SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141-78-6
Chemical Name	Ethyl acetate
Structural Formula	CH_3-COO-CH_2-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

No data on ethyl acetate is available for the developmental toxicity endpoint. As a result, data from ethyl acetate's metabolite, ethanol is being used to complete this endpoint, as ethyl acetate is rapidly converted to ethanol. Pharmacokinetic studies have demonstrated an elimination half-life for ethyl acetate of 33-37 seconds in blood *in vivo*. The rapid appearance of the ethanol metabolite due to hydrolysis allows the use of studies conducted directly with ethanol to be used in systemic hazard identification for ethyl acetate. In addition, supporting data from ethanol has been presented for the repeat dose and reproductive toxicity endpoints.

Human Health

Ethyl acetate is readily absorbed and rapidly hydrolyzed in mammals to acetic acid and ethanol. Ethyl acetate exhibits low acute toxicity by the oral, inhalation, and dermal routes. The oral LD_{50} ranges from 4,100 mg/kg in mice to 7650 mg/kg in rabbits. Inhalation LC_{50} values for vapor exposures in rats and mice range from the lowest value of 33.5 mg/l (2hr exposure) to the highest reported value of 200 mg/l (1hr exposure). A single dermal LD_{50} value is reported as above 18,000 mg/kg. In addition to the standard acute inhalation study, a functional observational battery and motor activity test was conducted prior to exposure and after a 6hr exposure at 7 and 14 days at doses of 600 (2.25 mg/l), 3000 (11.25 mg/l) and 6000 ppm (22.5 mg/l). A NOEL for systemic effects was not determined based upon transient decrease in body weights at all doses. At 3000 ppm (11.25 mg/l) decreases in motor activity were observed in both male and female rats and in the functional battery, sedation effects were observed at 3000 ppm (11.25 mg/l). The NOEL for neurotoxicity was 600 ppm with a LOEL (sedation) being 3000 ppm (11.25 mg/l). In addition, acute effects were observed in a 90-day study which resulted in a diminished response to delivery of an alterting stimuli at 750 ppm (3 mg/l) in which this response was attributed to ethyl acetate's acute sedative properties. The LOAEL from this study in rate would be 750 ppm. Ethyl acetate is not a dermal sensitizer or an acute eye or skin irritant based on information currently available. Inhalation of 400 ppm (1.4 mg/l) ethyl acetate vapor by humans produces mild sensations of irritation in some individuals but 200 ppm (.7 mg/l) is without effect.

In a 13 week inhalation study, LOELs of 350 ppm (1.3 mg/l) (reduced food consumption and body weights and lower serum triglyceride levels) and 750 ppm (2.7 mg/l) (sedative effects) for systemic effects were observed in rats. Minimal to moderate degeneration of the nasal epithelium was observed in both male and female rats at all ethyl acetate exposure concentrations. Degeneration of the olfactory epithelium within the nose is a common lesion in rats exposed by inhalation to acetate esters of short-chain alcohols due to the liberation of acetic acid in these cells from the hydrolysis of the ester linkage. The significance of this lesion in human health is not clear. Ethyl acetate is

not mutagenic in *in vitro* systems. Conflicting results were obtained in the in vitro assays for clastogenicity with positive results being reported only at excessively high dose levels. However, negative results were obtained in the in vivo bone marrow assays for clastogenicity (micronucleus assay) using high dose levels (administered i.p.). In addition, the metabolites, ethanol and acetic acid do not have any significant mutagenic potential. Sufficient data is not available for ethyl acetate for the endpoints of reproductive or developmental toxicity as a result, data from ethanol will be used as a surrogate. In an inhalation study designed to observe repeat dose effects of ethyl acetate, minor reproductive parameters were observed in the male rat, sperm parameters (number or concentration of spermatids in the testes or epididymide; sperm motility; or morphology) were not affected at concentrations up to the highest dose tested 1500 ppm (5 mg/l). This data was further supported by a study with limited design (methodology) in male rats where it was determined that transient exposure to extremely high levels of ethyl acetate may be able to cause these effects, but subchronic exposures to doses as high as 6000 ppm (22 mg/l) did not effect sperm counts, motility or sperm concentration. In ethanol, oral exposure effect levels of 6400mg/kg by gavage and even higher by dietary exposure have been observed. In inhalation studies using ethanol, rats exposed up to 20,000 ppm (72 mg/l), equivalent to a blood alcohol concentration of 180 mg/100 ml, have not produced fertility or developmental effects. Inhalation exposures at concentrations greater than 2000 ppm (7 mg/l) were required to show any accumulation of ethanol in the blood and esterases are not saturated at levels as high as 10,000 ppm (36 mg/l). Rats exposed for 13 weeks to concentrations as high as 1500 ppm (5 mg/l) did not exhibit any evidence of cumulative neurotoxicity when motor activity, functional observational batteries, and scheduled controlled operant behavior were evaluated. Transient diminished response to delivery of an alerting stimuli was noted at the 750 ppm (3 mg/l) and 1500 ppm (5 mg/l) doses and was attributed to the acute sedative properties of ethyl acetate. Therefore, other than transient reversible sedation during exposure, ethyl acetate is not considered a neurotoxicant.

Environment

The available physicochemical data are adequate to describe the properties of ethyl acetate. The melting point for ethyl acetate is -83 ^{o}C, the boiling point is 77.1^{o}C and the log K_{ow} is 0.73. Ethyl acetate has a measured vapor pressure of 113hPa at 20 °C. Ethyl acetate has a specific gravity (density) of 0.90 and a flashpoint of –4^{0}C. Its aqueous solubility has been reported as about 83,000 mg/L at 20°C. Henry's Law constants for ethyl acetate were calculated or measured to be about 14 to 24 Pa m^3/mol at 25°C. Ethyl acetate is considered moderately volatile. Using a measured Henry's Law constant of 14 Pa m^3/mol, half-lives of volatilization from model rivers and lakes were calculated. Calculated half-lives of volatilization of ethyl acetate from a model river or lake were 5 hours and 5.6 days, respectively. Ethyl Acetate is stable to hydrolysis under neutral to acidic conditions (pH 4-7) but readily hydrolyses under alkaline conditions (pH 9). Ethyl acetate is not persistent in the environment and is not likely to bioaccumulate in food webs. Based on Level III fugacity-based multimedia modeling and assuming equal emissions to air, water, and soil, 17.2 % will be in air, 47.6 % in water, and 35.1 % in soil. Ethyl acetate in water and soil is expected to be easily biodegraded based on laboratory studies indicating that ethyl acetate is readily biodegradable. The amounts of ethyl acetate in other compartments (e.g., sediment and biota) are expected to be small. These predictions are supported by the limited data available on prevailing concentrations in indoor/outdoor air and concentrations in river/drinking water. Since the primary use of ethyl acetate is as a solvent, it is expected that ethyl acetate will initially volatilize to the atmosphere in many of these applications. The total tropospheric lifetime of ethyl acetate is estimated to be 6.28 days with degradation due to hydroxyl radical-mediated photo-oxidation. As a volatile organic compound in the atmosphere, ethyl acetate is a potential contributor to tropospheric ozone formation under certain conditions, however its photochemical ozone creation potential is considered to be low. The aquatic toxicity data in fish, invertebrates, and algae indicate a low order of toxicity with LC_{50}/EC_{50} concentrations generally greater than 100 mg/L. A 21 day chronic daphnia study had a no observed effect concentration (NOEC) of 2.4 mg/l. The rapid biodegradability of ethyl acetate in water and soil and photo-oxidation in air all suggest a low likelihood of adverse outcomes in aquatic species. Terrestrial data are not available, but based on negligible soil release and low potential for bioaccumulation, adverse terrestrial outcomes are considered unlikely.

Exposure

Worldwide ethyl acetate production was 1,011 Ktonnes in 1998. US production in 1997 was 118 Ktonnes (259 million pounds). Ethyl acetate is manufactured by a continuous, closed process and during normal operating procedures, releases are anticipated to be low. Ethyl acetate is used in liquid formulation products, typically

lacquers, solvent mixtures, inks, coatings, and adhesives. There is limited use in consumer products (coatings, adhesives) plus products such as nail polish remover. Application of these materials results in exposure via the dermal and inhalation routes and release of ethyl acetate into the environment through the volatile release of the material. There is reasonable quantity of published data on exposure of workers to ethyl acetate. This data shows that the vast majority of exposures are well below current occupational exposure limits (OELs). In general, exposures are greatest in the adhesives sector but available data still shows exposures below prevailing OELs. Ethyl acetate is a natural component of many foods including a variety of fruits and vegetables, beer and bourbon.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation. The chemical is currently of low priority for further work because of low toxicity to humans and the environment and low potential for exposure.