Recommendation from the Scientific Committee on Occupational Exposure Limits for acetic acid

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8-hour TWA:	10 ppm (25 mg/m^3)
STEL (15-min):	20 ppm (50 mg/m^3)
BLV:	None
Notation:	None

Substance identification and physical-chemical properties

Chemical name:	acetic acid
Synonyms:	ethanoic acid, ethylic acid, methane carboxylic acid
Molecular formula:	$C_2H_4O_2$
Structural formula:	CH_3COOH
EINECS No.:	200-580-7
CAS No.:	64-19-7
Molecular weight:	60 g/mol
Boiling point:	118 °C
Melting point:	17 °C
Vapour pressure (20 °C):	1.47 kPa
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 2.5 mg/m^3; 1 mg/m^3 = 0.40 ppm

EU classification:

Flam. Liq. 3	H226	Flammable liquid and vapour
Skin Corr. 1A	H314	Causes severe skin burns and eye damage
Skin Corr. 1A; C ≥ 90 %	H314	Causes severe skin burns and eye damage
Skin Corr. 1B; 25 % ≤ C < 90 %	H314	Causes severe skin burns and eye damage
Skin Irrit. 2; 10 % ≤ C < 25 %	H315	Causes skin irritation
Eye Irrit. 2; 10 % ≤ C < 25 %	H319	Causes serious eye irritation

1. Occurrence/Use

The largest use of acetic acid is as a chemical intermediate in the manufacture of vinyl acetate monomer (VAM), which accounts for about one third of consumption. VAM is used to make emulsions as base resins for water-based paints, adhesives, paper coatings and textile finishes. Ethylene vinyl acetate copolymers are used as hot melt adhesives and coatings (ICIS 2011).

A stronger growth area for VAM is ethylene vinyl alcohol polymers which are reported to have excellent barrier properties enabling their use in flexible food packaging films, plastic bottles and gasoline tanks for motor vehicles. VAM is the raw material for polyvinyl alcohol (PVOH) used as a component of adhesives and paints. PVOH is, in turn, used to make polyvinyl butyral resins, the transparent adhesive film used to bond layers of safety glass (ICIS 2011).

A fast growing outlet for acetic acid is as a process solvent in the manufacture of terephthalic acid (PTA) which is used to make polyethylene terephthalate (PET) bottle resins and polyester fibre. Globally, PTA accounts for about 17 % of acetic acid consumption (ICIS 2011).

Acetate esters at present account for some 17 % of acetic acid production and are used as solvents in a wide variety of paints, inks and other coatings in addition to their use in many chemical processes (ICIS 2011).

Acetic acid is further used as a food and animal feed additive, a preservative in pickles, as a natural latex coagulant, and in textile dyeing and printing (ACGIH 1991).

Dilute solutions (0.25–5 %) are used to treat infections from several types of microorganisms (NDL 1992) and to remove lime scale.

2. Health significance

2.1. Toxicokinetics

Acetic acid is absorbed from the gastrointestinal tract and through the lungs. The acetate ion (the anion of acetic acid) is a normally-occurring metabolite in catabolism or in anabolic synthesis, e.g. in the formation of glycogen, cholesterol synthesis, degradation of fatty acids, and acetylation of amines.

It is estimated that the level of the acetate ion in humans is about 50–60 µmol/l (3.0–3.6 mg/l) in plasma and 116 µmol/l (7 mg/l) in cerebrospinal fluid (Lentner 1984). Daily turnover of the acetate ion in humans is estimated to be about 7.5 µmol/kg/min representing some 45 g/day (Simoneau *et al* 1994).

Acceptable daily intakes (ADIs) for acetic acid have not been proposed as sensory properties will limit intakes. Estimations of the daily intake of acetic acid vary from about 1 gram (Elias 1987) to 2.1 g/day for subjects older than 2 years (Katz & Guest 1994). No adverse health effects are reported at these intakes.

In rats given radiolabelled acetate in diet, 50 % of the radiolabel was excreted as CO_2 (Lundberg 1988).

2.2. Acute toxicity

2.2.1. Human data

Poisoning following incidental or accidental ingestion of concentrated acetic acid has often been reported. Doses of 20–50 g or 60–70 ml concentrated acetic acid have been calculated to be lethal. Survivors were treated for oesophageal constriction (Henschler 1973).

2.2.2. Animal data

The oral LD_{50} for acetic acid was 3 310 and 4 960 mg/kg bw in rats and mice, respectively.

The LC_{50} for mice was found to be 5 620 ppm for 1-hour exposures. Symptoms were mainly irritation of the upper respiratory tract and of the conjunctiva. Most of the surviving animals recovered quickly and showed no abnormal condition after 30–35 hours (Ghiringhelli and Fabio 1957).

2.3. Irritancy and corrosivity

2.3.1. Human data

Acetic acid at very high concentrations of 24 000 ppm and above causes irritation of the eyes and upper respiratory tract in humans (von Oettingen 1960).

In a study of 5 workers from the same cellulose acetate chemical plant (no data available on exposures to acetic acid or duration) reported effects included blackening and hyperkeratosis of the skin of the hands, conjunctivitis, pharyngitis, bronchitis (asthma-like in 3 cases, initial emphysema in one), and blackening and erosion of the teeth (Parmeggiani and Sassi 1954). It was reported that exposure for 7–12 years at concentrations of 60 ppm, plus one hour daily at 100–260 ppm, caused no injury except slight irritation of the respiratory tract, stomach and skin (Vigliani and Zurlo 1955).

Reports claim that persons unaccustomed to acetic acid vapours experience extreme irritation of the eyes and nose at concentrations of 25 ppm or more, and 50 ppm is considered unendurable. Acclimatised persons can tolerate 30 ppm without difficulty (no further data given, Hygienic Guide Series 1972).

Exposure over several years to concentrations higher than 10 ppm of acetic acid at workplaces producing acetic acid from wine caused no symptoms of poisoning leading to the view that concentrations of 20 to 30 ppm are not harmful (Vigliani and Zurlo 1955).

On the basis of industrial experience, it has been stated that exposure at 10 ppm is relatively non-irritating (no further data given, Henschler 1973).

The odour threshold for unacclimatised individuals is 1–5 ppm (Greim 2000).

In a well conducted human volunteer study, 11 individuals (5 men and 6 women) with a mean age of 27 years (range 21–40) were exposed on 3 separate occasions to air (the control exposure) and to acetic acid vapour at 5 and 10 ppm in an exposure chamber with 18–20 air changes per hour. One additional male subject was only exposed to air and the 10-ppm vapour concentration. Temperature, relative humidity, carbon dioxide and air outlet flows were routinely monitored. Subjects were exposed in pairs for 2 hours under resting conditions while seated. Exposure sessions were at

least two weeks apart. Acetic acid vapour was generated by injecting liquid acetic acid into inlet air by pump for dispersal in the chamber ceiling and samples were collected from the upper central chamber area to monitor vapour concentrations. No exposure related effects were observed on pulmonary function (measured before, immediately after, and 3 hours post-exposure) nasal swelling (assessed by acoustic rhinometry at the same intervals as pulmonary function), nasal airway resistance (obtained from nasal and mouth peak expiratory flows) or plasma inflammatory markers (C-reactive protein and interleukin-6) measured before and 3 hours post-exposure. Subjects were also asked to complete a questionnaire to rate their acute symptoms on a 0–100-mm visual analogue scale. Subjective ratings of nasal irritation and increased smell increased with exposure; for nasal irritation ratings were only significant at the 10-ppm concentration ($p < 0.049$) with the reported irritation constant throughout the 2-hour study suggesting a real irritant effect rather than a response simply to smell. Ratings for smell fell markedly to almost unnoticeable at both the 5- and 10-ppm concentrations when assessed 5 hours from the onset of exposure. Apart from smell, the ratings for nasal effects were at the lower end of the scale with median values of 4 mm (at 5 ppm) and 7.5 mm (at 10 ppm). A median value of 6 mm on the visual analogue scale is rated as 'hardly [noticeable] at all'. Median ratings for smell were 26 mm (at 5 ppm) and deemed somewhat noticeable, and 38 mm (at 10 ppm) and below the 48-mm rating which would be classed as 'rather' noticeable. Eye-blinking frequency increased during and after exposure to 10 ppm but was not significantly different from the control exposure (Ernstgård *et al* 2006).

In a second well conducted volunteer study, 24 subjects (13 male, 11 female) were all exposed over 4-hour intervals to 3 different concentrations of acetic acid at 0.6, 5 and 10 ppm (HVBG 2007, Kleinbeck 2009). The 0.6-ppm value was selected as a non-irritating odouriferous control (van Thriel 2006). An average 5-ppm concentration was achieved by varying levels between 0.3 and 10 ppm (with 4 peak exposures) over the 4-hour interval. A continuous exposure to 10 ppm represented the final exposure category. Volunteers were required to undertake three neurobehavioural tests, underwent physiological assessment for sensory irritation including rhinomanometry, and measurement of both substance P in nasal lavage fluid and eye blink frequency. In general, the intensity ratings decreased across the 4-hour exposure sessions. Only reported eye irritancy ratings increased slightly during the 10-ppm exposure scenario. Ratings between weak and moderate were recorded for the continuous exposure at 10 ppm. Significant differences were noted in 7 rating categories (eye and nasal irritation) for olfactory and trigeminal sensations between the 0.6- and the averaged 5-ppm exposures, and in 9 rating categories between 0.6- and 10-ppm exposures. Apart from a difference in reported olfactory sensations there were no significant differences in reported irritancy between the 5- and 10-ppm categories, so a clear-cut dose-dependency could not be confirmed. During all exposure conditions the rated olfactory symptoms declined over time reaching a plateau approximately 150 minutes after exposure onset. Average eye blink frequencies were similar in all exposure categories but increased in all groups between the start and end of the sessions. Nasal flow, as assessed by rhinomanometry, decreased in all exposure categories but was not statistically significant. The reduction in flow was attributed to higher pre-exposure measurements. Substance P concentrations were higher post- than pre-exposure but very variable between categories; the pre-exposure measurement before the 0.6-ppm exposure was higher than the 10-ppm post-exposure value. There were no significant differences in the ratio pre- to post-exposure substance P concentrations under any of the test conditions. Overall there were no physiological indicators of sensory irritation up to 10-ppm exposure, but some self-reported rating sensations in the 'weak' category for nasal irritation, pungency burning and nausea.

An irritation threshold for acetic acid was determined in a series of very brief exposures of no more than seconds (van Thriel 2006). This threshold, called the lateralisation threshold, is based on stimulation of trigeminal nerve endings and can be assigned to one nostril. The threshold is determined through subjects being asked to smell varying concentrations of the test agent and a control agent. Through a nose-piece, subjects use individual nostrils to identify the agent. Test and control agents are randomised between nostrils (Hummel 2000, Dalton and Dilks 2006). The lateralisation threshold for acetic acid was 40 ppm (van Thriel 2006).

A case of a chemical burn (necrosis, ulceration) following treatment under occlusion with gauze consisting of a 50:50 mixture of flour and rice vinegar containing 4.5 % acetic acid has been reported (Kuniyuki and Oonishi 1997).

In patch tests with human volunteers over 4, 24 and 48 hours, a 10 % aqueous solution of acetic acid caused slight irritation (Nixon *et al* 1975) that did not lead to EC classification as "irritant to the skin" (Griffiths *et al* 1997).

2.3.2. Animal data

In rats, 4 500 mg/kg bw/day for 30 days induced gastric lesions (Leung and Paustenbach 1990).

Administration of 0.01–0.25 % (i.e. 8–210 mg/kg bw/day) in the drinking water, for 9–15 weeks, did not affect food and water consumption and body weight gain. Doses of 0.5 % (i.e. 410 mg/kg bw/day), for 9 weeks, caused decreases in food consumption and body weight gain, but not in water consumption (Henschler 1973).

Rats that received 0.5 % acetic acid in drinking water for up to 15 weeks gained weight more slowly and ate less food than controls (Lundberg 1988).

Guinea pigs exposed for one hour to concentrations of 5, 39, 119 or 568 ppm of acetic acid showed an increase in pulmonary flow resistance, a decrease in pulmonary compliance and an increase in the time constant of lungs. These changes suggest bronchial constriction as the first action of acetic acid. At 5 ppm, there was a 20 % increase in airway resistance ($p = 0.001$) accompanied by a 15 % reduction in compliance. In the case of exposure to 100 ppm, recovery was complete within one hour while the recovery was not complete after exposure to 500 ppm (Amdur 1961).

Acute vasodilatory responses to sensory irritants were assessed in Fischer 344 rats (up to 8 per group) exposed to acetic acid vapour at concentrations of 20, 120 and 360 ppm in a stainless steel nose-only inhalation chamber. Nasal vascular responses were monitored during exposure by examining acetone uptake in a surgically isolated nasal cavity model. Thus acetone was also present in the inspired air. Reflex vascular responses shown by a 40 % increase in acetone uptake were observed after 3 minutes exposure at 120 and 360 ppm but there was no change at 20 ppm (Stanek *et al* 2001).

Instillation of 0.5 ml of a 1 % acetic acid solution in the eyes of rabbits caused a severe burn (Smyth *et al* 1951). Solutions of 5 % induced injury in eyes of rabbits which were healed by 14 days while a 10 % solution resulted in severe permanent damage (Henschler 1973).

No skin corrosion was observed when 0.5 ml undiluted glacial acetic acid was applied to the shaved backs and flanks of rabbits (patch testing for 4 hours) (Vernon *et al* 1977). Based on the average of mean scores for intact and abraded skin (readings at 4, 24 and 48 hours) a 10 % solution was concluded to be slightly and negligibly irritating to rabbits and guinea pigs, respectively (Nixon *et al* 1975).

2.4. Sensitisation

It was reported that a 68-year-old female patient showed type-I hypersensitivity-like reactions following ingestion of alcoholic beverages, medication containing ethanol and salad dressing with acetic acid. Based on the patient's history, as well as the results of allergological tests, the authors concluded that acetic acid was the likely causative agent for these reactions (Boehnke and Gall 1996).

2.5. Genotoxicity

2.5.1. In vitro

Acetic acid in concentrations of 100–6 666 µmole/plate with and without metabolic activation was negative in mutagenicity assays using *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 (Zeiger *et al* 1992). In *Saccharomyces cerevisiae,* acetic acid showed no mutagenic potential (Katz 1994). Acetic acid at concentrations close to those showing cytotoxicity (up to 16 mM) was concluded not to be clastogenic when tested in cultured Chinese hamster K1 cells; the observed induction of chromosome aberrations were considered to be due to pH-effects (Abernethy *et al* 1982). Acetic acid in concentrations of 250–1 500 µg/ml (LC_{50} 1 000 µg/ml) did not initiate transformation in C3H/10$T_{1/2}$ cells (Abernethy *et al* 1982).

2.5.2. In vivo

Acetic acid did not induce mutations or chromosomal recombination in *Drosophila melanogaster* (Mollet 1976).

2.6. Carcinogenicity

There were no carcinogenicity studies.

Application of acetic acid to the skin of mice was reported to stimulate the occurrence of epidermal hyperplasia, suggesting that it was a very weak tumour promotor (Slaga *et al* 1975).

2.7. Reproductive toxicity

There were no studies on reproductive toxicity.

3. Recommendation

The critical effect of occupational exposure to acetic acid is irritation of the skin and mucous membrane. There is reliable dose-response data on sensory irritation in human volunteers and this can be used to set limits for exposure. Minor subjective irritant effects have been reported in two volunteer studies at 10-ppm exposures (Ernstgård *et al* 2006, HVBG 2007). Although Ernstgård *et al* (2006) noted a non-significant increase in eye blink frequency at 10 ppm, this response was not observed in the larger study on volunteers observed over 4 hours and reported by HVBG (2007). Neither the Ernstgård nor the HVBG studies observed any physiological changes compatible with irritation at 10-ppm exposures.

Ernstgård *et al* studied 11 volunteers in a 2-hour exposure and HVBG 24 subjects over 4 hours. The results reported in the two studies are comparable. Given the minor subjective effects reported at 10 ppm, the absence of any physiological measurements of irritation at this concentration, the possibility that smell may be affecting some self-reported ratings of irritation by the volunteers and a laterilisation (irritation) threshold

of 40 ppm it is possible to recommend an 8-hour OEL of 10 ppm. Assuming 100 % respiratory uptake the inhaled dose over a working shift would be about 250 mg (25 mg/m^3 x 10 m^3). Given that the daily turnover of the acetate ion (the ionic form of acetic acid) is estimated to be about 45 g/day no systemic effects are expected at the proposed OEL. With an irritation (laterilisation) threshold identified at 40 ppm, it is unlikely that at exposures half of this there will be noticeable irritation over the short term and therefore a 20 ppm STEL can also be recommended.

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