SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-60-4
Chemical Name	n-Propyl Acetate
Structural Formula	CH_3-CH_2-CH_2-COO-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Justification

Data from the analogue substances n-propyl alcohol, ethyl acetate and n-butyl acetate have been included in the assessment of n-propyl acetate for repeated-dose, genetic toxicity and reproductive/developmental toxicity endpoints.

Data for n-propyl alcohol (CAS No. 71-23-8) can be used for the systemic toxicity endpoints of n-propyl acetate because inhalation exposure of rats to n-propyl acetate results in hydrolysis of the acetate to n-propyl alcohol, with blood levels of the alcohol that peak after 15 minutes exposure; concentrations of the alcohol in blood were between 2.6 to 7.7 times higher than n-propyl acetate throughout the 90-minute exposure period. Endpoints of n-propyl acetate toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from n-propyl alcohol data due to the difference in physical-chemical properties of the two materials.

Data for two analogue compounds, ethyl acetate (CAS No. 141-78-6) and n-butyl acetate (CAS No. 123-86-4), are also provided to address the above endpoints based on similar chemical structures. Ethyl acetate and n-butyl acetate exhibit similarities in mammalian toxicity. Effect levels are lower for ethyl acetate than for n-butyl acetate, and it is expected that n-propyl acetate would have effect levels between those of ethyl acetate and n-butyl acetate. Ethyl acetate and n-butyl acetate have previously been assessed in the OECD HPV programme.

Physical-Chemical Properties

n-Propyl acetate is a clear, colourless liquid with a melting point of -93 ºC, boiling point of 101.5 ºC, vapour pressure of 33.3 hPa at 20 ºC, and water solubility of 20,000 mg/L at 20 ºC. n-Propyl acetate has a density of 0.882 mg/m^3 at 25°C, a measured Henry's law constant of 2.2 x 10^{-4} atm-m^3/mol (22.3 Pa-m^3/mol) at 25 °C, and a measured log K_{ow} of 1.24. It is a flammable liquid with a flash point of 13°C (closed cup) and a flammable range of 1.7 to 8 volume percent. n-Propyl acetate has an odour threshold of 0.21 mg/m^3 or 0.88 ppm. It has a sweet, fruity odour and a bittersweet taste.

Human Health

As noted above, an *in vivo* respiratory bioavailability study in rats showed that n-propyl acetate hydrolyses to n-propyl alcohol. Blood levels of the alcohol exceeded the acetate levels by 2.6 to 7.7 times at each time point tested between 0 and 90 minutes. No data are available on kinetics and routes of excretion of n-propyl acetate *in vivo*.

In a 4-h acute inhalation study in female rats (6/concentration) exposed to n-propyl acetate vapour, the LC_{50} was greater than 4000 ppm. All rats died at 16,000 ppm; rats were unconscious and 4 of 6 died (mortality 67%) at 8000 ppm; and animals were inactive but conscious with no deaths at 4000 ppm. Necropsy of animals dying during exposure revealed pulmonary haemorrhage and necropsy of surviving animals after the 14-day observation period revealed evidence of earlier lung damage. The dermal LD_{50} in male rabbits after 24 hours of exposure was > 17,756 mg/kg bw. Erythema and necrosis of the skin were observed at the site of application. The acute oral LD_{50} value for n-propyl acetate was 8700 mg/kg bw for male rats. Signs of toxicity included sluggish behaviour and laboured breathing prior to death. Necropsy of animals that died revealed congestion of abdominal organs and surface "burns" of the viscera in contact with the stomach.

n-Propyl acetate was mildly irritating to skin under non-occluded conditions. However, prolonged skin exposure

under occlusive covering can cause necrosis. n-Propyl acetate induced diffuse corneal injury that healed quickly when instilled into rabbit eyes. No reliable studies are available for respiratory irritation for n-propyl acetate. There are no sensitisation studies for n-propyl acetate.

There were no repeated-dose data available for n-propyl acetate. However, data were available for the analogue substances, n-propyl alcohol, ethyl acetate and n-butyl acetate. In a repeated-dose inhalation toxicity study, rats (10/sex/concentration) were exposed to **n-propyl alcohol** vapour at 0, 100, or 500 or 1000 ppm (0, 0.246, 1.23 or 2.46 mg/L) for 6 h/day for 9 days. Rats exposed to 1000 ppm exhibited evidence of nasal and ocular irritation. Based on nasal and ocular irritation observed in one animal at 500 ppm, the NOAEC for this study was 100 ppm (0.246 mg/L). As noted earlier, the point of contact effects of n-propyl alcohol may not be predictive of effects for n-propyl acetate. In another repeated-dose inhalation study, rats (10/sex/ concentration) were exposed to **ethyl acetate** vapour at 0, 350, 750 or 1500 ppm (0, 1.28, 2.75, or 5.49, mg/L) for 6 h/day, 5 days/week for 13 weeks. Rats exposed to 750 and 1500 ppm exhibited decreased food consumption, decreased body weight gains, and decreased alerting response to an auditory stimulus that was transient and confined to the exposure period. Decreased numbers of circulating erythrocytes were seen in males at 1500 ppm. Lower serum triglycerides were also observed in both sexes at 1500 ppm and in males at 750 ppm. Serum albumin and total protein levels were mildly decreased in females at 1500 ppm. Necrosis of the olfactory epithelium was observed in some rats (8/20) exposed to 350 ppm and all rats exposed to 750 and 1500 ppm. The LOAEC for this study was 350 ppm (1.28 mg/L), the lowest dose tested. In another inhalation study, rats (10/sex/concentration) were exposed to **n-butyl acetate** vapour at 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05 or 14.1 mg/L) for 6 h/day, 5 days/week for 13 weeks. Nasal discharge of porphyrin was observed in all **n-butyl acetate** groups after exposure. Decreased food consumption was seen at all concentrations. Decreased body weight gains and increased salivation were observed at 3000 ppm. Reductions in mean body weights and minimal reductions in activity during exposure were seen at both 1500 and 3000 ppm. Organ weight changes independent of body weight included lower spleen and higher lung weights in males at 3000 ppm, and higher testes weights in males and higher adrenal weights in females at 1500 ppm and in both sexes at 3000 ppm. Necrosis of the olfactory epithelium was observed in some rats (10/20) exposed to 1500 ppm and all rats exposed to 3000 ppm. Signs of stomach irritation were observed in females at 3000 ppm. The NOAEC based on multiple effects was determined to be 500 ppm (2.35 mg/L).

Neurotoxicity studies have also been conducted for the analogue substances, **ethyl acetate** and **n-butyl acetate**. Rats (minimum 12/sex/concentration) were exposed to 0, 350, 750, or 1500 ppm (0, 1.28, 2.75, or 5.49 mg/L) **ethyl acetate** vapour for 6 h/day, 5 days/week for 100 days. Decreases in body weight, body weight gain and feed consumption and feed efficiency were seen at 750 and 1500 ppm. A diminished response to an alerting stimulus was noted during exposure at 750 and 1500 ppm, and females exposed to 1500 ppm exhibited a decrease in motor activity. The NOAEC for subchronic neurotoxicity for **ethyl acetate**, based on decreased motor activity observed in females at 1500 ppm, is 750 ppm (2.75 mg/L). Rats were exposed to 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05, or 14.1 mg/L) **n-butyl acetate** vapour for 6 h/day, 5 days/week for 13 weeks. Body weights and/or body weight gains were reduced at 1500 and 3000 ppm. There was no evidence of neurotoxicity based on functional observational battery testing and schedule-controlled operant behaviour endpoints or neuropathological examinations. The NOAEC for subchronic neurotoxicity for n-butyl acetate was determined to be 3000 ppm (14.1 mg/L). For both ethyl acetate and n-butyl acetate, the results of the neurotoxicity tests support the conclusion that these chemicals show minimal neurological effects.

In a bacterial reverse mutation assay, n-propyl acetate was negative both in the presence and absence of metabolic activation. n-Propyl acetate was also negative when tested in a mitotic aneuploidy assay in yeast. n-Propyl alcohol was negative when tested in a yeast forward gene mutation assay in the presence and absence of metabolic activation. n-Propyl alcohol was also negative in two *in vitro* SCE assays conducted in Chinese hamster ovary or lung (V79) cells, and in an *in vitro* micronucleus test conducted in V79 cells. **Ethyl acetate** did not induce chromosomal aberrations in three *in vivo* micronucleus assays (one in mice, two in Chinese hamsters). Although weakly positive for chromosomal aberrations in Chinese hamster lung cells at the highest dose tested *in vitro*, **ethyl acetate** was negative in other *in vitro* tests using Chinese hamster ovary cells both with and without metabolic activation. **n-Butyl acetate** was negative for chromosomal aberrations in an *in vitro* test using Chinese hamster lung cells. The available data on n-propyl acetate and related compounds suggest that it is unlikely to induce genotoxic effects *in vivo*.

No carcinogenicity data are available for n-propyl acetate. There are no valid studies available for n-propyl alcohol or the structural analogues of n-propyl acetate (n-butyl acetate, ethyl acetate).

There are no reproductive or developmental toxicity studies available for n-propyl acetate. Studies are available for the supporting chemicals n-propyl alcohol and n-butyl acetate. Rats (18/sex/concentration) were exposed to 0,

3500 or 7000 ppm (0, 8.61 or 17.2 mg/L) **n-propyl alcohol** vapour for 7 h/day, 7 days/week for 62 days prior to being mated with unexposed rats of the opposite sex. Females exposed to 7000 ppm displayed decreased food consumption and reduced body weight gains. There was no effect on female fertility, reproduction or neonatal survival. Among offspring from rats maternally exposed to 7000 ppm n-propyl alcohol, there was an increase in the incidence of pups with crooked tails. Among males, there was a marked reduction in fertility in the 7000 ppm group, which was reversed after a 13-week recovery interval. The NOAEC for female fertility was 7000 ppm or 17.2 mg/L, and the NOAEC for male fertility was 3500 ppm or 8.61 mg/L. Among offspring from rats paternally or maternally exposed to 7000 ppm n-propyl alcohol, there were no significant differences relative to controls on any of the neurodevelopmental tests (MA, SCOB, FOB, neurochemistry). Groups of rats (10/sex/group) were exposed to **n-butyl acetate** at concentrations of 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05 or 14.1 mg/L) for 6 h/day, 5 days/week for 13 weeks. Among males, there was no difference in testicular spermatid head counts and epididymidal spermatozoa counts relative to controls. Mating and reproductive performance were not affected in female rats exposed to 1500 ppm (7.05 mg/L) **n-butyl acetate** for 7 h/day, 5 days/week for 3 weeks prior to mating.

In a developmental toxicity study**,** pregnant female rats were exposed to **n-propyl alcohol** vapour at 0, 3500, 7000 or 10,000 ppm (0, 8.61, 17.2 or 24.6 mg/L) for 7 h/day during gestation days 1 to 19. Decreased maternal food consumption, decreased maternal body weight gain and increased incidence of malformations, including pups with crooked tails, were observed at 10,000 ppm (24.6 mg/L); increased pre-and post-implantation loss was also reported. Decreased maternal food intake and body weight gain and increased incidence of pups with rudimentary cervical ribs were observed at 7000 ppm. In groups exposed to 7000 and 3500 ppm n-propyl alcohol, there was no effect on litter size, gestation length, birth weight, pup weight or pup survival. The NOAEC for maternal and developmental toxicity for **n-propyl alcohol** in rats in this study was 3500 ppm (8.61 mg/L). In a behavioural teratogenicity study, female rats were exposed to 3500 or 7000 ppm (8.61 or 17.2 mg/L) **n-propyl alcohol** vapour from gestation days 1 to 20. Increased incidence of crooked tails were observed in offspring of dams exposed to 7000 ppm (17.2 mg/L); however, behavioural testing of offspring revealed no differences from controls after maternal exposure to n-propyl alcohol. The NOAEC for behavioural effects for this study was 7000 ppm (17.2 mg/L) n-propyl alcohol.

Female rats and rabbits were exposed to 1500 ppm (7.05 mg/L) **n-butyl acetate** vapour for varying intervals during pregnancy. In rats, maternal food consumption and body weight gains were decreased. Foetal body weights and crown-rump measurements were reduced in exposed animals. There was no increase in the incidence of malformations among exposed rats nor treatment-related anomalies. In the rats administered n-butyl acetate prior to mating and through gestation/lactation, an increased incidence of hydroureters was seen. In rabbits, maternal food consumption and body weight gains were reduced. There was no effect on foetal body weights or measurements and there was no increase in malformations. There was an increase in two minor anomalies (misaligned sternebrae and retinal folds) as well as increased incidence of clear gall bladders. Both studies resulted in LOAECs for developmental toxicity of 1500 ppm (7.05 mg/L). Based on data for the analogue substances (**n-propyl alcohol** and **n-butyl acetate**), n-propyl acetate has the potential for reproductive and developmental toxicity at high doses.

n-Propyl acetate may present a hazard for human health (skin and eye irritation and potential reproductive/developmental toxicity at high doses). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

n-Propyl acetate is a naturally-occurring material and has been detected but not quantified in surface waters in the United States and Europe. The stability of n-propyl acetate in water is pH dependent. Hydrolysis is expected to occur slowly at neutral or acidic pH, but increase at pH > 8. The half-lives of n-propyl acetate in water at 25 ºC and at pH 7, 8 and 9 are 3 years, 119 days and 12 days, respectively, as calculated using measured data. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a calculated half-life of 75 to 80 hours. A ready biodegradation test using a closed bottle method resulted in 72% biodegradation after 20 days. n-Propyl acetate is readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that n-propyl acetate will partition primarily into water (42.7%) and soil (42.6%), with a smaller amount in air (14.6%). A Henry's law constant of 22.3 Pa-m^3/mol at 25 ºC suggests that volatilisation of n-propyl acetate from water bodies may not be rapid but could be significant. Koc values of 11.2 and 100 were estimated, indicating a low sorption potential to organic content of soil.

The bioaccumulation potential is estimated to be low based on the log Kow of 1.24, which is supported by a calculated BCF of 1.8 estimated with BCFWIN.

Fish	*Pimephales promelas*	OECD TG 203	96 h LC_{50} = 60 mg/L
Invertebrate	*Daphnia magna* Straus	OECD TG 202	48 h EC_{50} = 91.5 mg/L
Algae	*Pseudokirchnerilla subcapitata*	OECD TG 201	72 h ErC_{50} = 672 mg/L (growth rate method) 72 h EbC_{50} = 366 mg/L (biomass/area under growth curve) 72 h NOEC = 83.2 mg/L (growth rate, biomass)

The following acute toxicity test results* have been determined for aquatic species:

*all results are based on measured test concentrations

n-Propyl acetate may present a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). However, the chemical biodegrades rapidly and exhibits limited potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

In 2006, consumption of n-propyl acetate in North America was estimated to be 29,000 metric tons; in Western Europe consumption was estimated to be 5,000 metric tons; and in Japan consumption was estimated to be 7,700 metric tons. In the United States, n-propyl acetate is manufactured by three producers.

n-Propyl acetate is used as a raw material in the chemical and pharmaceutical industry and as a solvent in the manufacture and use of liquid flexographic and rotogravure inks. n-Propyl acetate is used to control viscosity and modify the drying rate of ink, and to prevent smearing and ink accumulation on printing presses. The use of n-propyl acetate as an ink solvent is decreasing as water-based inks are developed. n-Propyl acetate is also used in the production of nitrocellulose lacquers, resins and waxes, and in the manufacture of artificial fragrances. n-Propyl acetate is an ingredient used in the manufacture of some consumer products including nail polish and glue. It is found naturally in fruits and is used as a synthetic flavouring substance and adjuvant.

In occupational settings, enclosed equipment and engineering controls are used during production, transfer and loading operations to minimize exposure and flammability hazards. The 8-h occupational exposure limit for n-propyl acetate in the U.S. is 200 ppm (835 mg/m^3). Exposure to the general population or consumers to n-propyl acetate occurs naturally in a variety of foods that are consumed by the general population. Exposure can also occur through fugitive emissions from manufacturing sites, landfills, and sewers, or during the use of consumer products such as nail polish and glues. Considering the many uses of the substance in different industrial sectors, the potential for dermal and inhalation exposure should be anticipated and monitored by industrial health and safety professionals.