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NEG and DEC Basis for an Occupational Health Standard:

Ethyl Acetate

Vesa Riihimäki

ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

The Swedish National Institute of Occupational Health employs over 300 scientists in research on the work environment. The research is led by 30 professors. The Institute does mostly applied research, but some question also require basic research.

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PREFACE

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DEC) of the Dutch Directorate-General of Labour and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities both in the Netherlands and in the Nordic Countries.

This document on health effects of ethyl acetate was prepared by Dr. V. Riihimäki from the Institute of Occupational Health in Helsinki, Finland, and was reviewed by the Dutch Expert Committee as well as by the Nordic Expert Group.

J.J. Kolk
Chairman
Dutch Expert Committee

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Chairman
Nordic Expert Group

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1 PHYSICAL-CHEMICAL DATA

Chemical name:	ethyl acetate
CAS registry number:	141-78-6
Synonyms:	acetic acid ethyl ester, acetic ester, acetic ether, acetoxyethane, ethyl ethanoate
Molecular formula:	$C_4H_8O_2$
Structural formula:	$H_5C_2\text{-}O\text{-}C(=O)\text{-}CH_3$
Molecular weight:	88.11
Boiling point:	77°C
Melting point:	-83°C
Vapour pressure (20°C):	9.73 kPa
Relative density (20°C):	0.90 (water = 1)
Vapour density:	3.04 (air = 1)
Flash point:	-4.4°C
Conversion factors (101 kPa, 25°C):	1 ppm = 3.60 mg/m^3 1 mg/m^3 = 0.278 ppm

At room temperature ethyl acetate is a clear, colourless liquid with a fruity odour. Published odour threshold values vary significantly (Ruth 1986). When extremes are omitted, the lowest

concentration perceived as an odour has been given as 0.2 - 0.6 mg/m^3 (71) while on the average (geometric mean) 14 mg/m^3 has been detected (3, 56). Saturation vapour concentration in air at 20°C is 9.6 %. The range of explosive limits is 2.0 - 11.5 %.

Ethyl acetate is moderately soluble in water (about 10 % v/v), more soluble in ethanol and acetone and completely soluble in diethylether.

Ethyl acetate has a significant affinity for fat, water and serum (22). Imbriani et al. (27) determined some Ostwald partition coefficients for ethyl acetate; the coefficient between human blood and air was 86 and that between urine and air 193. The partition coefficient iso-octane/water for ethyl acetate was 0.2 (24).

2 USES AND OCCURRENCE

2.1 Uses

Ethyl acetate is commonly used as a solvent for nitrocellulose, varnishes, lacquers and printing inks. It is also used as a solvent or extractant in the manufacture of smokeless powder, artificial leather and silk as well as photographic films and pharmaceuticals. Limited use may occur as a flavouring agent and fragrance in domestic and industrial purposes (58).

2.2 Natural occurrence

Ethyl acetate occurs naturally in yeast and sugarcane in which it is photosynthetically produced (58). Bourbon whisky was found to contain significant amounts (825 mg/l) of ethyl acetate (41).

2.3 Occupational exposure

Ethyl acetate was a solvent component in several products applied for the groundwork and lacquering of parquet surfaces (35). High concentrations with median values in the range of 490 to 1300 mg/m^3 were measured over 10 - 30 min when the fillers and primers were applied.

Conversely, very small concentrations were found when lacquering the floors (35) and when painting kitchen fixtures with acid curing paints (2). A recent survey concerning exposures to organic solvents at workplaces in Finland (55) pointed out that the highest air levels of ethyl acetate occurred when washing paint mixing vessels in paint factories (8-h time-weighted average concentration 265 mg/m^3, range 109 - 650 mg/m^3) and in the manufacture of printing inks (119 mg/m^3, range 84 - 180 mg/m^3). A slight exposure to ethyl acetate was found in flexo prints with an average air level of 16 mg/m^3.

2.4 Measurement of ethyl acetate in air

The preferred method is based on adsorption of ethyl acetate in charcoal tubes, desorption with carbon disulfide and analysis with a gas chromatograph equipped with a flame ionization detector (45). An air sampling rate of 0.2 l/min or less and a maximum sample volume of 6 liters is recommended. Under these conditions the useful range of the method is 140 - 4200 mg/m^3 of ethyl acetate in air.

Passive dosimeters have also been tried for the measurement of ethyl acetate in air. In comparisons with the conventional method (see above), somewhat lower (but significantly correlated) results were obtained with the passive sampler (66, 6).

3 KINETICS

3.1 Absorption and uptake

Uptake of ethyl acetate in the lungs of human volunteers exposed for some hours at concentrations ranging from 360 to 2800 mg/m^3 (100 - 770 ppm) was efficient as indicated by a high measured retention (46) and low alveolar (about 7 % of the inspired) concentrations (14). There are no reports concerning actual measurement of ethyl acetate absorption by the oral route or via the skin. The considerable lipid and water solubilities of the compound imply that penetration of membranes is probably efficient. However, the high volatility of ethyl acetate decreases the likelihood that significant amounts are taken up through the exposed skin when handling the compound. It is probable that a considerable part of an administered dose, at least via the gastrointestinal route, will be metabolized during the absorption phase.

3.2 Distribution

The rapid hydrolysis of ethyl acetate in tissues makes it difficult to ascertain how the compound was originally distributed. In a rat study, when five animals inhaled ethyl acetate at 5 % in air for 15 minutes and were subsequently killed with immediate specimen collection, ethyl acetate was detected in the blood of three animals and in the brain of all five (32). The concentrations ranged in the blood from 0.01 to 0.02 mg/g and in the brain from 0.03 to 0.15 mg/g, respectively. No ethyl acetate was detected in the liver. The corresponding ethanol levels (mg/g) varied from 0.51 to 0.97 in the blood, from 0.34 to 0.70 in the liver and from 0.39 to 0.80 in the brain. When another group of five rats was exposed in a similar way but allowed to breathe clean air for five minutes before termination, ethyl

acetate was found in the blood (0.01 mg/g) and brain (0.02 mg/g) of only one animal (32).

3.3 Biotransformation

Ethyl acetate undergoes in the body rapid biotransformation catalyzed by a variety of esterases. Hydrolysis yields ethanol and acetic acid which are metabolized further. Ethyl acetate (20 mM) was hydrolyzed *in vitro* at 37°C by whole rat blood with a half-time of 65 - 70 min (17). Human and rabbit blood were also found to catalyze this reaction. Ghittori et al. (18), however, noted that ethyl acetate disappeared from human blood at a rate of 20 % in 8 hours (37°C).

In an *in vivo* study (17), rats were given intraperitoneally 1.6 ml/kg of ethyl acetate. During the first 20 minutes low (< 200 mg/l) concentrations were detected in the blood and none later. The disappearance of ethyl acetate coincided with the peak blood ethanol concentration. The elimination half-time of ethyl acetate in blood was approximately 5 - 10 min. In an inhalation study with rats it was found that when the inspired concentration of ethyl acetate exceeded 7200 mg/m^3 (2000 ppm), ethanol started to accumulate in the blood. Thus at 18000 mg/m^3 (5000 ppm) blood ethanol rose steadily and reached about 0.4 g/l by 5 hours; at 36000 mg/m^3 (10000 ppm) the corresponding ethanol concentration approached 1.2 g/l (17).

It is well known that liver tissue contains high carboxylesterase activities (23); therefore the liver is likely the main ethyl acetate metabolizing organ. However, rat ethmoturbinate S9 homogenate also effectively catalyzed hydrolysis of various acetates, including ethyl acetate (10). Hydrolysis rates were increased with increasing alcohol chain length up to pentyl(amyl)acetate. Rat ethmoturbinate S9 hydrolyzed ethyl acetate at about one third of the rate characteristic for pentyl

acetate. Using pentyl acetate as a model, the authors found generally the highest hydrolytic activities in the liver tissues of rats, rabbits and hamsters, about 50 % lower rates in the turbinates and somewhat less activity in the trachea and lung (10). Hamster tissues exhibited the highest activities followed by rat and rabbit. The authors estimated that in the rat the hydrolytic enzymes of the nasal cavity can hydrolyze a major portion of esters inhaled at commonly encountered air concentrations.

3.4 Elimination

As shown above ethyl acetate is cleared very effectively by metabolism; very little unchanged substance will undergo excretion. Nomiyama and Nomiyama (47) estimated that the respiratory elimination after inhalation exposure of volunteers to ethyl acetate amounted to 0.2 %. The apparent elimination half-time was 9 minutes. Fernandez and Droz (14) also measured ethyl acetate concentration in alveolar air after inhalation exposure of human subjects. Two elimination rates were found corresponding to half-times of 1.6 min and 10 min, respectively. After 50 min ethyl acetate was no more detected in alveolar air.

3.5 Factors affecting the metabolic model

There is no information concerning interference by other substances or altered physiology on the kinetics of ethyl acetate. Since cholinesterases, pseudocholinesterases and other carboxylesterases play an important role in the hydrolysis (17), the question may be raised as to whether their inhibition (by organophosphorus or carbamate compounds) could modulate the biotransformation of ethyl acetate.

Inhalation exposures of rats over 2 hours to high (3600 or

14400 mg/m^3) concentrations of ethyl acetate in combination with one at a time of the following: toluene, ethyl benzene, m-xylene and mesitylene decreased, mostly dose dependently, the blood levels of the latter compounds (16). Kinetic interaction with an unknown mechanism was proposed but it can be speculated that depression of respiration owing to the irritating effect by ethyl acetate may have played a significant role.

3.6 Biological monitoring

Biological monitoring based on the measurement of ethyl acetate in alveolar air has been proposed (8). These authors could not find ethyl acetate in concomitantly collected blood samples. Fernandez and Droz (14) pointed out that ethyl acetate in alveolar air, either during or (at specified times) after exposure, only depended on inhalation concentration, not the duration of exposure. By contrast, ethanol concentration in alveolar air increased greatly during ethyl acetate exposure and proportionally to the exposure level. Thus, ethanol in the blood or exhaled air might serve as a measure of ethyl acetate uptake (provided that ethanol ingestion can be excluded).

A method to analyze organic solvents, among them ethyl acetate, in blood samples for medico-legal purposes has been elaborated (53). To prevent hydrolysis of ethyl acetate in a standing blood sample, the addition of 1 % sodium fluoride to inhibit esterase activity, was proposed.

4.1 Toxicological mechanisms

Ethyl acetate is an irritant and a central nervous system depressant in high concentrations. In view of the rapid transformation of ethyl acetate to ethanol and acetate, effects attributable to the parent compound and metabolites are plausible. The effects of ethyl acetate on membranes have been studied (24, 54, 21). Ethyl acetate, like other anesthetically active agents, stabilized the erythrocyte membrane against hypotonic haemolysis. Maximal stabilization (about 28 %) of human cells was found at about 100 mM concentration; ethanol had a clearly less potent stabilizing effect. In comparison to ethanol, ethyl acetate is more lipid soluble and therefore more penetrating into the membrane. Gustafson and Tagesson (21) could not demonstrate a damaging effect (release of ^{14}C-phospholipid) by a buffer solution saturated with ethyl acetate (concentration not given) on biosynthetically produced E. coli membranes. Ethanol (33 %) caused some release of radioactivity and this effect was potentiated by the addition of ethyl acetate dissolved in the buffer.

Ethyl acetate irritates the mucous membranes of the eye and the upper respiratory tract with an RD_{50} value in the mouse (for a definition, see 5.2) of 580 ppm (11). The corresponding values for acetic acid and ethanol were 163 and 27314 ppm, respectively (1). It is likely, therefore, that hydrolysis of ethyl acetate to acetic acid has a role in the irritant response.

In vivo ethyl acetate produced severe respiratory depression in rats anesthetized with pentobarbital at 36000 mg/m^3 (10000 ppm) over 4 hours while the blood ethanol concentration rose only to about 1,2 g/l (17). Von Oettingen (72), in a review of studies made in the early 1900's, points out that in many cases animals

made narcotic with ethyl acetate first appeared to recover but then subsequently died in coma with convulsions and respiratory depression. Pulmonary oedema and haemorrhages were cited as characteristic pathological findings. Munch (40) has demonstrated with rabbits that the narcotic dose of ethyl acetate (the dose producing stupor and loss of voluntary movements in half of the animals) was almost identical to the lethal (LD_{50}) dose, 51 mmol/kg and 56 mmol/kg, respectively. Hence, there is only a narrow margin of safety between the narcotic and lethal concentrations of ethyl acetate in air.

Ethyl acetate (28 mM solution) had a strong stimulatory effect on the net Na^+, water and glucose transport in a hamster gut preparation (13). Ethanol and acetate were ineffective. Apparently, owing to its lipid solubility, ethyl acetate is able to cross the membranes into the cell and subsequently releases free acetate to be used as a source of energy for membrane transport functions.

4.2 Factors affecting toxicity

Acute oral and inhalation toxicities in rats of ethyl acetate in combination with another compound were tested in two series of 23 and 36 pairs (50, 62). Equal volume mixtures and both compounds of the pair alone were given, and LD_{50} values (LC_{50} for inhalation) were determined. The predicted LD_{50} and LC_{50} values for the combination were also calculated on the basis of a simple additive effect. Out of 26 pairs in which ethyl acetate was a component, in 9 cases the ratio of predicted/observed oral LD_{50} was greater than one, in 17 cases less than one (62). The mixtures of ethyl acetate with toluene as well as with carbon tetrachloride appeared to be less toxic than predicted by simple addition both orally and via inhalation (50, 62). By way of comparison, ethanol in combination with toluene exhibited slightly more than additive toxicity. It is noteworthy that ethyl

acetate was less acutely toxic than toluene and carbon tetrachloride. The interaction therefore concerns more likely the diminution of the toxicities by the latter compounds.

4.3 Acute toxicity

Ethyl acetate possesses little toxicity acutely. The following LD_{50}-values or lethal doses have been given:

Rat	oral	10.1 g/kg	(61)
Rabbit	oral	4.9 g/kg	(40)
Guinea pig	subcut	3 - 5 g/kg	(15)
Cat	subcut	3 g/kg	(15)
Rat	skin	> 20 g/kg	(61)

Via inhalation, the LC_{50} concentration for rats in a 4-h exposure was 40700 mg/m^3 (14640 ppm) (50). For mice LC_{50} in a 3-h exposure was 44000 mg/m^3 (65). Earlier investigations have demonstrated that lethal inhalation concentrations vary from 36000 to more than 72000 mg/m^3 depending on the exposure time and species involved (72). For mice 36000 mg/m^3 could be lethal in 45 min whereas guinea pigs died at 77000 mg/m^3 over 60 min. Cats survived a 45-min exposure to 72000 mg/m^3 of ethyl acetate but died after 15 min at 155000 mg/m^3.

4.4 Subacute and subchronic toxicity

There are few published studies concerning repeated exposures of animals to ethyl acetate. A series of experiments by Vernetti Blina (69) involved exposures of four rats to about 16000 mg/m^3 (4450 ppm) of ethyl acetate one hour daily over 40 consecutive days as well as exposures of seven rabbits to about 30000 mg/m^3 (8340 ppm) of ethyl acetate according to a similar scheme. The study was incompletely reported. Nevertheless, it appears that at

postmortem the rats showed congestion in the lungs, liver, kidneys and spleen. Bronchial mucosa was found atrophic with peribronchial infiltration and the liver showed fatty degeneration. As regards rabbits the main findings were pulmonary congestion and chronic bronchial inflammation, congestion of the liver accompanied with fatty degeneration and hyperplasia of the reticuloendothelial system, congestion of the kidneys with early degeneration of the tubular epithelium as well as chronic congestion and follicular atrophy of the spleen. When three guinea pigs were exposed to 7200 mg/m^3 (2000 ppm) of ethyl acetate 4 hours daily over 65 days no harmful effects were detected (63).

5 EFFECTS ON ORGAN SYSTEMS

5.1 Effects on skin and mucous membranes

Several investigators have reported on symptoms among workers exposed to acetates (ethyl, butyl and amyl acetate) in car repair shops, furniture factories and textile industry (68, 52, 64, 9). One of the leading symptoms was eye irritation. Valvo et al. (68) described a series of 13 painters who according to the report were exposed up to 15000 - 50000 mg/m^3 (4170 - 13900 ppm) of ethyl acetate. All workers had been employed for at least 2 weeks, some for several years. New workers showed lachrymation, chemosis and oedema of the eyelids; old workers showed hyperaemia and chronic conjunctival irritation. There was no corneal involvement.

According to Nelson et al. (44) 1440 mg/m^3 (400 ppm) of ethyl acetate was felt irritating to the eyes, nose and throat by human subjects in experimental exposure over 3 to 5 minutes.

Repeated skin contact to ethyl acetate causes drying and defatting of the skin. Experimental application of the compound for 60 min per day over six consecutive days onto the volar forearm skin of three volunteers was found to injure the stratum corneum (36). Sequential measurements of water vapour loss through the treated and neighbouring skin areas indicated that the skin of two young subjects was more susceptible; recovery followed the slow regrowth of a new horny layer. In the middle-aged subject the injury was only slight. The effects of ethyl acetate, ethyl alcohol, methyl ethyl ketone and toluene on the skin were very similar.

Ethyl acetate tested at 10 % in petrolatum produced no irritation after a 48-h closed-patch test in 25 human subjects (48).

5.2 Effects on the respiratory tract

In addition to eye symptoms, workers who were exposed primarily to various acetate solvents frequently complained of upper airway irritation (52, 64). In a textile factory where ethyl acetate concentrations in air at certain phases of work rose up to seven times the Italian MAC (800 mg/m^3; 26) concentration, four out of seven examined workers showed signs of bronchial constriction (9).

Sensory irritation in the upper respiratory tract of the mouse is accompanied by a decrease in the respiration rate. Based on accumulated evidence concerning several substances, the concentrations of a chemical in air causing a 50 % decrease in the respiratory rate (RD_{50}) of the mouse has been regarded as "intolerable to humans" whereas one tenth of RD_{50} causes some sensory irritation and one hundredth of RD_{50} is non-irritating (30). Two studies on ethyl acetate yielded RD_{50} values of 614 and 580 ppm (2210 and 2090 mg/m^3, respectively) (31, 11); furthermore, the dose response curves were characteristically

quite steep. Nelson et al. (44) reported that a 3 - 5 min exposure to ethyl acetate at 400 ppm (1440 mg/m^3) irritated the eyes, nose and throat of human volunteers. These authors did not single out ethyl acetate as particularly irritating in a group of solvents tested. However, in mouse studies sensory irritation by ethyl acetate developed rather slowly, over about 5 minutes, and persisted as long as the exposure continued (31). It is therefore possible that the irritating potential of ethyl acetate in humans has not been fully appreciated because of inadequate documentation.

A reference has earlier been made to the findings of pulmonary oedema, haemorrhages and hyperaemia of the respiratory tract in animals exposed to anesthetic/lethal concentrations of ethyl acetate (15). A worker who died in a tank from ethyl acetate inhalation was reported to have hyperaemia of the upper respiratory tract (72). After inhalation exposures of rats to 16000 mg/m^3 and of rabbits to 30000 mg/m^3 of ethyl acetate, respectively, one hour daily over 40 days, pulmonary congestion and chronic bronchial inflammation was found (69).

5.3 Effects on the liver

There are some observations from workplaces and a few experimental studies on animals which seem to indicate that exposure to acetates may cause changes in the liver. Querci et al. (52) investigated a group of 15 painters, mainly exposed to butyl and amyl acetates in a furniture factory, three times over a working week and observed an increase of succinic dehydrogenase activity in serum and a less consistent slight increase of ASAT. Schüttmann and Ullmann (59) examined altogether 56 operatives who were exposed to the solvents of nitrocellulose lacquer in machine shops. Concentrations of ethyl acetate in air exceeded the MAK limit of DDR (500 mg/m^3; 26) up to seven times and those of toluene/xylene up to five times, respectively. Some exposure to

mineral spirits also occurred. Most workers had raised serum aldolase and almost a half showed serum iron values and serum lactic dehydrogenase activities above the reference range. Serum ASAT and ALAT were only occasionally increased. One worker had an enlarged liver which histologically presented moderate steatosis - transaminases were slightly elevated. In this case the authors felt that they could exclude the etiology of excessive use of alcohol and prediabetes and therefore attributed the clinical state to a long-term, intensive solvent exposure. Their contention was further supported when, in a follow up group of 13 persons, the clinical chemical findings improved among 10 subjects after improvements were made in the working conditions.

Exposure to a variety of solvents (including low levels of ethyl acetate) in the paint manufacturing industry and in car painting, the workers did not have higher serum activities of the liver enzymes than the controls (34, 33). However, a sensitive method of detecting hepatic effects of alcohol (analysis of different forms of transferrin), showed that workers in a paint industry deviated from the non-exposed controls while the alcoholics had still much more pronounced changes than the solvent exposed workers (49).

Exposure of rabbits (51) to a mixture of acetates at 22000 - 30000 mg/m^3 repeatedly over 15 weeks caused lipid accumulation in the centrilobular region and some periportal fibrosis accompanied with increased liver enzyme activities in the serum. Vernetti Blina (69) also reported that in rats and rabbits 40-day exposure, one hour daily, to 16000 mg/m^3 and 30000 mg/m^3 of ethyl acetate, respectively, caused fatty degeneration of the liver.

Intraperitoneal administration of 1.0 ml/kg of ethyl acetate to rats daily for eight days caused an increase of serum and liver pyruvate and lactate and a reduction of liver glycogen (60).

Lactic dehydrogenase activity in the liver was also increased.

5.4 Effects on the kidneys

There are no reports available pointing to renal effects by occupational ethyl acetate exposure. The worker who died of ethyl acetate anaesthesia showed in the post mortem examination hyperaemia of the kidney (72). In the subacute toxicity study on ethyl acetate by Vernetti Blina (69), described above, congestion of the kidneys was found in both rats and rabbits. The latter even showed early degeneration of the tubular epithelium.

5.5 Gastrointestinal effects

Workers exposed to mainly propyl and amyl acetates in furniture factories complained of many symptoms, among them digestive troubles (52). Similarly, many workers exposed in machine shops to nitrocellulose lacquer solvents, mainly ethyl acetate and toluene/xylene, had dyspepsia and poor appetite which the authors attributed to solvent induced vegetative disorders (59).

5.6 Cardiovascular effects

About half of the fifteen workers exposed to acetates (especially butyl and amyl acetate) in furniture factories complained of thoracic ("precardial") pain and pressure and the authors thought that there were some characteristic changes of repolarization in the electrocardiogram (52). There were no other reports on cardiovascular toxicity by ethyl acetate in humans.

Intravenous infusion of ethyl acetate (5 mg/kg/min) in anaesthetized, open-chest dogs decreased heart rate and systemic arterial pressure progressively (42). Myocardial contractile

force initially increased and then decreased progressively as the blood ethyl acetate concentration reached more than 0.3 mg/ml. Ethanol caused corresponding effects when the blood ethanol exceeded 3 mg/ml. Essentially similar negative inotropic action by ethyl acetate was demonstrated in guinea pig isolated ventricular strips (43). Ethyl acetate was ten times more potent than ethanol.

The arrhythmogenic effects of several volatile compounds were studied on beating rat heart cell cultures (39). Ethyl acetate made 50 % of the culture tubes arrhythmic at a concentration of about 3000 mg/l in the medium. Halogenated hydrocarbons, particularly carbon tetrachloride and chloroform, were much more potent - ethanol was arrhythmic at a three times higher concentration.

5.7 Haematologic effects

No consistent effects on blood and blood forming organs by ethyl acetate have been reported in man. In the 40-day inhalation study at 16000 mg/m^3 for rats and 30000 mg/m^3 for rabbits by Vernetti Blina (69) rats tended to show decreased numbers of red blood cells and leucocytosis in the peripheral blood at termination; rabbits developed secondary anaemia, lower haemoglobin concentration and a reduced number of red blood cells.

5.8 Effects on central nervous system

Workers exposed to high concentrations of acetates, frequently in combination with other solvents such as toluene and xylene experienced symptoms of fatigue, headache, giddiness, irritability, vegetative dysregulation and sleep disturbances (52, 64, 59).

Corradini et al. (9) examined seven workers of a textile factory where ethyl acetate concentration in air was found to reach about 5600 mg/m^3 (1560 ppm) at certain phases of work. The symptoms described above were of common occurrence. Three subjects had generalized changes in the EEG and one subject showed a bilateral symmetrical vestibular hyperreflexia. Within 3 months away from work the abnormal findings had disappeared.

In a Danish study on 21 flexoprinters exposed to ethanol, isopropanol and ethyl acetate at concentrations which had decreased from about the occupational exposure limit (1100 mg/m^3) to much lower levels in the years preceding the study, eight subjects complained of increased fatigue, failing memory, difficulty in concentrating and lack of initiative (7). In three cases, a slight or slight to moderate toxic encephalopathy, evaluated according to agreed criteria (74) was found. The authors felt that concerning one subject, organic solvent exposure was the only conceivable cause.

Ethyl acetate has been (mostly a minor) component of solvent exposure in car painting and paint industry. The behavioural and neuropsychiatric effects among workers in these trades, researched and demonstrated in epidemiological studies, are well known (25, 12, 4).

Glowa and Dews (19) studied the effect of ethyl acetate on schedule-controlled responding of mice. Cumulative concentration - effect functions were obtained by increasing the solvent concentration in the chamber at 30-min intervals until the responding was abolished. Exposure to 300 ppm of ethyl acetate was without effect, 560 ppm decreased responding by about 75 %, 1000 ppm abolished responding in most mice, and 2000 - 3000 ppm abolished responding in all mice. The concentration which decreased responding by 50 % (EC_{50}) was 594 ppm (2140 mg/m^3). Thirty minutes after the last exposure was discontinued, responding recovered completely in all mice. The EC_{50} value for

ethyl acetate was low in comparison to other solvents studied (acetone 10694 ppm, methyl ethyl ketone 2891 ppm and toluene 1784 ppm, respectively). The authors underlined, therefore, the acute behavioural toxicity of ethyl acetate but they did not consider the possibility that the effect could be related to the potent irritancy of the compound.

Ethyl acetate caused a depression of the vestibulo-oculomotor reflex (VOR) in rats at an intravenous infusion rate of 210 nmol/kg/min (measured concentration in arterial blood 0.5 mmol/l) (67). The depression of the VOR occurred before signs of general depression of the central nervous system appeared.

5.9 Effects on peripheral nervous system

No reports were found concerning effects by ethyl acetate on the peripheral nervous system. The peripheral symptoms suggesting vegetative disturbances among acetate exposed workers are probably mediated centrally.

6 IMMUNOTOXICITY AND ALLERGY

Eyeglass contact dermatitis limited to the nose occurred in a woman patient. Skin testing showed that the likely allergen was ethylene glycol monomethyl ether acetate, used to weld the nosepads chemically to the eyeglass frame. Skin testing also revealed that the patient was sensitized to ethyl acetate (29).

Maximization test according to Kligman was performed with 10 % ethyl acetate in petrolatum on 25 volunteer subjects; no sensitization reactions were found (48).

7 MUTAGENICITY AND GENOTOXICITY

Ethyl acetate dissolved in DMSO (maximum dose 5 mg/plate) gave negative results in the conventional Salmonella/microsome test (Ames test) whereas the compound in ethanol (maximum concentration 9 mg/ml) caused structural chromosome aberrations in a Chinese hamster fibroblast cell line (28).

In yeast Saccharomyces cerevisiae ethyl acetate (concentration in the medium 2.44 %) was shown to be a powerful inducer of aneuploidy, a result of chromosomal malsegregation, but it did not cause mitotic recombination or point mutations (75). The test was most sensitive with cold treatment. The authors proposed that the effect was not due to any primary reaction with DNA or secondary alterations in DNA but because of interference with the functioning of the spindle apparatus. Indeed, ethyl acetate slowed down and reduced the extent of tubulin assembly in the porcine brain in vitro at lower concentrations than those required for aneuploidy induction (20). When another solvent methyl ethyl ketone, which was shown to induce aneuploidy probably by the same mechanism, was studied together with ethyl acetate, a potentiation effect was found (37).

In an in vivo study with Chinese hamsters a single intraperitoneal (473 mg/kg) or oral (2500 mg/kg) administration of ethyl acetate did not increase the number of micronuclei in polychromatic erythrocytes in the bone marrow (5). In the mouse micronucleus test ethyl acetate also gave negative results (28).

8 CARCINOGENICITY

No data were found concerning carcinogenicity of ethyl acetate.

9 REPRODUCTIVE AND TERATOGENIC EFFECTS

In a study on flexoprinters exposed to ethanol, isopropanol and ethyl acetate, 18 out of 19 individuals were found to have normal sperm quality. The abnormal findings in one worker was due to a known non-occupational cause (7). The current exposure was quite low.

Injection of chemicals into the air cell or the yolk sac of developing chicken embryos have been used to screen toxicity and teratogenic potential. McLaughlin et al. (38) found that 22.5 mg of ethyl acetate per egg reduced hatchability by 50 %; a clear dose response was demonstrated. No teratogenic effects were observed. By comparison, ethanol was about four time less toxic to the chicken embryo. Later, the sensitivity of the method to differences in injection technique and form of injected material was demonstrated (73). For instance, ethyl acetate dissolved in corn oil was much more toxic than in a saturated salt solution.

A careful new testing of ethyl acetate with the chicken embryo method indicated that even the highest dose used (25 mg/egg) did not kill half of the embryos (hence LD_{50} could not be determined). No teratogenic effects were detected (70).

10 RELATION BETWEEN EXPOSURE, EFFECT AND RESPONSE

10.1 Observations in man

Dose effect and dose response data concerning human exposure to ethyl acetate are scarce. Exposures to very high concentrations (15000 - 50000 mg/m^3) were accompanied by lachrymation, chemosis, oedema of eyelids and chronic conjunctivitis (68). At

somewhat lower levels with peaks at about 10000 mg/m^3 symptoms of irritation were frequent and about half of the workforce showed signs of bronchial constriction (9). Furthermore, the workers felt headache, nausea and giddiness during the workshift and three out of seven examined subjects showed generalized changes in the EEG (the abnormalities disappeared during 3 months away from work).

Subjective symptoms pointing to functional disturbances in the central nervous system, vegetative disorders and, possibly, early changes in liver function were found in workers exposed to about 3500 mg/m^3 of ethyl acetate in combination with significant concentrations of toluene and xylene (59).

Exposure to about 1440 mg/m^3 of ethyl acetate caused irritation of the eyes, nose and throat in human subjects (44).

Among flexoprinters exposed to ethyl acetate in combination with ethanol and isopropanol at about 1100 mg/m^3 in earlier years and to much lower levels at the time of examination, many (about a third of the workforce) complained of increased fatigue, failing memory, difficulty in concentrating and lack of initiative (7). There was a possibility that in one person solvent exposure had caused toxic encephalopathy.

The data concerning exposure, effect and response relationships in humans are presented in concise form in table 1.

Table 1. Relation between exposure, effect and response of ethyl acetate in man

Population	Concentration (other solvents)	Duration of exposure	Effect	Ref.
Car painters	15000-50000 mg/m^3	Weeks to years	Lachrymation, chemosis, oedema of eyelids, chronic conjunctivitis	68
Textile factory workers	10000 mg/m^3 peaks	Years	Irritation, bronchial constriction, headache, nausea, giddiness, EEG abnormalities	9
Machine painters	3500 mg/m^3 (toluene and xylene)	Years	Nervous symptoms, vegetative disorders, liver function changes	59
Flexo-printers	About 1100 mg/m^3 before, about 60 mg/m^3 currently (ethanol, isopropanol)	Years	Nervous symptoms	7
Volunteer subjects	1440 mg/m^3	3 - 5 minutes	Irritation of the eyes, nose and throat	44
Volunteer subjects	14 mg/m^3		Odour threshold	3

10.2 Observations in animals

Acutely lethal concentration of ethyl acetate in air for rats (LC_{50}) over 4 hours was 40700 mg/m^3 (50).

In a subacute study on rats and rabbits exposed to 16000 mg/m^3 and 30000 mg/m^3 of ethyl acetate, respectively, for 60 minutes daily on 40 days, the animals developed bronchial inflammation and congestion in the lungs, liver, kidneys and the spleen (69). Especially in rabbits fatty degeneration of the liver, hyperplasia of the reticuloendothelial system, follicular atrophy of the spleen, slight degeneration of renal tubular epithelium and anemia were found. When three guinea pigs were exposed to 7200 mg/m^3 of ethyl acetate 4 hours daily over 65 days no harmful effects were detected (63).

In a behavioural study with mice it was found that 594 ppm (2140 mg/m^3) of ethyl acetate caused a 50 % reduction in schedule-controlled responding (19). Exactly the same concentration caused significant sensory irritation in the mouse resulting in a 50 % decrease of the respiration rate (31, 11).

11 NEEDS FOR FURTHER RESEARCH

There is practically no information concerning the health status of workers exposed to moderate concentrations of ethyl acetate.

Further studies should be made to explore and assess the risk of mutagenic and genotoxic effects by ethyl acetate in humans.

12 DISCUSSION AND EVALUATION

Information on the human toxicology of ethyl acetate is scarce and difficult to evaluate. This is due to two factors: i) human exposures have almost invariably involved several solvents, at least other acetates, jointly with ethyl acetate and ii) the data concerning exposure levels and exposure durations are only summary. Moreover, the available data mainly relate to very high exposures in the past. That could mean that low exposures have not caused harmful effects or that workers exposed to such low levels have not been investigated. Ethyl acetate has been commonly regarded as rather non-toxic [it is on the FDA GRAS (generally recognized as safe) list of food additives].

Overall, the evidence indicates that ethyl acetate is an irritant, harmful to the functioning of the central nervous system and possibly, at high levels, it may cause metabolic disturbances in the liver. The manifestations of central nervous system effects look very similar to those known for aromatics, mineral spirits or mixed solvent exposures. There is no way, on the basis of current evidence, to make an assessment about the potency; on the other hand, we cannot conclude with any certainty that ethyl acetate is less toxic to the central nervous system than organic solvents in general.

On the basis of experience gained from sensory irritation studies with mice the RD_{50} concentration of 2090 mg/m^3 (580 ppm) for ethyl acetate ought to be "intolerably irritating in humans". Moreover based on evidence from several chemicals it appears that one tenth of the RD_{50} level would represent a concentration which humans experience as tolerable (30, 11).

Ethyl acetate was shown to cause aneuploidy in yeast. It was a highdose effect sensitized by artificial conditions (cold treatment). It can be anticipated that this type of effect

follows the traditional dose response curve and that there is a threshold below which disturbance of the spindle apparatus does not occur. Nevertheless, the mutagenic and genotoxic risk to man, if any, should be properly assessed.

The critical effects of ethyl acetate are mucous membrane irritation and central nervous system effects.

13 SUMMARY

DEC and NEG Basis for an Occupational Exposure Limit. Ethyl acetate. V. Riihimäki. Arbete och Hälsa, 1990: 35, pp 1-36.

Literature on ethyl acetate was reviewed with a view to establishing scientific basis for the setting of occupational health standards.

Data concerning long term effects of ethyl acetate in man are sparse. High concentrations have caused irritation in the eyes and respiratory tract, central nervous system effects and, possibly, metabolic disturbances of liver function. There is virtually no information concerning effects by ethyl acetate at moderate to low concentrations. Functional disturbances in the central nervous system may be possible at this concentration range. Ethyl acetate is considerably irritating on mucous membranes: about 210 mg/m^3 (58 ppm) may, based on extrapolation from the mouse sensory irritation test and inference, be uncomfortable but tolerated in man. Ethyl acetate caused aneuploidy in yeast and chromosome aberrations in a mammalian cell culture. The significance of these findings to man is unknown.

The critical effects of ethyl acetate are mucous membrane irritation and central nervous system effects.

Key words: Ethyl acetate, irritation, central nervous system effects, liver effects, mutagenicity, genotoxicity, occupational health standard.

SAMMANFATTNING

DEC och NEG Basis for an Occupational Exposure Limit. Ethyl acetate. V. Riihimäki. Arbete och Hälsa, 1990:35, sid 1-36.

En genomgång av litteraturen har gjorts i avsikt att ta fram ett vetenskapligt underlag för hygieniskt gränsvärde.

Det finns endast få data avseende långtidseffekter på människa. Höga koncentrationer har orsakat irritation i ögon och andningsvägar, centralnervösa effekter och troligen störningar av leverfunktion. Det saknas nästan helt information om etylacetats effekter vid måttliga eller låga koncentrationer. Funktionella störningar i centrala nervsystemet kan dock tänkas förekomma. Etylacetat är synnerligen slemhinneirriterande: ca 210 mg/m^3 (58 ppm) kan, baserat på irritationstest på mus, vara obehagligt men tolerabelt för människa. Etylacetat har orsakat aneuploidi i jäst och kromosomaberrationer i mammalieceller in vitro. Signifikansen av dessa fynd är inte känd.

Den kritiska effekten av etylacetat är slemhinneirritation och centralnervösa effekter.

Nyckelord: Etylacetat, irritation, centralnervösa effekter, mutagenicitet, genotoxicitet, hygieniskt gränsvärde.

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2 Söderberg I. Ändrad kurs – om organisationsförändring och datorisering i en kommunal förvaltning. Arbete och Hälsa 1989:5.

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6 Toropkov V. The toxicology of trimellitic acid. Prof Zabol 4 (1968) 12–16 (på ryska, engelskt abstract).

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