SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-09-3
Chemical Name	2-Ethylhexyl Acetate
Structural Formula	CH3-C(=O)-CH-CH(CH2-CH3)-CH2-CH2-CH2-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Several of the health endpoints for 2-ethylhexyl acetate that are dependent upon systemic exposure make use of data from 2-ethylhexanol experiments. Acetate esters of primary alcohols undergo rapid hydrolysis, catalyzed by esterases and proteases found in mammalian tissues and gastric fluids. The rapid and complete hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol has been demonstrated to occur *in vitro* within blood (half life of 2.3 minutes) and *in vivo*. The use of 2-ethylhexanol studies to identify hazards associated with 2-ethylhexyl acetate exposure are limited to toxicity endpoints dependent upon systemic exposure (e.g. repeated exposure, reproductive and developmental toxicity carcinogenicity) and not for direct exposure to the parent compound (e.g. eye and skin irritation) Therefore, toxicity data from studies conducted with 2-ethylhexanol have been used to identify the these hazards associated with 2-ethylhexyl acetate exposures.

Physical-Chemical Properties

2-Ethylhexyl acetate is a liquid at standard temperature and pressure, with a boiling point of 199 ºC and a melting (freezing) point of –93 ºC. It is less dense than water with a specific gravity of 0.8718 g/cm^3 at 20ºC. The solubility limit in water has been measured as 3.9 mg/L at 20°C. 2-Ethylhexyl acetate is combustible with a flash point of 76 ºC and a flammability range of 0.76 to 8.14% by volume. It has a vapour pressure of 0.31 hPa at 25 ºC. Given its solubility limits of 3.9 mg/L at 20 ºC and its molecular weight of 172.27 g/mole, the Henry's law constant at 25 ºC has been calculated to be 1.51 x 10^{-3} atm-m^3/mole (153.0 Pa-m^3/mol). An octanol/water partitioning coefficient (Log K_{ow}) value of 3.74 has been estimated for 2-ethylhexyl acetate.

Human Health

The hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol is rapid as demonstrated with in vitro and in vivo experiments. The subsequent metabolism of 2-ethylhexanol to 2-ethylhexaldehyde is presumed to occur with subsequent oxidation of the aldehyde intermediate to 2-ethylhexanoic acid. Metabolism and toxicokinetics studies with 2-ethylhexanol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine following intravenous, dermal and oral exposures. Elimination of 2-ethylhexanol metabolites following oral exposure was complete within 24 hours. Comparison of 2-ethylhexanol and 2-ethylhexanoic acid metabolic/toxicokinetics information and toxicity databases suggests that the metabolic processes necessary to convert 2-ethylhexanol to 2-ethylhexanoic acid explain the difference in toxicity of these chemicals. 2-Ethylhexanol toxicity information is most relevant for 2-ethylhexyl acetate hazard identification since 1) 2-ethylhexanol is the product of the initial hydrolysis reaction of 2-ethylhexyl acetate and 2) the limited toxicity information for 2-ethylhexyl acetate suggests a similar toxicity profile with 2-ethylhexanol. Metabolism data in humans for 2-ethylhexyl acetate is not available.

The oral LD_{50} value for 2-ethylhexyl acetate is >3200 mg/kg bw in rats and mice, with weakness and ataxia reported at this dose level. The dermal LD_{50} in rabbits is >20 ml/kg (17,436 mg/kg bw); the substance was applied undiluted and under occlusion for 24 hours followed by a 10-day observation

interval. Inhalation exposure of rats (3/group) for 6 hours caused no deaths at 7.8 mg/L (1106 ppm). 2-Ethylhexyl acetate is a mild skin irritant and a mild eye irritant in rabbits. No respiratory irritation has been reported in the acute inhalation study in rats. 2-Ethylhexyl acetate was negative for skin sensitisation when applied as 4% in petrolatum in humans.

There were no repeated dose toxicity studies conducted with 2-ethylhexyl acetate. There are thirteen week oral and inhalation studies available with 2-ethylhexanol. The NOEC from the thirteen week inhalation rat study with 2-ethylhexanol was 0.639 mg/L (120 ppm; the highest vapour concentration achievable). A thirteen week gavage study with 2-ethylhexanol in rats caused stomach irritation, increased reticulocytes and liver effects (increased liver weight, decreased serum cholesterol, albumin and total protein, liver histopathology (reduced number and incidence of fatty infiltration of the peripheral lobules) and peroxisome proliferation) in the 500 mg/kg bw/day male and female rats. Milder liver effects indicative of peroxisome proliferation was noted in male and female rats at 250 mg/kg bw/day. The NOAEL in male and female rats was 125 mg/kg bw/day. A similar study in mice produced a NOAEL of 125 mg/kg bw/day based on increases in relative liver weights in male mice at the 250 mg/kg bw/day dose level. The ability of 2-ethylhexanol to induce hepatic peroxisome proliferation in rats and mice following 14 days of oral exposure has been demonstrated.

In vitro studies demonstrate that 2-ethylhexyl acetate was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* at concentrations up to 5000 µg/plate with and without metabolic activation. In addition, 2-ethylhexanol was not genotoxic in four Ames assays, an *in vitro* cell transformation assay, a mouse lymphoma assay, a CHO mutation assay and was negative for unscheduled DNA synthesis in primary rat hepatocytes. In vivo, 2-ethylhexanol did not induce an increase in micronuclei in peripheral erythrocytes and was negative in a dominant lethal assay in mice. 2-Ethylhexanol also did not cause chromosomal aberrations in CHO cells at concentrations up to 500 µg/mL, with and without metabolic activation. 2-Ethylhexyl acetate and the primary metabolite, 2-ethylhexanol, is not genotoxic in vitro or in vivo.

In oral (gavage) assays with 2-ethylhexanol in rats using dose levels of 0, 50, 150 or 500 mg/kg bw/day (24 months), reduced body weight gain was noted in rats in the 150 (males, 11%; females, 9%) and 500 (males, 23%; females, 21%) mg/kg bw/day dose groups. Laboured breathing and poor condition was noted in the 500 mg/kg bw/day animals. Dose-related increases in relative liver, stomach, and kidney weights were noted at sacrifice in the 150 and 500 mg/kg bw/day groups. Mortality in female rats (52%) was markedly increased at 500 mg/kg bw/day. The sum of the hepatocellular adenomas and carcinomas was less in the male treated groups (7) than in the two male control groups (8). The incidence of hepatocellular carcinomas in the female water control group was 1, in the 500 mg/kg bw/day was 0, and were a total of three in the 50 and 150 mg/kg bw/day groups combined. 2-Ethylhexanol was not oncogenic in rats

In oral (gavage) assays with 2-ethylhexanol in mice, using dose levels of 0, 50, 200 or 750 mg/kg bw/day (18 months), no dose-related changes were noted in mice receiving 50 or 200 mg/kg/day. At 750 mg/kg/day, reduced body weight gain (12% in males and 14% in females), decreased feed consumption (9% in males and 12% in females) and increased mortality were noted (30% in males and females by weeks 79-81). Increases in relative kidney (females only), liver (females only) and stomach weights (males and females) were noted at sacrifice in the 750 mg/kg bw/day group. The test material was not considered oncogenic in male mice. An increase in hepatocellular carcinomas in the female 750 mg/kg bw/day group was statistically significant when compared to the vehicle control group but not when compared to the concurrent water control group. This lead to the conclusion that 2-ethylhexanol was considered a weak or equivocal liver carcinogen in female mice at this dose level. Interpretation of this data is complicated by the severe toxicity (increased mortality) noted in mice at the 750 mg/kg bw/day dose level, the known ability of 2-ethylhexanol to induce peroxisome proliferation in rodent liver (as a potential mechanism of action for tumour formation) and the background incidence of liver tumours in this strain of mice.

No reproductive or developmental toxicity studies were available for 2-ethylhexyl acetate. 2-Ethylhexanol is not considered a reproductive toxicant based on data from repeated exposure studies as well as in vitro investigations. 2-Ethylhexanol causes developmental toxicity (reduced foetal body weights (-9.5%), a single type of skeletal vertebral malformation, reduced skeletal ossification) in rats only at oral dose levels of 650 mg/kg bw/day (861 mg/kg bw/day for 2-ethylhexyl acetate), a dose level causing significant maternal toxicity. The highest dose level (1300 mg/kg bw) caused

maternal deaths, reduced feed consumption and body weight gain in the dams, increased resorptions, foetal death and decreased foetal weights and malformations in the surviving foetuses. 2-Ethylhexanol is not a developmental toxicant via the dermal (up to 2,520 mg/kg bw/day) or inhalation routes of exposure (up to 0.85 mg/L) in rats. There were no treatment-related histological changes in either the testes or ovaries (in mice and rats) after 13 weeks of treatment with 2-ethylhexanol at dosages up to 500 mg/kg bw/day.

2-Ethylhexyl acetate possesses properties indicating a hazard for human health (mild skin and eye irritation). Adequate screening-level data are available to characterize the hazard for the human health purposes of the OECD HPV Programme.

Environment

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with an estimated half-life of 11.723 hours. Abiotic hydrolysis is predicted to occur with an estimated half-life of 121 days at pH 8 and 3.3 years at pH 7. A 28-day aerobic test, OECD TG 301B, using 2-ethylhexyl acetate, was conducted using municipal wastewater activated sludge. Biodegradation was 16%, 49%, 66%, and 70% after 3, 7, 12, and 28 days, respectively. These data indicate the material is readily biodegradable.

Fugacity modelling (Level III) was conducted for 2-ethylhexyl acetate. The resulting distributions are 7.65% to air, 25.7% to water, 65.4% to soil and 1.23% to sediment Using the log K_{ow} of 3.74, a BCF of 151 was calculated for 2-ethylhexyl acetate.

The Henry's law constant is 1.51 X 10^{-3} atm-cu m/mole at 25°C. This value suggests that volatilization of 2-ethylhexyl acetate from the water phase is not expected to be significant. The K_{oc} of 2-ethylhexyl acetate is estimated at approximately 222, which suggests that 2-ethylhexyl acetate has moderate mobility in soil.

The critical study that evaluated the toxicity of 2-ethylhexyl acetate to fish was conducted in a 96 hour static-renewal assay with *Oncorhynchus mykiss*. The study used a water accommodated fraction (WAF) with measured concentrations of 0, 0.284, 0.57, 1.34 or 2.51 mg/L. The 96-h LC50 was reported as 8.27 mg/L.

The critical study that evaluated the toxicity of 2-ethylhexyl acetate to aquatic invertebrates was conducted with *Daphnia magna* using static-renewal 48 hour exposure according to OECD TG 202. The study used a WAF with measured concentrations of 0, 0.828, 2.06, 4.12, 7.99, or 15.7 mg/L. The 48-hour EC_{50} for immobilization of *Daphnia magna* is 22.9 mg/L.

Results are available from a 72 hour growth inhibition study in green algae (*Pseudokirchneriella subcapitata*, formerly known as *Selenastrum capricornutum*). The study used a WAF with measured concentrations of 0, 1.42, 2.70, 5.27, 10.3, or 21.0 mg/L. The 72-hour EC_{50} for growth inhibition for 2-ethylhexyl acetate was >21.9 mg/L, and the $NOEC_{growth\ inhibition}$ was 10.3 mg/L.

2-Ethylhexyl acetate possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The chemical is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

2-Ethylhexyl acetate had a production and/or import volume in the United States between 454 and 4,540 tonnes during 2005. 2-Ethylhexyl acetate is produced by the esterification of 2-ethylhexanol with acetic acid. Virtually all of the 2-ethylhexyl acetate produced is used as a solvent in the manufacture of various types of industrial and consumer paints and coatings. Minor use as a component of fragrances is also reported. No monitoring data within production and processing sites in the United States are available. It has a low odour threshold (0.007 ppm) and a sweet odour. 2-Ethylhexyl acetate is manufactured in an enclosed, continuous process and engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to minimize workplace exposure and odour complaints. Workplace and consumer exposure may occur via the inhalation of vapours during the application and drying of paints and coatings containing 2-ethylhexyl acetate. Minor dermal exposure may also occur. Some consumer

exposure occurs due to the reported use of 2-ethylhexyl acetate as a component in fragrances. Scrubbers and other emission controls are usually employed to minimize release of 2-ethylhexyl acetate during manufacture and use. However, 2-ethylhexyl acetate may be released to the environment as a fugitive emission during production.