 2002). In addition, sister chromatid exchanges and micronuclei were more frequently found in lymphocytes of habitual drinkers with *ALDH2*1-2* than in lymphocytes of drinkers with fully active ALDH2 (Seitz and Stickel 2007).

Research needs and recommendations:

An epidemiologic study that evaluates the association between acetaldehyde exposure and upper digestive tract cancer will require evaluation of all potential sources of exposure to acetaldehyde, to address their contribution to the overall risk.

Different study designs could be proposed for such a study. Prospective studies could be designed to assess all sources of exposure using a combination of questionnaires and environmental and biological monitoring, as well as genotyping to identify individuals with ALDH2, ADH1C, and ADH1B deficiencies. However, given the long induction and latency of most cancers, such a study may not be feasible. Retrospective studies, conversely, have the limitation that exposures have to be evaluated retrospectively, increasing the potential for misclassification. Alternatively, acetaldehyde-derived DNA adducts could be used as biomarkers of exposure to acetaldehyde (Matsuda et al., 2006).

On the other hand, there is substantial evidence that acetaldehyde, the first product of ethanol metabolism, is predominantly responsible for carcinogenesis of alcoholic beverages. Numerous epidemiologic studies in alcohol drinkers with ALDH2 deficiency or low ADH1B activity described above, strongly suggest that acetaldehyde derived from the metabolism of ethanol contributes towards causing upper digestive tract cancers. This notion is also supported by two meta-analyses that used a Mendelian randomization approach (Boccia et al., 2009) and a recent large-scale case-control study that reported a multiplicative combined risk for esophageal cancer among alcohol and tobacco consumers, who were low ADH1B and ALDH2-deficient carriers (Lee et al., 2008).

The IARC Working Group that evaluated the carcinogenicity of alcoholic beverages (2007, Monograph 96) concluded that “acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to causing malignant esophageal tumors” (Baan, 2007). Furthermore, recent risk assessments that consider individual sources of exposure such as acetaldehyde in alcoholic beverages, acetaldehyde in saliva after alcohol drinking and cigarette smoking, acetaldehyde levels in foods and beverages such as yogurt, homemade beer and apples, have concluded that the lifetime cancer risks for many of these sources of exposure greatly exceed the usual limits for cancer risks from the environment ($1:10^4$ - $1:10^6$). Acetaldehyde exposure is cumulative and in some cases synergistic (as occurs with alcohol exposure and smoking) (Salaspuro, 2009a). Exposure scenarios that consider multiple sources of exposure and genetic deficiencies in alcohol metabolism convey increased risks. It is thus recommended that the IARC classification of acetaldehyde is reviewed in a Monograph meeting.

Selected relevant publications since IARC review:

Boccia S, Hashibe M, Galli P, De Feo E, Asakage T, Hashimoto T, et al. Aldehyde dehydrogenase 2 and head and neck cancer: A meta-analysis implementing a mendelian randomization approach. *Cancer Epidemiol Biomark Prev* 2009; 18: 248-254.

Lachenmeier DW, Kanteres F, Rehm J. Carcinogenicity of acetaldehyde in alcoholic beverages: Risk assessment outside ethanol metabolism. *Addiction* 2009; 104: 533-550.

Lee CH, Lee JM, Wu DC, Goan YG, Chou SH, Wu IC, et al. Carcinogenetic impact of adh1b and ald2 genes on squamous cell carcinoma risk of the esophagus with regard to the consumption of alcohol, tobacco and betel quid. *Int J Cancer* 2008; 122: 1347-1356.

Matsuda T, Yabushita H, Kanaly RA, Shibutani S, Yokoyama A. Increased DNA damage in ald2-deficient alcoholics. *Chem Res Toxicol* 2006; 19: 1374-1378.

Muttray A, Gosepath J, Brieger J, Faldum A, Pribisz A, Mayer-Popken O, et al. No acute effects of an exposure to 50 ppm acetaldehyde on the upper airways. *Int Arch Occup Environ Health* 2009; 82: 481-488.

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Soffritti M, Belpoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann N Y Acad Sci* 2002; 982: 87-105.