Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for ethyl acetate

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8 hour TWA:		200 ppm (734 mg/m^3)
STEL (15 mins)	:	400 ppm (1468 mg/m^3)
Notation:		none

SUBSTANCE IDENTIFICATION:

Ethyl acetate : $CH_3COOC_2H_5$

Synonyms : Ethyl acetic ester, ethyl ethanoate
EINECS No : 205-500-4
EEC No: 607-022-00-5
EU Classification: F; R11 Highly flammable, Xi; R36, R66,R67.
CAS No : 141-78-6
MWt : 88.12

Conversion factor (20°C, 101kPa): 3.67 mg/m^3 = 1 ppm

1. Occurrence/use

Ethyl acetate is a clear volatile and highly flammable liquid, with a characteristic fruity odour. It has a MPt of -84°C, a Boiling Point of 77°C and a vapour pressure of 13.3kPa at 27°C. The odour threshold is 3.6 to 245 ppm (24 to 900 mg/m^3). The explosive limits are 2.2% to 11% by volume in air.

Ethyl acetate occurs in small quantities in some plant material and in particular in some plant aromas. Its main occurrence is as a high volume solvent with a production rate in the European Communities in excess of 1000 tonnes per annum. It is produced synthetically by esterification between acetic acid and ethanol. As a solvent its use is widespread in the preparation of paints, plastics, foodstuffs, pharmaceuticals and printing inks. It is also often used as a laboratory agent.

2. Health significance

The acute toxicity of ethyl acetate is low. LC50 values in the region of 10000 to 16000 ppm (36.7 to 58.7 g/m^3) have been determined in mice and rats (von Oettingen, 1960). Effects on the CNS, respiratory tract, liver and kidney occur at these high concentrations.

The RD_{50} value in mice is around 600 ml/m^3 (2100 to 2200) mg/m^3. Such a concentration has been judged "intolerable" in humans (NEG 1991). In the case of ethyl acetate, this conclusion is contradicted by several studies in humans who could well tolerate concentrations in the range of 400 ppm for up to 8 hours (see below).
The toxic mechanism of this simple carboxylic acid ester is well understood. Due to the rapid enzymatic cleavage into acetic acid and ethanol, even by the epithelial cells of the respiratory tract, ethyl acetate is unlikely to cause systemic effects at low exposure levels. The critical effect is therefore irritation of the mucous membranes of the upper respiratory tract.

In a case of acute intoxication by ethyl acetate, the victim was found dead lying on his abdomen with his clothes soaked in ethyl acetate. In blood, rapid hydrolysis of ethyl acetate occurred by plasma esterases resulting in acetic acid and ethanol was detected. The highest concentration of ethyl acetate was found in the testis indicating that post-mortem percutaneous absorption may have occurred (Coopman et al. 2005).

A 3-5 minute exposure of volunteers led to self-reported irritation symptoms at 400 ppm (1468 mg/m^3) concerning eyes, nose and throat. 200 ppm (734 mg/m^3)was objectionable to some because of the strong odour (Nelson *et al*., 1943). However, the exposure atmosphere was not controlled analytically. The irritancy of airborne ethyl acetate has later been confirmed in an experimental study on volunteers exposed to 400 ppm ethyl acetate for 4 hours which pointed to some irritation and annoyance occurring at this level (Seeber et al., 1992). Another publication showed that the level of irritation did not increase between 4 and 8 hours exposure to 400 ppm (Seeber et al., 1992a). In terms of irritation, 400 ppm ethyl acetate was considered about equipotent compared to 1000 ppm acetone whilst, in terms of annoyance, ratings were slightly higher for 400 ppm ethyl acetate than for 1000 ppm acetone (Seeber *et al.*, 1997). In these studies the influence of odour on irritation was not considered. It was, however, later shown that odour has a strong influence on the self-reported level of "irritation" (Arts et al. 2006). The reported "irritation" observed in the aforementioned studies was likely influenced by the strong odour of ethyl acetate.

Another experimental study on irritancy of ethyl acetate in volunteers has been presented by McCallum *et al*. (1997). The irritancy effects as measured by participants' reporting of a greater number and severity of symptoms in completing the irritancy questionnaire, appeared to be related to the level and length of exposure. The authors stated that irritancy effects were not observed at exposure levels of 200 ppm (734 mg/m^3; 4 hour exposure; n=5) but were observed at exposure levels of 400 ppm (1468 mg/m^3; 4 hour exposure; n=6) (particularly as length of exposure increased) and during short-term (15 min; n=9) exposures at 600 to 1000 ppm (2202 to 3670 mg/m^3). Symptoms were mild irritations in eyes, throat and nose as well as headache at 400 ml/m^3 (2 vs. 0) at 600 and 1000 (3 vs 1), not at 800 ppm, and distraction. No symptoms were reported as "severe". Physiological indicators of eye irritation (blink rate) were not found to be increased.

A newer study with volunteers accounted for discrimination between effects due to odour and to sensory irritation: Twenty-four subjects were challenged with ethyl acetate in concentrations of 2 ppm (odour control group), 400 ppm and 400 ppm including peaks of 800 ppm for 4 hours. While the odour intensity was rated "strong", trigeminal perceptions (=irritation) were rated less than "moderate" according to an extended version of the Swedish performance evaluation system and to ratings on a visual analogue scale. The absence of substantial trigeminal ratings was supported by physiological data. There was neither an effect of concentration on eye blinking frequency nor on nasal resistance which both are indicators of irritation. Furthermore, there were no effects of ethyl acetate concentration on behavioural measures indicating no olfactory or trigeminally mediated disturbance of cognitive processing. In conclusion, the results revealed no adverse chemosensory effects of ethyl acetate at 400 ppm with peaks of 800 ppm (Kleinbeck et al., 2008).

The acute neurobehavioral effects of ethyl acetate was investigated after 20 minute inhalation exposures to 0, 500, 1000 or 2000 ppm in mice (n=8) using locomotor activity and a functional observational battery (FOB). Ethyl acetate produced significant decreases in locomotor activity, arousal, rearing and handling-induced convulsions at the highest concentration. Clonic movements were observed at concentrations $\geq$ 500 ppm. Recovery from the acute effects was rapid and began within minutes of removal from the exposure chamber (Bowen and Balster 1997). The data indicate significant behavioural effects at 2000 ppm; the effects on clonic movement at $\geq$ 500 ppm cannot be evaluated as the data were no presented by the authors.

In a subchronic inhalation neurotoxicity study, rats were exposed to 0, 350, 750 or 1500 ppm of ethyl acetate by inhalation for 6 h per day, 5 days per week for 13 weeks. Functional observational battery (FOB) and motor activity tests occurred on non-exposure days during weeks 4, 8 and 13, after which tissues were microscopically examined for neuropathology. A subset of rats was monitored during a 4-week recovery period. Exposure to 750 and 1500 ppm, diminished behavioral responses to unexpected auditory stimuli during the exposure session and appeared to be an acute sedative effect. There were no signs of acute intoxication 30 min after exposure sessions ended. Rats exposed to 750 and 1500 ppm had reduced body weight, body weight gain, feed consumption, and feed efficiency, which fully or partially recovered within 4 weeks. Reductions in body weight gain and feed efficiency were observed in male rats exposed to 350 ppm. The principal behavioural effect of subchronic exposure was reduced motor activity in the 1500 ppm females, an effect that was not present after the 4-week recovery period. All other FOB and motor activity parameters were unaffected, and no pathology was observed in nervous system tissues. Operant sessions were conducted in another set of male rats preconditioned to a stable operant baseline under a multiple fixed ratio-fixed interval (FR-FI) schedule of food reinforcement. FR response rate, FR post-reinforcement pause duration, and the pattern of FI responding were not affected during or after the

exposure series. In contrast, within-group FI rate for the treatment groups increased over time whereas those of the controls decreased. A historical control group, however, also showed a similar pattern of increase, indicating that these changes did not clearly represent a treatment-related effect. Results from these studies indicate a LOEL of 350 ppm for systemic toxicity based on the decreased body weight gain in male rats, and a LOEL of 1500 ppm for neurotoxicity based on the transient reduction in motor activity in female rats. In conclusion, there was no evidence that subchronic exposure up to 1500 ppm ethyl acetate produced any enduring neurotoxic effects in rats (Christoph et al. 2003). Histopathological evaluations of the respiratory tract were not performed; therefore, no conclusion about the irritating properties of ethyl acetate in rats can be derived.

Liquid ethyl acetate is mildly irritating but strongly defatting on contact with skin.

RECOMMENDATION

On the basis of the irritant properties of ethyl acetate an 8 hour TWA of 200 ppm (734 mg/m^3) is recommended. Up to 400 ppm no significant irritation occurred in a modern volunteer study with 4 hours exposure which discriminated between the effects of odour and trigeminally mediated sensory irritation. Also no neurobehavioral effects were seen in that study. An earlier study had shown no increase in irritation symptoms from 4 to 8 hours exposure. The TWA of 200 ppm is supported by a 13-week neurotoxicity study in rats, in which body weight gain of male but not of female rats was reduced to a small extent at 350 ppm, indicating that the effect is close to the threshold. Neurotoxic effects are not to be expected at the TWA as motor activity was decreased in rats at 1500 ppm and in mice at 2000 ppm. An STEL (15 min) of 400 ppm (1468 mg/m^3) is recommended.

There are no quantitative data available on the dermal absorption of ethyl acetate. No absorption was detected in experiments on the acute dermal toxicity in rabbits. The fact that the substance is highly volatile also speaks against a danger of additional internal exposure due to dermal exposure to liquid ethyl acetate at the workplace. Moreover, the systemic toxicity of ethyl acetate is low. Therefore, no "skin" notation is required.

At the levels recommended no measurement difficulties are foreseen.

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