Acetic acid

(CAS No: 64-19-7)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of acetic acid by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by A Wientjes, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of acetic acid has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1999, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, starting from 1966, 1999, 1965, and 1967, respectively, and using the following key words: acetic acid and 64-19-7.

In February 2001, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional search in Toxline and Medline in January 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	acetic acid
synonyms	:	ethanoic acid; ethylic acid; methane carboxylic acid
molecular formula	:	$C_2H_4O_2$
structural formula	:	CH_3-COOH
CAS number	:	64-19-7

3 Physical and chemical properties

molecular weight	:	60
boiling point	:	118°C
melting point	:	17°C
flash point	:	39°C (closed cup)
vapour pressure	:	at 20°C: 1.5 kPa
solubility in water	:	miscible
log $P_{octanol/water}$	:	-0.17 (experimental); 0.09 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 2.5 mg/m^3 1 mg/m^3 = 0.40 ppm

Data from ACG98, Lun88, NLM04, Ric92, http: //esc.syrres.com.

Acetic acid is a clear, colourless, flammable liquid with a pungent odour. Odour thresholds of 0.48 and 1 ppm (1.3 and 2.5 mg/m^3) were reported for acetic acid (Amo83, Rut86).

4 Uses

Acetic acid is used in the manufacture of organic compounds such as acetic anhydride, acetic esters, and chloroacetic acid, of synthetic fiber materials such as cellulose acetate and acetate rayon, of plastics, pharmaceuticals, dyes, insecticides, and photographic chemicals. It is also used as a food additive (as vinegar), as a natural latex coagulant, and in textile dyeing and printing (ACG98, Kat94, Ric92).

Dilute solutions (0.25-5%) are used to treat infections from several types of microorganisms (Kat94).

5 Biotransformation and kinetics

Acetic acid is absorbed from the gastrointestinal tract and through the lungs. The acetate ion is a normally occurring metabolite. As shown by *in vivo* and *in vitro* experiments, it is an intermediate in catabolism or in anabolic synthesis, e.g., in the formation of glycogen, fatty acid synthesis as well as cholesterol synthesis, in the acetylation of amines, in the conversion into alanine and, thence, incorporation into proteins of plasma, liver, kidney, gut mucosa, muscle, and brain (FAO74, Kat94, Lun88).

In rats orally (diet) given radiolabelled acetate, 50% of the radiolabel was excreted as CO_2 (Lun88).

6 Effects and mechanism of action

Human data

When tested for its skin irritation potential in human volunteers by 3 different laboratories, a 10% solution of acetic acid gave such a low level of reaction in the 4-hour patch tests that an EC classification as ‘irritant to the skin’ is not warranted (Gri97). In a separate 4-hour patch test with human volunteers, a 10% solution was concluded to be slightly irritating based on the average of mean scores for intact and abraded skin (score: 1.0/8.0; readings at 4, 24, and 48 hours) (Nix75). 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 (Kun97).

Splashing into the eyes of diluted (e.g., vinegar) or concentrated (e.g., vinegar essence, glacial acetic acid) acetic acid has been reported to cause, amongst others, photophobia, conjunctival hyperaemia, and corneal opacification. Some of these effects were permanent. Furthermore, it was stated that the severity of the injury became evident a day or two after the incident (Gra86).

Based on - not further documented - industrial experience and animal experiments, exposure to 25 mg/m^3 (10 ppm) for 8 hours could induce some irritation of the eyes, the nose, and throat while levels of 250 mg/m^3 (100 ppm) were supposed to cause marked irritation of the respiratory tract and the eyes (Kat94, Smy56). Levels of 2000-3000 mg/m^3 (800-1200 ppm) were stated to be tolerable for 3 minutes only, resulting in marked eye and upper respiratory tract irritation (Oet69).

Studies among workers in Italian cellulose acetate plants, exposed for 7-12 years to average concentrations of 150 mg/m^3 (60 ppm) and daily 1-hour peak levels of 250-650 mg/m^3 (100-260 ppm), mentioned that the workers had no general injury except for slight irritation of the respiratory tract, the stomach, and the skin (Vig55). However, in a separate study concerning 5 workers, probably from the same plants based on exposure levels and duration, effects including 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 were reported (Par54). In a separate investigation on 12 workers employed in this industry for 2-19 years and exposed at the time of study to average levels of 300 mg/m^3 (125 ppm) with excursions to approximately 1000 mg/m^3 (400 ppm), irritation of the conjunctiva and the upper respiratory tract and hyperkeratotic dermatitis of the hand palms were observed (Ghi57). Although some authors conclude from the data from these industries that exposure to 50-75 mg/m^3 (20-30 ppm) is tolerable (Vig55), others state that exposure to 25 mg/m^3 or below may induce conjunctival irritation with reddening and lachrymation (Bal53). Hardly any case of poisoning has been reported from Italian workers exposed to levels in excess of 25 mg/m^3 (10 ppm) for decades in the production of vinegar from wine (Vig55).

Since exposure was to both acid aerosol and spice dust, the committee cannot draw definite conclusions on the causal role of acetic acid with respect to prevalence of acute and chronic respiratory symptoms and lung function changes found in a group of 117 woman occupationally exposed to undefined levels of aerosols dusts in the Croatian pickling industry (Zus93).

Due to an accident, workers at a plant producing acetic acid were exposed to an aerosol of acetic acid and acetic acid anhydride during their luncheon in the cafeteria. The acute effects were severe irritation of eyes and upper respiratory tract and, in some cases, dyspnoea. Clinical examination of the 14 exposed persons 2 hours after the accident revealed intense conjunctivitis and acute pharyngo-laryngitis, corneal ulcers, necrotic areas in the nasal mucosa, and spastic bronchitis. Two workers also had second-degree burns on their legs. Upon medical treatment, all had recovered within 25 days (Cap67).

Rajan and Davies reported a patient who developed both reversible airway obstruction and steroid responsive interstitial pneumonitis after accidental exposure to glacial acetic acid (Raj89).

Based on a questionnaire survey conducted among 56 hospital employees 8 months after a chemical spill of 100% acetic acid, Kern concluded that 8 workers had developed an asthma-like syndrome within 24 hours of the spill and that 4 of them satisfied all criteria for the reactive airways dysfunction syndrome (RADS; i.e., a chronic asthma-like illness with airway hyperresponsiveness that develops within 24 hours of a single, brief, highly irritating inhalation exposure) (Ker91).

Poisoning following incidental or accidental ingestion of concentrated acetic acid has been frequently 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 (Gre97). Doses of approximately 100 mg (1.5 mg/kg) were reported to induce gastrointestinal ulcerations and bleeding (Kat94).

It is reported that acetic acid can function as causative agent for type-I hypersensitivity-like reactions to alcoholic beverages. A 68-year-old Caucasian female patient suffered numerous episodes of conjunctivitis, swelling of the tongue and lips, dyspnoea, and an urticarial rash. These symptoms occurred 5 to 15 minutes after ingestion of even minor amounts of beer, wine, or other alcoholic beverages. More recently, she observed similar signs when taking medication containing ethanol or after eating salads with dressings containing acetic acid. All symptoms resolved spontaneously within several hours. Clinical investigation revealed an elevated serum IgE (Boe96). Przybilla and Ring already established this reaction in 1983. Severe anaphylactic reactions after ingestion of as little as 1 mL ethanol associated with a positive prick test reaction to acetic acid in a definitely non-irritating concentration strongly suggest that the patient’s anaphylactic reactions are based on an immediate-type allergy to acetic acid, the main metabolite of ethanol (Prz83).

Animal data

Irritation and sensitisation

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) (Ver77). Acetic acid was mildly irritating (readings at 24 and 72 hours) when 0.5 mL of a 4% solution was applied to the clipped intact or abraded skin (back or abdomen) of rabbits and guinea pigs (Rou65). Based on the average of mean scores for intact and abraded skin (readings at 4, 24, and 48 hours), Nixon et al. concluded that a 10% solution was slightly and negligibly irritating to rabbits and guinea pigs, respectively (scores: 0.9/8.0 and 0.1/8.0, respectively) (Nix75). Uncovered application of undiluted acetic acid to the clipped abdomen of rabbits produced a primary irritation score of 5 (i.e., undiluted material causes strong erythema, oedema, or slight necrosis; see Smy49), on a scale from 1 to 10 (Smy51). Referring to unpublished industrial data, it was stated that solutions of 5-10% and 10-50% were not and mildly irritating, respectively, while solutions of 50-80% and >80% produced moderate to severe and severe burns, respectively (Gre97, Kat94).

When instilled into the eyes of rabbits, acetic acid scored 10 (i.e., 0.5 ml of a 1% solution causes a severe burn; see Car46) on a scale of 1 to 10 (Smy51). In other rabbit studies, it was reported that a 1% solution had caused considerable inflammation and permanent opacity while a drop of a 2% solution did not have produced damage when washed off immediately. Solutions of 5 % gave undefined injury that was healed by 14 days while a 10% solution resulted in severe permanent damage (Gre97). In guinea pigs, solutions of 6-9% had caused transient loss of epithelium (Gre97).

Acute toxicity

Inhalation of 40,000 mg/m^3 (16,000 ppm), for 4 hours, killed 1 out of 6 exposed rats (observation time: 14 days) (Smy56). In rats exposed to levels of 30,000-87,500 mg/m^3 (12,000-35,000 ppm), for 30 minutes, effects on the nose and on the trachea and other parts of the upper respiratory tract were seen at the lower and higher end of this concentration range, respectively (Gre97). In mice, a 1-hour LC_{50} of 14,050 mg/m^3 (5620 ppm) was found (Ghi57). At concentrations of >2500 mg/m^3 (1000 ppm), transient irritative symptoms of the conjunctiva and upper respiratory tract were observed. Post-mortem examinations of the deceased animals revealed congestion of the viscera; histologically, foci of

peribronchitis, areas of emphysema, and cloudy swelling, particular of the liver, were seen. In guinea pigs, similar irritative effects were seen, but they were less susceptible than the mice (Ghi57). When guinea pigs were exposed to 13-1425 mg/m^3 (5-568 ppm), for 1 hour, changes suggestive of bronchial constriction (an increase in pulmonary flow resistance, a decrease in pulmonary compliance, an increase in time constant of the lungs) were observed. Concentrations of 300 and 1425 mg/m^3 (119,568 ppm) also caused a decrease in respiration rate and minute volume and an increase in 'the work of respiration'. In case of the exposure to 300 mg/m^3, recovery was complete within 1 hour. At 1425 mg/m^3, there was some recovery but values for resistance, compliance, time constant, frequency, and minute volume still were still statistically significantly different from control values (Amb61). The sensory irritation of the upper respiratory tract was studied in mice and rats by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). RD_{50} values of 163 and 227 ppm (408, 568 mg/m^3) were found in male Swiss OF1 mice (DeC81, Gag02). In male F344 rats, the RD_{50} was estimated to be 1040 ppm (2600 mg/m^3). Furthermore, the upper respiratory tracts of anaesthetised rats were isolated by insertion of an endotracheal cannula, and acetic-acid-laden air was continuously drawn through that site at a continuous flow rate for 50 minutes. Acetic acid vapours of 130 ppm (325 mg/m^3) and above induced an immediate sensory-nerve-dependent nasal vasodilatory response (Sta01).

Oral LD_{50} values of 3310 and 4960 mg/kg bw were found in rats and mice, respectively (Gre97, Kat94).

Aqueous concentrations of acetic acid of 0.5% or more were fatal to rabbits if given orally or per rectum (Kat94).

Repeated-dose toxicity

Referring to a Russian study, it was stated that exposure to 27 to 86 mg/m^3 (100-350 ppm) of acetic acid for 3 to 35 days caused behavioural changes (treadmill run duration, open field activity) in not specified experimental animals (Kat94).

Oral (gavage) administration to rats of doses of acetic acid of 1800 mg/kg bw/day or of sodium acetate of 4200-4800 mg/kg bw/day did not induce mortality, while an acetic acid dose of 2400 mg/kg bw/day caused the death of all rats (n=3-4) after 3 to 5 days (FAO74). 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., 360 mg/kg bw/day), for 9 weeks, caused decreases in food consumption and body weight gain, but not in water consumption (Gre97). In rats, given 4500

mg/kg bw/day, for 30 days, gastric lesions were seen (Leu90). Oral (gavage) treatment with 3% acetic acid for 6 months resulted in chronic inflammation of the oesophageal mucosa (Russian study; no more details presented) (Kat94).

Carcinogenicity

There were no experimental animal studies on the potential carcinogenicity of acetic acid. When tested in a multistage mouse skin model for chemical carcinogenesis including tumour initiation, promotion, and progression, acetic acid was found to be a very weak tumour promotor and a strong tumour-progressing agent in which selective cytotoxicity may have been a major component (Rot88, Sla75).

Mutagenicity and genotoxicity

Acetic acid, tested at 5 dose levels ranging from 100 to 6666 µg/plate with and without metabolic activation, was negative in mutagenicity assays using *S. typhimurium* strains TA97, TA98, TA100, and TA1535 (Zei92).

No mutagenic response was seen in *S. cerevisiae* when tested with or without liver preparations from mouse, rat, or monkey (Kat94).

Acetic acid, at concentrations close to those showing cytotoxicity (up to 16 mM), was concluded not to be clastogenic upon testing in cultured Chinese hamster ovary K1 cells. Although induction of chromosome aberrations was found, they were considered to be artifacts due to pH effects (Kat94).

Acetic acid was not found to induce mutations or chromosomal recombinations in *D. melanogaster* (Lun88) while in another experiment, a variety of genetic effects among which non-disjunction, crossing over, deletion, and possibly mutation were induced following treatment with vapours of glacial acetic acid at various stages of development (Blo52).

Treatment of C3H/10T½ cells with acetic acid (250-1500 µg/mL; LC_{50}: 1000 µg/mL) did not cause or initiate transformation (Abe82).

Reproduction toxicity

No increases in maternal or fetal mortality or other fetal abnormalities were seen following oral (gavage) administration of 1600 mg of apple cider vinegar/kg bw to pregnant rats, mice, or rabbits, on gestational days 6 to 15 (rats, mice) or 6 to 18 (rabbits) (Foo74).

No teratogenic effects on developing chicken embryos were observed after injecting sodium acetate (100 mg/kg) into the yolk or air cell of eggs and incubating for 96 hours. The LD_{50} of sodium acetate after injection into the yolk of unincubated eggs was 91.5 mg/kg, whereas 200 mg/kg injected into the air cell was not toxic (Kat94).

Chicks with some deformities were hatched from eggs injected with acetic acid during the early stages of incubation (Kat94).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for acetic acid in the Netherlands is 25 mg/m^3 (10 ppm), 8-hour TWA.

Existing occupational exposure limits for acetic acid in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find valid human or experimental animal studies in which well-characterised exposure by inhalation of acetic acid was related to systemic effects.

Upon oral administration, a few cases of type-I hypersensitivity-like reactions to acetic acid in humans have been reported. In experimental animals, acetic acid did not induce maternal or fetal mortality or any other fetal abnormalities upon administration of doses of 1600 mg/kg bw to pregnant rats, mice, or rabbits. There were no studies on the carcinogenic potential of acetic acid; the compound appeared to be a weak tumour-promoting and a strong tumour-progressing agent. The compound was not genotoxic in bacteria, yeast, or mammalian cells (Chinese hamster ovary cells).

The acetate ion is a normal endogenous compound in humans. Furthermore, acetic acid and acetate are occurring naturally in food, food products, and beverages. The possible average daily intakes for persons more than 2 years old were calculated to be 2.1 and 0.23 g/day for acetic acid and sodium acetate, respectively (Kat94). Therefore, no systemic effects are expected from the amount that would be taken up by inhalation of the current occupational exposure level of 25 mg/m^3 (which results in a daily dose of 0.25 g assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day, and an absorption of 100%).

The most outstanding effect of acetic acid is its local irritation and corrosion. These effects on skin and eyes of liquid acetic acid are frequently reported.

Poorly documented data on occupational exposed workers suggest that exposure levels of 25 mg/m^3 (10 ppm) induced slight irritation while more severe effects (conjunctivitis, pharingitis, bronchitis, erosion of teeth) were reported at average concentrations of 150 mg/m^3 (60 ppm) with regular peak levels of 250-650 mg/m^3 (100-260 ppm).

The committee considers the toxicological database on acetic acid too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

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Annex

Occupational exposure limits for acetic acid in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	10	25	8 h	administrative		SZW04
Germany						
- AGS	10	25	8 h			TRG03
	10	25	15 min			
- DFG MAK-Kommission	-[c]	-[c]				DFG03
Great Britain						
- HSE	10	25	8 h	OES		HSE02
	15	37	15 min			
Sweden	5	13	8h			Swe00
	10	25	15 min			
Denmark	10	25	8 h			Arb02
USA						
- ACGIH	10	-	8 h	TLV		ACG04
	15	-	15 min	STEL		
- OSHA	10	25	8 h	PEL		ACG03
- NIOSH	10	25	10 h	REL		ACG03
	15	37	15 min	STEL		
European Union						
- SCOEL	10	25	8 h	ILV[d, e]		EC04

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.

[d] Listed among compounds for which OELs are already included in Commission Directives.

[e] In June 2001, SCOEL (SCOEL/SUM/98 final) concluded that, based on the data available, it was not possible to establish a health-based occupational exposure limit.