SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-21-4
Chemical Name	Isopropyl Acetate
Structural Formula	CH_3-C(=O)-O-CH(CH_3)-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue justification

Based on rapid and complete conversion of isopropyl acetate to isopropyl alcohol in vivo, isopropyl alcohol toxicity data have been used to support the health effects of isopropyl acetate. Exposure to isopropyl acetate via dermal, inhalation, and oral routes is expected to result in the rapid appearance of isopropyl alcohol in the systemic circulation. Therefore, systemic toxicity of isopropyl alcohol is relevant in identifying hazards associated with isopropyl acetate exposure. The toxicokinetics of the hydrolysis reaction is documented and explained below. In addition, based on their structural similarities to isopropyl acetate, analog data for propyl acetate and n-butyl acetate, a chemical whose toxicity was evaluated at SIAM 13, have been used for ecotoxicity endpoints.

Human Health

Respiratory bioavailability studies showed that inhalation of 2000 ppm isopropyl acetate in a closed chamber resulted in isopropyl acetate whole blood levels up to 54 μM and isopropyl alcohol levels up to 268 μM. Within 5 minutes into exposure, isopropyl alcohol whole blood levels exceeded that of isopropyl acetate. Isopropyl alcohol levels were between 2 and 10-fold higher than isopropyl acetate levels throughout the 90-minutes exposure period. Therefore, toxicity studies conducted with direct isopropyl alcohol administration are relevant to identifying hazards associated with isopropyl acetate exposures.

Isopropyl acetate has low acute toxicity by all routes. The oral LD50 in female rats is 12,500 mg/kg bw and in rabbits was 6,945 mg/kg bw. Dermal LD50 in male rabbits was >17,436 mg/kg bw. Inhalation LC_{50} values for vapor exposures were 12,114 ppm (50.6 mg/L) in female rats (8 hours of exposure). Isopropyl acetate is a slight skin irritant and a severe eye irritant. Data for skin sensitisation are not available.

Repeated inhalation exposures for 13-weeks to 500 to 5000 ppm (1.23 to 12.23 mg/L) concentrations of isopropyl alcohol caused depressed central nervous system function (e.g. narcosis, hypoactivity, ataxia, loss of startle reflex) in rats and mice. Exposure of female rats to 5000 ppm (12.25 mg/L) also increased motor activity during nine and 13 weeks of the study. No persistent neurotoxicity was noted in the neurotoxicity study conducted in rats. The NOAEL in the 13-week rat study was 500 ppm (1.23 mg/L) based on decreases in red blood cell parameters in the male and female rats and the during-exposure clinical signs noted in the 1500 and 5000 ppm (3.68 and 12.23 mg/L) groups. The NOAEL in the 13-week study in mice was 500 ppm (1.23 mg/L) based on during-exposure clinical signs (male and female mice) and increased relative liver weights (female mice only) at 1500 and 5000 ppm (3.68 and 12.23 mg/L). A NOAEL of 500 ppm isopropyl alcohol corresponds to 394 ppm (1.65 mg/L) isopropyl acetate and a LOAEL of 1500 ppm isopropyl alcohol corresponds to 1181 ppm (4.9 mg/L) isopropyl acetate after correcting for differences in total respiratory bioavailability.

An *in vitro* mutagenicity study in bacteria indicates that isopropyl acetate is not a genotoxicant. In addition, isopropyl alcohol was negative in an *in vivo* mouse micronucleus study and in inhalation cancer bioassays conducted with rats and mice. Based on these results, isopropyl acetate is unlikely to possess carcinogenic potential.

The reproductive toxicity of isopropyl alcohol has been investigated in a one-generation drinking water study and a two-generation oral gavage study. Data from a developmental neurotoxicity study provides additional information on litter size and postnatal survival. A parental NOAEL of 100 mg/kg bw/day (170 mg isopropyl acetate/kg bw/day) was determined based on increased liver and kidney weights, centrilobular hepatocyte hypertrophy and hyaline droplet degeneration of the proximal convoluted tubular cells of the kidney at 500 mg/kg bw/day. Using a weight-of-evidence approach, a NOAEL for reproductive/developmental toxicity (decreased litter size and decreased postnatal survival) of 1338 mg/kg bw/day from a drinking water study for isopropyl alcohol was determined. The corresponding value for isopropyl acetate would be 2275 mg/kg bw/day. No effects were reported in an oral gavage developmental neurotoxicity study (NOAEL 1200 mg/kg bw/day; corresponding to 2040 mg/kg bw/day for isopropyl acetate).

The NOAEL from a rat developmental toxicity study in rats—conducted with 400, 800, or 1200 mg/kg/day isopropyl alcohol during days 6-15 of gestation—was 400 mg/kg bw/day for both maternal and fetal endpoints based on death in the dams and reduced fetal body weights noted at 800 mg/kg bw/day and above. No developmental effects were noted in rabbits exposed to 120, 240, or 480 mg/kg bw/day isopropyl alcohol by oral gavage during gestation days 6-18. Exposure of rats to vapor levels of isopropyl alcohol of 3500 ppm and above caused a decrease in fetal body weights, and the 10,000 ppm group had an increased incidence of failure of implantation, fully resorbed litters, increased resorptions per litter, and increased incidence of cervical ribs when administered 7 hr/day from gestation days 1 through 19. Maternal toxicity (decreased rate of weight gain) was noted at all exposure concentrations and the effect on fetal weight at the 3500 ppm group was slight (<5%) and correlated with increased litter size in that group. An inhalation exposure of 3500 ppm isopropyl alcohol is calculated to equal 2760 ppm (11.5 mg/L) isopropyl acetate after correcting for differences in respiratory bioavailability. Isopropyl alcohol was not a developmental neurotoxicant in rats when exposed by oral gavage at dose levels of 200, 700, or 1200 mg/kg bw/day. The NOAEL for isopropyl alcohol for developmental endpoints (400 mg/kg bw/day) from oral exposures would equal 680 mg/kg bw/day for isopropyl acetate after correcting for differences in gram molecular weight.

Environment

Isopropyl acetate is a liquid with a melting point of –73.4 ^{o}C and a boiling point of 88.6 ^{o}C. It has a vapor pressure of 80.5 hPa at 25^{0}C, a water solubility of 30,900 mg/l at 20^{0}C and a log K_{ow} of 1.02. The photochemical removal of isopropyl acetate as mediated by hydroxyl radicals occurs with a calculated half-life of 3.073 days. Isopropyl acetate is readily biodegradable under aerobic conditions. Isopropyl acetate volatilises easily from moving rivers, but volatilises only moderately from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 3.285 hours from a river and 5.024 days from a lake). Isopropyl acetate is not persistent in the environment and is not likely to bioaccumulate in food webs. Using the Log K_{ow} value, the BCF is 1.2. Based on Level III distribution modelling it is estimated that the majority of isopropyl acetate released to the environment will partition into water (45.3%) and soil (37.8%), with a smaller amount into air (16.8%). The stability of isopropyl acetate in water is pH dependent: at neutral pHs (7) the $T_{1/2}$ = 2.418 years at 25^{0}C and at higher pHs (8) the $T_{1/2}$ is shortened to 88.3 days.

Since the duration of the isopropyl acetate study with green algae was longer than current OECD guidelines, green algae data for an analogous compound, n-butyl acetate (CAS# 123-86-4) is presented. The rationale for the use of the analogous compound n-butyl acetate is based on the log Kow and water solubility values. The log Kow values are 1.02 and 1.82 for isopropyl acetate and n-butyl acetate, respectively. The water solubility values are 30,900 mg/L and 14,000 mg/L for isopropyl acetate and n-butyl acetate, respectively. For isopropyl acetate, a static test with fathead minnows (*Pimephales promelas*) was conducted and a 96-hour LC_{50} of 390 mg/L (ECOSAR 96-h LC_{50} = 632.4 mg/L) was reported. For n-butyl acetate, a flow-through test with fathead minnows (*Pimephales promelas*) gave a 96-hour LC_{50} of 18 mg/L (ECOSAR 96-h LC_{50} = 22 mg/L). The invertebrate (*Artemia salina*) study with isopropyl acetate reported a 48-h LC50 of 110 mg/L (ECOSAR daphnid 48-h EC50 = 51.7 mg/L). The invertebrate (*Artemia salina*) study with n-butyl acetate reported a 48-h LC_{50} of 32 mg/L (ECOSAR 48-h EC_{50} = 135 mg/L), while the study for green algae (*Scenedesmus subspicatus*) reported a 72-h EC_{50} of 674.7 mg/L. Based on physical properties data and valid ecotoxicity studies for both isopropyl acetate and n-butyl acetate, data for n-butyl acetate can be used to reliably and conservatively predict the toxicity of isopropyl acetate to green algae.

Exposure

Environmental release during manufacture is limited by the enclosed nature of the process and equipment. Inhalation and dermal exposure may occur during manufacture, transport, processing into formulations containing isopropyl acetate as solvent (e.g., coatings and inks), and the use or application of formulations and products containing isopropyl acetate. U.S. manufacturers indicate that exposure to isopropyl acetate in the workplace is limited during manufacture and formulation of products by the enclosed nature of these processes. The American Conference of Governmental Industrial Hygienists (ACGIH) has established an 8 hour Time Weighted Average Threshold Limit Value (TLV) of 1040 mg/m^3 (250 ppm) and a Short Term Exposure Limit (STEL) of 1290 mg/m^3 (310 ppm). Greater exposure potential exists during use as an industrial solvent, especially in coatings applications or printing where the processes may be more open. Exposure is typically limited in these cases by the use of engineering controls. Isopropyl acetate is present at 1-5 % concentrations in some consumer products, such as insecticides, shellacs and lacquers, which offer opportunity for occasional exposure. Perfumes containing isopropyl acetate as a diluent/fragrance can result in exposure of low concentrations to this substance. General population exposure may occur through industrial releases via inhalation of ambient air, and through ingestion of drinking water. Ingestion of foods naturally containing isopropyl acetate or due to its use as a food additive (21 CFR § 175.105 and 21 CFR § 172.515) is a further source of general population exposure.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (eye irritation, reproductive and developmental toxicity at high doses, repeated-dose toxicity at high doses). These hazards do not warrant further work as they are related to reversible effects (eye irritation) or effects seen at high doses. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently of low priority for further work due to its low hazard profile.