Workplace Exposure Standard (WES) review

ACETALDEHYDE
(CAS NO: 75-07-0)

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WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for acetaldehyde should be changed.

It considers the potential for exposures to acetaldehyde in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for acetaldehyde, which is currently set at a **WES-TWA** of 20**ppm** with a **WES-STEL** of 50ppm, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: acetic aldehyde; acetylaldehyde; ethanal; ethyl aldehyde; acetic ethanol.

2.0 Chemical and physical properties

Acetaldehyde is a colourless, flammable liquid or gas with a pleasant fruity odour at dilute concentrations that becomes pungent and suffocating at higher concentrations (**ACGIH**®, 2014; **IARC**, 1999; **NTP RoC**, 2016).

Acetaldehyde is reported to have an odour threshold at 0.21ppm (Leonardos *et al*., 1969 as cited in ACGIH®, 2014).

Chemical and physical properties of acetaldehyde include:

Molecular weight	44.05
Formula	C_2H_4O
Specific gravity	0.788 at 20°C
Boiling point	20.16°C
Melting point	-123.5°C
Vapour pressure	755 torr at 20°C; 98 kPa at 20°C
Vapour density	1.52 (air = 1.0)
Flash points	open cup: -40°C; closed cup: -38°C
Explosive limits	lower: 4.5%; upper: 60.5% by volume in air
Autoignition temperature	165°C
Solubility	soluble in water, ethyl alcohol, ethyl ether, acetone, acetic acid, benzene, toluene, solvent naphtha, turpentine, and gasoline
Reactivity	polymerizes violently in the presence of trace amounts of metals or acids; can react violently with acid anhydrides, alcohols, ketones, phenols, ammonia, hydrocyanic acid, hydrogen sulphide, halogens, phosphorus, isocyanates, strong alkalis and amines
Conversion factors	1ppm = 1.80mg/m^3; 1mg/m^3 = 0.556ppm at 25°C, 760 torr

ACGIH®, 2014; **DECOS**, 2014; IARC, 1999

TABLE 1: Physicochemical properties of acetaldehyde

Health-related hazard classifications for acetaldehyde:

SUBSTANCE	HSNO CLASSIFICATION
Acetaldehyde	6.1D (All); 6.1D (O); 6.4A; 6.6A; 6.7B; 6.8B; 6.9B (All); 6.9B (I)

TABLE 2:
HSNO health-related hazard classifications of acetaldehyde (**EPA**, 2018)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[I] Inhalation exposure route.

3.0
Uses

Acetaldehyde is produced on a large industrial scale for many purposes and uses, but particularly as an intermediate (DECOS, 2014).

Acetaldehyde is used in the production of acetic acid, pyridine and pyridine bases, peracetic acid, pentaerythritol, butylene glycol, and chloral; in the synthesis of crotonaldehyde, flavour and fragrance acetals, acetaldehyde 1,1-dimethylhydrazone, acetaldehyde cyanohydrin, acetaldehyde oxime, various acetic acid esters, paraldehyde, metaldehyde (a molluscicide widely used to kill slugs and snails), polymers, and various halogenated derivatives; in the manufacture of aniline dyes, plastics, and synthetic rubber, to silver mirrors, and to harden gelatine fibres; in the production of polyvinyl acetal resins, in fuel compositions, to inhibit mould growth on leather, and in the manufacture of disin-fectants, pesticides, drugs, explosives, lacquers and varnishes, photographic chemicals, phenolic and urea resins, and rubber accelerators and antioxidants; and, as a flavouring agent and adjuvant in food (NTP RoC, 2016; DECOS, 2014; ACGIH®, 2014).

Acetaldehyde occurs widely in nature (NTP RoC, 2016; DECOS, 2014). Acetaldehyde is the immediate metabolite of ethanol and exposure occurs after drinking alcohol (ACGIH®, 2014; IARC, 2010).

Occupational exposure to acetaldehyde can occur during production, storage, transportation and end-use, although production is reported to be in closed continuous systems (ACGIH®, 2014). Occupational exposure to acetaldehyde can also occur when fires involving wood and certain plastics and foams release acetaldehyde, and also with diesel and petrol engine emissions (NTP RoC, 2016).

Workers can be exposed to acetaldehyde liquid and/or gas via inhalation, eye and dermal contact.

The number of workers exposed or potentially exposed to acetaldehyde in New Zealand workplaces is unknown.

Statistics New Zealand 2017 data indicate that 14,140 New Zealand workers were working in the areas of:

- leather tanning and fur dressing
- chemical manufacturing
- basic polymer manufacturing
- polymer product manufacturing (NZ Stat, 2018).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

Acetaldehyde vapour was reported to cause coughing and burning pain in the nose, throat and eyes. Exposure to acetaldehyde solution caused burning, lacrimation and blurred vision (**CERIJ**, 2007). After 15-minute exposure to acetaldehyde vapour at a concentration of 50ppm (90mg/m^3) in 12 human volunteers, mild irritation to eyes was observed (Silverman *et al*., 1946 as cited in CERIJ, 2007). Transient conjunctivitis was observed in humans exposed to acetaldehyde at a concentration of 200ppm (360mg/m^3) for 15 minutes (Proctor and Hughes, 1978 as cited in CERIJ, 2007). All of 14 males (18–45 years old) exposed to acetaldehyde at a concentration of 134ppm (241mg/m^3) for 30 minutes showed mild irritation in the respiratory tract (Sim and Pattle, 1957 as cited in CERIJ, 2007).

Prolonged dermal exposure to acetaldehyde probably caused erythema and burning, and repeated exposure caused dermatitis induced by dermal irritation or sensitisation (Proctor and Hughes, 1978 as cited in CERIJ, 2007).

Alcohol consumption can have serious effects on reproduction in both males and females, and is a well-documented human teratogen, but the EU Scientific Committee on Consumer Safety (**SCCS**) review noted that:

> "... it is not known whether acetaldehyde, the primary metabolite of ethanol, is involved in the aetiology of the human foetal alcohol syndrome." (SCCS, 2012).

Animals

Oral **LD_{50}** values were reported at > 600 to 1,930**mg/kg b.w.** for rats; 1,230mg/kg b.w. for mice; and, > 600mg/kg b.w. for dogs (SCCS, 2012). A dermal LD_{50} value was reported at 3,540mg/kg b.w. for rabbits (SCCS, 2012). Inhalation 4-hour **LC_{50}** values were reported at 13,000mg/m^3 for rats; 1,500ppm (2,700mg/m^3) for mice; and, 17,000–24,000ppm (30,600–43,200mg/m^3) for hamster (SCCS, 2012). The major general symptoms were central nervous system depression, decrease in respiration rate, increases in heart rate and blood pressure, pulmonary oedema and proteinuria (Environment Canada, Health Canada, 2000 as cited in CERIJ, 2007).

A reported test with rabbits that was carried out according to **OECD** Test Guideline 404, found that acetaldehyde was not irritating to the skin, but another test not conducted in accordance with test guidelines, found in the same species 500mg acetaldehyde produced slight irritation of the skin (SCCS, 2012). In the rabbit eye, 40mg acetaldehyde was reported to produce marked irritation. Long-term inhalation exposures of experimental animals to acetaldehyde vapour were reported to cause irritation of the mucous membranes of the eye, nose and upper respiratory tract (SCCS, 2012).

A modified cumulative contact enhancement test with guinea pigs was used to test the sensitisation potential of acetaldehyde with formaldehyde as a positive control, and reported a statistically significant increase in responses with both acetaldehyde and formaldehyde after challenges at 48 and 72 hours. Formaldehyde exhibited a sensitising capacity on re-challenge at 78 days, whereas acetaldehyde did not (ACGIH®, 2014). The SCCS review of the same study commented that "it is unknown whether the reactions observed were irritant (false positive) in nature" (SCCS, 2012).

Several repeated inhalation exposure studies with acetaldehyde have been reported but most were noted as not conforming to international study or **GLP** guidelines (SCCS, 2012; ACGIH®, 2014; CERIJ, 2007). Male Wistar rats

were exposed to 110, 150 and 500ppm for 6 hours per day/5 days per week for 4 weeks (whole-body or nose-only was not stated). Reduced phagocytotic index of lung macrophages and degeneration of the nasal olfactory epithelium was observed in rats uninterruptedly exposed to 500ppm acetaldehyde (Appelman *et al*., 1986 as cited in SCCS, 2012). SCCS considered the **NOAEC** of 150ppm robust enough to be used in their safety assessment for non-cancer effects by inhalation (SCCS, 2012). Male F344 rats were exposed (whole-body) to acetaldehyde for 6 hours/day, 5 days/week for up to 65 days (Dorman *et al*., 2008 as cited in ACGIH®, 2014). Histological examination revealed olfactory neuronal loss at ≥ 150ppm with inflammation, hyperplasia and squamous metaplasia of the respiratory epithelium at 1500ppm, giving a NOAEC of 50ppm (ACGIH®, 2014).

The IARC evaluation of alcohol consumption summarised the reproductive toxicity potential of acetaldehyde:

> "Several studies on the developmental effects of acetaldehyde have been conducted, primarily to investigate its role in ethanol-induced teratogenicity (O'Shea & Kaufman, 1979, 1981; Bariliak & Kozachuk, 1983; Webster *et al*., 1983; Ali & Persaud, 1988). In these studies, acetaldehyde was given by amniotic or intraperitoneal injection, not by ingestion or inhalation. Dose-related embryotoxic, fetotoxic and teratogenic effects were seen in most of these studies, particularly in rats, but maternal toxicity was often not assessed adequately or reported in any of these investigations. Dose-related embryotoxic effects were observed in *in-vitro* studies on rat embryos exposed to acetaldehyde (Popov *et al*., 1981; Campbell & Fantel, 1983). Effects on the placenta have been observed following intraperitoneal injection of acetaldehyde into pregnant rats (Sreenathan *et al*., 1984).
>
> "Rat postimplantation embryos at gestation day 9.5 were cultured for 48 h and observed for morphological changes following treatment with acetaldehyde. There was significant cytotoxicity in embryonic midbrain cells. In this tissue, the levels of p53, bcl-2, 8-hydroxydeoxyguanine and the number of cells damaged by reactive oxygen species were increased by the treatment. Co-treatment with acetaldehyde and catalase decreased the cytotoxicity. In postimplantation culture, acetaldehyde-treated embryos showed retardation of embryonic growth and development in a concentration-dependent manner. These results show that acetaldehyde induces fetal developmental abnormalities by disrupting cellular differentiation and growth. Some antioxidants can partially protect against the embryonic developmental toxicity (Lee *et al*., 2006)." (IARC, 2010).

Acetaldehyde is classified by the EPA as a 6.6A substance – a substance that is a known or presumed mutagen.

4.2 Cancer

The International Agency for Research on Cancer (IARC) evaluation of acetaldehyde concluded that:

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

With an overall evaluation that:

> Acetaldehyde is possibly carcinogenic to humans (Group 2B) (IARC, 1999).

The IARC evaluation of alcohol consumption, in relation to acetaldehyde, concluded that:

> There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancers of the oesophagus and of upper aerodigestive tract combined.
>
> There is *sufficient evidence* for the carcinogenicity of acetaldehyde in experimental animals.

With an overall evaluation that:

> Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1)* (IARC, 2012).

The US National Toxicology Program (NTP) Report on Carcinogens (RoC), Fourteenth Edition concluded that:

> Acetaldehyde is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. (NTP RoC, 2016).

Acetaldehyde is classified by the EPA as a 6.7B substance – a substance for which data indicate limited evidence in humans or limited evidence in animals that exposure to the substance may lead to the development of cancer or an increased incidence of tumours, where the strength and weight of the evidence indicate to an expert that the evidence is not sufficient to classify the substance in hazard classification 6.7A.

Humans

The genotoxicity potential of acetaldehyde has been summarised by IARC and SCCS (IARC, 2012; IARC, 2010; SCCS, 2014): numerous *in vitro* studies have consistently shown that acetaldehyde caused **DNA**-protein cross-links, DNA strand breaks, DNA adducts, sister chromatid exchanges (Chinese hamster ovary cells), chromosomal aberrations, and micronuclei in eukaryotic cells. Acetaldehyde did not cause differential killing of repair-deficient *Escherichia coli* K-12 *uvrB/recA* cells and was not mutagenic to *Salmonella typhimurium* or *E. Coli* WP2 *uvrA* after vapour exposure, with or without metabolic activation. Acetaldehyde induced chromosome malsegregation in *Aspergillus nidulans* and was mutagenic in *Drosophila melanogaster* after injection but not after feeding. *In vitro* and without exogenous metabolic activation, acetaldehyde induced gene mutations in mouse lymphoma L5178T cells, and aneuploidy in embryonic Chinese hamster diploid fibroblasts. Acetaldehyde induced also DNA-protein cross-links, sister chromatid exchanges and chromosomal aberrations in rodents *in vivo* (IARC, 2012; IARC, 2010; SCCS, 2014).

N^2-ethylidenedeoxyguanosine (N^2EtidG) is reported to be the most abundant acetaldehyde-DNA-adduct that is quickly reduced to the stable N^2-Ethyl-2'-deoxyguanosine (N^2EtdG). Elevated levels of N^2EtdG have been found in the lymphocytes, granulocytes and leukocytes of alcohol drinkers (IARC, 2012). Three other acetaldehyde-derived DNA adducts have been reported: N^2-(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine (N^2-Dio-dG); an interstrand crosslink, and two diastereisomers (R and S) of α-methyl-γ-hydroxy-1,N^2-propanodeoxyguanosine (α-Me-γ-OH-PdG) (Wang *et al*., 2000 as cited in IARC, 2012).

No case-control or epidemiological studies appear to have been reported that involve only exposure to acetaldehyde (DECOS, 2014; SCCS, 2012; ACGIH®, 2014). The NTP RoC profile on acetaldehyde concluded that:

> The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acetaldehyde. (NTP RoC, 2016).

In the former German Democratic Republic, nine cancer cases were found in a factory where 150 workers had more than 20 years exposure, where the cohort was followed 1967–1972. The main process was dimerization of acetaldehyde and where the main exposures were to acetaldol (3-hydroxybutanal), acetaldehyde, butyraldehyde, crotonaldehyde and other higher, condensed aldehydes, as well as to traces of acrolein. The acetaldehyde concentrations in the workplace were reported at 1 to 7mg/m^3 (0.56-3.88ppm) after equipment leakages. Of the cancer cases, five were bronchial tumours (squamous cell carcinoma) and two were squamous cell carcinomas of the oral cavity. All nine patients were smokers. The relative frequencies of these tumours were reported to be higher than those expected in the German Democratic Republic. The study is noted as having limitations (DECOS, 2014; SCCS, 2012; ACGIH®, 2014).

Much of the evidence for the carcinogenic potential of acetaldehyde in humans has come from investigations into the role that acetaldehyde plays in the carcinogenic potential of alcohol consumption (IARC, 2010; 2012):

> "Acetaldehyde is formed metabolically from the oxidation of ethanol, and is further metabolized, predominantly by nicotinamide adenine dinucleotide-dependent aldehyde dehydrogenases, to acetic acid. The importance of aldehyde dehydrogenase in the oxidative pathway of ethanol is emphasized in drinkers of alcoholic beverages who are deficient in this enzyme: the alcoholic flush reaction that they experience correlates with the accumulation of acetaldehyde in the blood." (IARC, 2010).
>
> "Epidemiological evidence of enhanced cancer risks among heterozygous carriers of the inactive **ALDH** (aldehyde dehydrogenase) enzyme has become much stronger, in particular for oesophageal cancer: practically all studies conducted in East-Asian populations who consumed alcoholic beverages show significantly increased odds ratios for carriers of the inactive ALDH allele. In addition, several studies have demonstrated associations between the polymorphism of **ADH1B** (alcohol dehydrogenase 1B encoded by the ADH 1B gene) and upper aerodigestive tract cancers, which have been explained either by more active **ADH** (alcohol dehydrogenase) producing more acetaldehyde or by less active ADH causing prolonged exposure to lower levels of ethanol-derived acetaldehyde.
>
> "These data imply that acetaldehyde is the key compound in the development of cancers of the oesophagus and other upper aerodigestive tract cancers associated with alcoholic beverage consumption. The considerations that support this suggestion are:
>
> 1. there is an established causal relationship between alcoholic beverage consumption and cancers of the oesophagus, oral cavity, pharynx and larynx;
> 2. it is generally accepted that ethanol in alcoholic beverages is the principal ingredient that renders these beverages carcinogenic;
> 3. in the body, ethanol is converted by ADH and **CYP2E1** (cytochrome P450 family 2; subfamily E; member 1) to acetaldehyde, which is oxidized by ALDH to acetate;

4. the formation of acetaldehyde starts in the mouth, mediated mostly by oral bacteria, and continues along the digestive tract;
5. the main production of acetaldehyde occurs in the liver and in the gut. However, the highest levels of acetaldehyde after consumption of alcoholic beverages are found in the saliva of the oral cavity, which is in the vicinity of the target organ sites known to be susceptible to ethanol-induced cancer;
6. the upper digestive tract is also the site that is in first contact with the acetaldehyde content of the alcoholic beverages, which in turn are known to increase the salivary acetaldehyde levels;
7. acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound. It is carcinogenic in experimental animals;
8. after alcoholic beverage consumption, carriers of an inactive allele of the **ALDH2** (aldehyde dehydrogenase 2 encoded by the ALDH2 gene) enzyme show accumulating levels of acetaldehyde in the peripheral blood, a direct consequence of their enzyme deficiency, and show increased levels of N^2EtdG and methylhydroxypropano-dG adducts in lymphocyte DNA. The latter adducts have been shown to be formed from acetaldehyde; during DNA replication, these methylhydroxypropano-dG adducts cause mutations;
9. consumers of alcoholic beverages have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronucleus formation in the peripheral lymphocytes than non-consumers. These effects may be attributable to acetaldehyde, which is a clastogen;
10. several of the observations made in ALDH2-deficient individuals have been confirmed in ALDH2-knockout mice." (IARC, 2012).

The NTP RoC profile on acetaldehyde noted that:

"a number of review articles and meta-analyses have summarized the results of subsequent studies that found dose-response relationships between alcohol consumption and cancer of the oral cavity, pharynx, larynx, and esophagus, and possibly the stomach and colorectum, among individuals with genetic polymorphisms that increase blood or salivary levels of acetaldehyde (Bagnardi *et al*. 2001, Zeka *et al*. 2003, Boffetta and Hashibe 2006, Baan *et al*. 2007, Boccia *et al*. 2009, Salaspuro 2009). In 2009, IARC concluded that acetaldehyde associated with alcohol consumption was carcinogenic to humans (Secretan *et al*. 2009). Few studies have been conducted on the association of these polymorphisms with cancer at other tissue sites, and the role of acetaldehyde in pancreatic, liver, bladder, or breast cancer is not clear (van Dijk *et al*. 2001, Terry *et al*. 2006, Seitz and Becker 2007, Visvanathan *et al*. 2007, Druesne-Pecollo *et al*. 2009)." (References as cited in NTP RoC, 2016).

Animals

The CERIJ hazard assessment report on acetaldehyde summarised the carcinogenic potential in test species:

"In an inhalation study, male and female Wistar rats were exposed to acetaldehyde at concentrations of 0, 750, 1,500 and 3,000 to 1,000ppm (equivalent to 0, 1,350, 2,700 and 5,400 to 1,800mg/m^3; the exposure concentration of 3,000ppm at week 20 was gradually reduced to 1,000ppm

at week 52) for 6 hours/day, 5 days/week, for 28 months. Carcinoma (carcinoma in situ, squamous cell carcinoma and adenocarcinoma) was induced in the nasal cavity of the male and female rats at 750ppm and above (Woutersen and Appelman,1984; Woutersen *et al*.,1985; Woutersen *et al*., 1986).

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

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

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

"In summary, an inhalation study in Wistar rats shows dose-dependent increases in nasal adenocarcinoma and squamous cell carcinoma at 750ppm (1,350mg/m^3) and above for 28 months. In hamsters, exposure of acetaldehyde for 52 weeks causes significant increases in the incidence of respiratory tract tumors (including primarily laryngeal cancer, and also laryngeal polyp and carcinoma in the nasal cavity). Acetaldehyde is considered a carcinogenic substance in experimental animals in this assessment." (CERIJ, 2007).

The SCCS review of acetaldehyde considered the induction of nasal carcinomas in male rats after inhalation exposure for 28 months (Woutersen *et al*., 1986 as cited in SCCS, 2012) robust enough to base the point of departure, **T25** (the dose eliciting a 25% increase in the incidence of a specific tumour above the background level (that is, after correction for spontaneous incidence) within the standard lifespan of that species) at 100ppm for their risk assessment (SCCS, 2012).

4.3 Absorption, distribution, metabolism and excretion

The DECOS review of acetaldehyde summarised the toxicokinetics:

> "In human volunteers, a significant uptake (45–70%) by the respiratory tract of inhaled acetaldehyde was observed after a very short exposure duration of 45 to 75 seconds. In various tissues of rats, acetaldehyde was found to be increased after a single exposure by inhalation, compared to unexposed control animals. Limited data obtained from animal experiments suggest that acetaldehyde (administered by intraperitoneal injection) may be partially transferred from maternal to foetal blood. It is also found in foetal liver. In a few studies acetaldehyde was detected in the blood and brain of animals, which were given the substance by intragastric administration or intraperitoneal injections. No data are available on dermal or percutaneous absorption. Data on elimination are very limited. In one study using dogs, a single administration of acetaldehyde via a stomach tube revealed the presence of the substance in urine in minor quantities, but in most dogs no urinary acetaldehyde could be detected at all. Most likely this is due to the rapid metabolism of the substance in the liver.
>
> "Quantitative data on metabolism of acetaldehyde are based on animal experiments. Acetaldehyde is rapidly oxidized into acetate by **NAD**+-dependent acetaldehyde dehydrogenases. These enzymes are located in the cells of most tissues, including the liver, mucosal tissue of the respiratory tract, and the testes of mice. Acetaldehyde dehydrogenases show genetic polymorphism that gives rise to differences in vulnerability in humans concerning toxicity. To a minor part, the substance is probably oxidized by cytochrome P450 2E1, and by different aldehyde oxidases. Acetate is further metabolised into carbon dioxide and water by the citric acid cycle. There is no reason to believe that metabolism of acetaldehyde in rodents is significantly different from that of humans.
>
> "In general, data indicate a highly effective metabolism, in that half-time values in the blood for acetaldehyde were found to be three minutes in rats (after repeated exposure by inhalation) and mice (single intraperitoneal injection). For humans, no reliable data on half-times are available.
>
> "Acetaldehyde is a highly reactive electrophile, which reacts with nucleophilic groups of cellular macromolecules, such as proteins and DNA, to form adducts." (DECOS, 2014).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows the acetaldehyde exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2018).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	20	36	50	91
Austria	50	90	50	90
Belgium	25	46		
Canada – Ontario			25[1]	
Canada – Quebec			25[1]	45[1]
Denmark	25	45	25	45
Finland			25[2]	46[2]
France	100	180		
Germany (AGS)	50	91	50[2] 100[1]	91[2] 182[1]
Germany (DFG)	50	91	50[2,3]	91[2,3]
Hungary		25		25
Ireland	25	45	25[4]	45[4]
Japan (JSOH)	50[5]	90[5]		
Latvia		5		
New Zealand	20		50	
People's Republic of China				45[1]
Poland		5		45[1]
Singapore			25	45
South Korea	50	90	150	270
Spain			25	46
Sweden	25	45	50[2]	90[2]
Switzerland	50	90	50	90
The Netherlands		37		92
USA – NIOSH	18 (**LOQ**[6])			
USA – OSHA	200	360		
UK	20	37	50	92

TABLE 3: Exposure standards for acetaldehyde from around the world

[1] Ceiling limit value.

[2] 15 minutes average value.

[3] A momentary value of 100ml/m³ (180mg/m³) should not be exceeded.

[4] 15 minutes reference period.

[5] Occupational exposure limit ceiling: reference value to the maximal exposure concentration of the substance during a working day.

[6] Limit of quantitation.

It is noted that the only organisations from whom we got information as to how and why they set occupational exposures standards on acetaldehyde was ACGIH® and Safe Work Australia.

5.2 ACGIH®

The ACGIH® review of acetaldehyde recommended a **TLV-Ceiling** of 25ppm (45mg/m^3) for occupational exposure to protect workers against the potential for eye and upper respiratory tract irritation (ACGIH®, 2014).

The rationale for the TLV-Ceiling was:

> "Several of the (approximately) 12 workers are reported to have experienced eye irritation at acetaldehyde concentrations as low as 25ppm for 15 minutes, with the majority of persons experiencing irritation at a concentration of 50ppm (Silverman *et al*., 1946). At 200ppm, all subjects had eye irritation and most experienced nose and throat irritation. In another controlled exposure study, 14 humans were exposed to 135ppm for 30 minutes. All 14 subjects reported mild upper respiratory tract irritation (Sim and Pattle, 1957). In a more recent study, no significant effects on nasal mucosa were seen (other than a slight increase in mucociliary transport time) in an exposure chamber study where 20 young adult males were exposed to 50ppm for 4 hours (Muttray *et al*., 2009). An immediate concentration-dependent increase in nasal vasodilation at concentrations of 25ppm and greater was seen in a study of F344 rats (Stanek *et al*., 2001). In a 65-day whole-body study of F344 rats, the **NOAEL** for nasal pathology was 50ppm (Dorman *et al*., 2008). Excess nasal and laryngeal carcinomas have been reported in rats exposed to acetaldehyde vapor at a concentration of 750ppm and higher (Woutersen *et al*., 1986) and in hamsters exposed at approximately 1650ppm (Feron *et al*., 1982). The mechanisms of action for the nasal and laryngeal cancers appear to be genotoxicity, cytotoxicity, and inflammation caused by repeated irritation of the olfactory and respiratory epithelium followed by regenerative growth (Teeguarden *et al*., 2008).
>
> "An epidemiological study of 150 workers found an excess risk of respiratory tract (N = 5) and oral cavity (N = 2) cancers in a factory producing aldehydes, but is considered supportive (*) evidence of carcinogenicity in humans due to multiple chemical exposures and failure to follow-up (Bittershol, 1975). (* Note this quote from ACGIH may have a typographical error in that it appears it should read 'unsupportive'.)
>
> "Acetaldehyde is considered to be a clastogen and an inducer of sister-chromatid exchanges and micronuclei in culture mammalian cells (Dellarco, 1988). Other, more recent reviews have been in general agreement (Feron *et al*., 1991; WHO, 1995; Morris, 1997; Brooks and Theruvathu, 2005; Yu *et al*., 2010). In a study evaluating the effects of acetaldehyde on human lymphocytes, DNA breaks occurred in a dose-related manner after exposure to acetaldehyde, but not after exposure to ethanol (Singh and Khan, 1995). Average levels of DNA adducts of acetaldehyde measured in human granulocytes and lymphocytes were an order of magnitude higher in alcoholics compared to control subjects (Fang and Vaca, 1997). Acetaldehyde produced dose-dependent increases in micronucleus induction in a study using the MCL-5 genetically engineered human lymphoblastoid cell line. These results were ascribed by the authors to a clastogenic mechanism (Kayani and Parry, 2010). There was a significant increase in DNA-protein cross-links from nasal respiratory mucosa in an *in vivo* study of rats exposed at 1000 and 3000ppm for 6 hours (Lam *et al*., 1986).

> "The combination of positive inhalation bioassays in two species showing excess of nasal and laryngeal carcinomas, positive *in vitro* and *in vivo* results for genotoxicity, the ability to form DNA adducts, DNA breaks, and micronuclei in human cell lines, plus upper respiratory tract irritation seen in humans warrants the classification of acetaldehyde as an A2, Suspected Human Carcinogen. A TLV-Ceiling of 25ppm is recommended to prevent acute ocular and respiratory tract irritation, which occurs at levels between 25–50ppm. By preventing ocular and respiratory irritation, this TLV is expected to protect against the possibility of increased risk of cancer." (References as cited in ACGIH®, 2014).

The ACGIH® review of acetaldehyde stated that the recommended TLV-Ceiling should be protective against the reproductive effects seen at higher doses in rats and mice. The ACGIH® review also noted that although there were some positive results for sensitisation in both animal models and humans, there was insufficient data available to recommend either **DSEN** or **RSEN** notations; and there was insufficient data available to recommend a **Skin** notation (ACGIH®, 2014).

5.3 Safe Work Australia

Safe Work Australia proposed an interim Peak limitation of 20ppm to protect for eye and respiratory tract irritation and the consequent risk of cancer in exposed workers.

In their review, they say:

> "Data in humans from observational studies indicate that acute exposures above 25ppm result in irritation of the eyes, and exposures above 135ppm result in upper respiratory tract irritation. An experimental study in humans demonstrated no significant effects below 50ppm (ACGIH, 2018; DFG, 2008)" and "The recommended peak limitation is expected to prevent the possibility of excess cancers in workers". (Safe Work Australia, 2019).

5.4 New Zealand

WorkSafe's WES for acetaldehyde has been unchanged since 2002.

The toxicological database reviewed above indicates that acetaldehyde is locally and systemically toxic to humans, causing irritation to the skin, eyes and respiratory tract; and, locally and systematically toxic to laboratory species causing irritation of the mucous membranes of the eye, nose and upper respiratory tract, nasal and laryngeal cancers, and embryotoxic and developmental effects. Acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound.

Based on the aforementioned documentation, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 20ppm with a WES-STEL of 50ppm for acetaldehyde, to be inadequate to manage health risks from possible workplace exposure:

- Acetaldehyde induced gene mutations in mouse lymphoma L5178T cells, sister chromatid exchanges in Chinese hamster ovary cells and aneuploidy in embryonic Chinese hamster diploid fibroblasts *in vitro* and without exogenous metabolic activation. Acetaldehyde induced DNA-protein cross-links, sister chromatid exchanges and chromosomal aberrations in rodents *in vivo*. Increased frequency of acetaldehyde DNA adducts in humans has been found in relation to alcohol use (SCCS, 2012).

- The mechanisms of action for the nasal and laryngeal cancers reported in rats and hamsters after chronic inhalation exposures to acetaldehyde appear to be genotoxicity, cytotoxicity, and inflammation caused by repeated irritation of the olfactory and respiratory epithelium followed by regenerative growth (Teeguarden *et al*., 2008 as cited in ACGIH®, 2014).
- As acetaldehyde is considered a genotoxic carcinogen it may induce cancer by all routes of exposure and the site of tumour formation in humans may be different from that found in rodents (SCCS, 2012). Since some of the cancer risk is from a direct genotoxic mechanism, no threshold can be assumed, although SCCS considered acetaldehyde to be a 'low potency' carcinogen based on the T25 value (SCCS, 2012).
- In studies in humans, some report eye irritation at acetaldehyde concentrations of 25ppm for 15 minutes with the majority reporting irritation at 50ppm, when a slight increase in mucociliary transport time was reported after 4 hours exposure in another study. At 135ppm for 30 minutes all subjects reported mild upper respiratory tract irritation, while at 200ppm for 15 minutes all subjects had eye irritation and most reported nose and throat irritation (ACGIH®, 2014).
- Studies on alcohol consumption in humans have found dose-response relationships between alcohol consumption and cancer of the oral cavity, pharynx, larynx, and oesophagus, and possibly the stomach and colorectum, among individuals with genetic polymorphisms (for aldehyde dehydrogenase, ALDH with variant allele *ALDH2* gene encoding an enzyme that has little capacity to detoxify acetaldehyde) that increase blood or salivary levels of acetaldehyde (NTP RoC, 2016).

6.0 Analytical methods for the assessment of airborne acetaldehyde

One method available in New Zealand to determine the airborne concentration of acetaldehyde is to conduct passive sampling, analysing the sample using a modification of the Compendium Method TO-11A (**U.S. EPA**, 1999).

Using this method an adsorbent is used to collect the sample, and following an appropriate exposure time, the sample is analysed by high-performance liquid chromatography using ultraviolet detection. The modified method has been quoted as having a detection limit of 0.02µg per sample.

The sampling rate of one such adsorbent, for acetaldehyde, has been quoted by the manufacturer as 22.8mL per minute.

This would allow quantification of airborne acetaldehyde at concentrations well below 1ppm over a 15 minute period.

7.0
Discussion and recommendation

WorkSafe considers its current WES-TWA of 20ppm with a WES-STEL of 50ppm for acetaldehyde to be inadequate to protect workers exposed in the workplace, based current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-Ceiling for acetaldehyde at 20ppm
2. remove the WES-TWA for acetaldehyde at 20ppm, and
3. remove the WES-STEL for acetaldehyde at 50ppm.

The proposed WES-Ceiling value is based on the conclusions of the ACGIH® and Safe Work Australia reviews, and considered:

- acetaldehyde dehydrogenases show genetic polymorphism that gives rise to differences in vulnerability in humans concerning toxicity
- acetaldehyde is a direct acting gene mutagen in mammalian cells *in vitro*; induces DNA-protein cross-links, sister chromatid exchanges and chromosomal aberrations in rodents *in vivo*
- the mechanisms of action for the nasal and laryngeal cancers reported in rats and hamsters after chronic inhalation exposures to acetaldehyde appear to be genotoxicity, cytotoxicity, and inflammation caused by repeated irritation of the olfactory and respiratory epithelium followed by regenerative growth
- since some of the cancer risk is from a direct genotoxic mechanism, no threshold can be assumed, although the irritation-regeneration cycle appears to be a critical feature
- reports of eye irritation by a proportion of exposed individuals at acetaldehyde concentrations of 25ppm for 15 minutes with the majority reporting irritation at 50ppm, when a slight increase in mucociliary transport time was reported after 4 hours exposure in another study. At 135ppm for 30 minutes all subjects reported mild upper respiratory tract irritation, while at 200ppm for 15 minutes all subjects had eye irritation and most reported nose and throat irritation (ACGIH®, 2014)
- the proposed WES-Ceiling of 20ppm for acetaldehyde is protective of symptoms of irritation, occurring at concentrations as low as 25ppm (ACGIH®, 2014)
- noting that the proposed WES-Ceiling of 20ppm for acetaldehyde may not eliminate all risk, due to the direct genotoxic potential of acetaldehyde, exposures to acetaldehyde should be minimised.

The reviewed toxicological database indicates that acetaldehyde does not need additional notations.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADH	Alcohol dehydrogenase.
ADH1B	Alcohol dehydrogenase 1B encoded by the ADH1B gene.
AGS	Ausschuss für Gefahrstoffe (Committee for Hazardous Substances) is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
ALDH	Aldehyde dehydrogenase.
ALDH2	Aldehyde dehydrogenase 2 encoded by the ALDH2 gene.
CERIJ	Chemicals Evaluation and Research Institute, Japan.
CYP2E1	Cytochrome P450 family 2; subfamily E; member 1.
DECOS	Dutch Expert Committee on Occupational Standards. A committee of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DNA	Deoxyribonucleic acid.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
EPA	The New Zealand Environmental Protection Authority.
GLP	Good Laboratory Practice.
GST-P	Glutathione S-transferase (placental type).
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	The International Agency for Research on Cancer – an agency of the World Health Organisation.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance).
JSOH	Japan Society for Occupational Health.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LOQ	Limit of quantitation.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
mg	Milligram or one thousandth of a gram.
mg/kg b.w.	Milligram of substance per kilogram body weight.
mg/kg/day	Milligram of substance per kilogram body weight per day (exposure rate).

TERM	MEANING
mg/m³	Milligrams of substance per cubic metre of air.
NAD	Nicotinamide adenine dinucleotide.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NOAEC	No Observed Adverse Effect Concentration.
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OSHA	Occupational Safety and Health Administration, US Department of Labor.
ppm	Parts of vapour or gas per million parts of air.
RoC	Report on carcinogens.
RSEN	A notation indicating the substance is a respiratory sensitiser. RSEN is used in place of SEN when specific evidence of sensitisation by the inhalation route is confirmed by human or animal data. An ACGIH® term.
SCCS	The Scientific Committee on Consumer Safety of the European Commission - provides opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products and services.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
T25	The dose eliciting a 25% increase in the incidence of a specific tumour above the background level (that is, after correction for spontaneous incidence) within the standard lifespan of that species.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-Ceiling	Threshold Limit Value – Ceiling: the concentration that should not be exceeded during any part of the working exposure. If instantaneous measurements are not available, sampling should be conducted for the minimum period of time sufficient to detect exposures at or above the ceiling value. An ACGIH® term.
US EPA	United States Environmental Protection Agency.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-Ceiling	A concentration that should not be exceeded at any time during any part of the working day.
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

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