SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-85-8
Chemical Name	Isobutyl isobutyrate
Structural Formula	CH_3-CH(CH_3)-CH_2-O-C(=O)-CH(CH_3)-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue justification

Data from isobutanol toxicity studies have been included in the human health section. Data from isobutanol are useful when assessing the hazards associated with the systemic toxicity of isobutyl isobutyrate exposure due to the rapid and complete metabolism of isobutyl isobutyrate to isobutanol and isobutyric acid in vivo. Isobutanol is then further metabolized to isobutyric acid. Therefore, exposure to isobutyl isobutyrate via dermal, inhalation, and water or dietary administration is expected to result in the rapid appearance of isobutanol and isobutyric acid in the systemic circulation. Since exposure to either isobutyl isobutyrate or isobutanol results in systemic exposure to isobutanol and isobutyric acid, systemic toxicity data from studies that administer isobutanol directly are useful in identifying hazards associated with isobutyl isobutyrate exposure. Data from studies conducted with isobutyric acid were not included, since there were none available. The toxicokinetics of the metabolic reaction is documented and explained below.

The acute aquatic toxicity database of isobutyl isobutyrate was supported using data from a structural analog, compound, 2-ethylhexyl acetate (CAS# 103-09-3), alleviating the need for additional testing on isobutyl isobutyrate. Data from structurally similar compounds may be used to address the aquatic toxicity of isobutyl isobutyrate.

Human Health

Metabolism/toxicokinetic studies have been conducted with isobutyl isobutyrate using intravenous injections. Isobutyl isobutyrate levels peaked immediately after injection and rapidly decreased thereafter. The calculated T1/2 by one-compartment modeling was 11.1 seconds. Isobutyl isobutyrate is metabolized extremely rapidly in vivo to isobutanol and isobutyric acid. Isobutanol is then further oxidized to isobutyric acid.

The oral LD_{50} in rats is >6400 mg/kg bw. Dermal LD_{50} in male rabbits was >10 ml/kg bw. Inhalation LC_{66} values for vapor exposures were 5423 ppm (31.94 mg/L) in rats (6 hours of exposure). Exposures to 658 ppm caused no deaths in 6 hours. Isobutyl isobutyrate is a slight skin irritant. Data for eye irritation and skin sensitisation are not available.

An 18-week oral gavage study in rats at dose levels of 0,10,100, and 1,000 mg/kg/bw/day with isobutyl isobutyrate reported an increase in relative spleen weights following a slight decrease in terminal body weights in the male animals treated with 1,000 mg/kg/bw/day. The lack of histopathological findings in the spleen and the lack of effect in the female animals resulted in the NOAEL being 1,000 mg/kg/bw/day. Studies with isobutanol generally corroborate this value although acute signs of toxicity were noted immediately after oral dosing with isobutanol. The use of different vehicles (corn oil with isobutyl isobutyrate and distilled water with isobutanol) affects the rate of absorption of these related materials and explains the presence or absence of clinical signs immediately after oral exposures. An *in vitro* mutagenicity study in bacteria indicates that isobutyl isobutyrate is not a genotoxicant. In addition, isobutanol was negative in an *in vivo* mouse micronucleus study. An inhalation two-generation reproductive toxicity study conducted with Isobutanol (up to 2500 ppm; 7.58 mg/L) did not cause any parental systemic, reproductive, or neonatal toxicity when administered for two generations via whole-body exposure. No adverse developmental effects were noted in rats or rabbits exposed up to 10mg/L Isobutanol during gestation.

Environment

The available physicochemical data are adequate to describe the properties of isobutyl isobutyrate. Isobutyl isobutyrate has a melting point of -80.7 ^{o}C, boiling point of 148.6 ^{o}C and vapor pressure of 5.8 hPa at 25^{0}C, a water solubility of 520 mg/L at 20^{0}C and a calculated log K_{ow} of 2.68. The photochemical removal of isobutyl isobutyrate as mediated by hydroxyl radicals occurs with a calculated half-life of 1.947 days. Isobutyl isobutyrate is readily biodegradable under aerobic conditions, based on data for isopropyl- and isobutyl-acetate. Isobutyl isobutyrate volatilizes easily from moving rivers, but volatilizes only moderately from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 1.67 hours from a river and 4.955days from a lake). Isobutyl isobutyrate is not persistent in the environment and is not likely to bioaccumulate in food webs. Using a calculated log K_{ow} of 2.68, the BCF is 23.1. Based on Level III distribution modeling (assuming equal releases to water, air, and soil) it is estimated that the majority of isobutyl isobutyrate released to the environment will partition into water (34.4%) and soil (52.7%), with a smaller amount in air (12.6%). The stability of isobutyl isobutyrate in water is pH dependent, at neutral pHs (7) the $T_{1/2}$ = 9.2 years at 25^{0}C and at higher pHs (8) the $T_{1/2}$ is shortened to 337 days.

Except for a study with the aquatic invertebrate, *Daphnia magna*, aquatic toxicity data are not available for isobutyl isobutyrate. Data for the structurally similar 2-ethylhexyl acetate (CAS# 103-09-3) were used to supplement the data for isobutyl isobutyrate. For fish, two studies with rainbow trout (*Oncorhynchus mykiss*) and 2-ethylhexyl acetate are available. Acute 96-h LC_{50}s of 8.27 and >4.2 mg/L were reported for 2-ethylhexyl acetate, respectively. Data are available with isobutyl isobutyrate and the invertebrate *Daphnia magna* with 48-h EC50 values of 55.8 to 59.3 mg/L reported. In addition, a daphnid study with 2-ethylhexyl acetate reported a 48-h EC_{50} of 22.9 mg/L. Data are available with 2-ethylhexyl acetate and the green alga *Selenastrum capricornutum* with a 72-h EC_{50} value of >21.9 mg/L and a 72-h NOEC of 10.3 mg/L reported. ECOSAR values for isobutyl isobutyrate were calculated to be 9.455 mg/L for fish, 27.556 mg/L for daphnids, and 0.771 mg/L for green algae. ECOSAR values for 2-ethylhexyl acetate were calculated to be 3.057 mg/L for fish, 3.571 mg/L for daphnids, and 0.260 mg/L for green algae. Data for 2-ethylhexyl acetate can be used to estimate the acute toxicity of isobutyl isobutyrate to fish and algae.

Exposure

Isobutyl isobutyrate occurs naturally in fruits and essential oils. Environmental concentrations of isobutyl isobutyrate may also occur from waste streams during manufacture or through solvent use in lacquers and thinners. Workplace exposure may occur via inhalation or dermal contact. Exposure during manufacture is limited by the enclosed nature of the process and by bulk handling and good manufacturing practices. Industrial and occasional consumer exposure can occur both dermally and via inhalation during application of lacquer and thinner formulations containing isobutyl isobutyrate. General population exposure can occur through inhalation of ambient air that may contain low concentrations resulting from industrial or commercial releases. General population exposure also occur through ingestion of foods containing isobutyl isobutyrate either naturally or as a synthetic flavorant (21 CFR § 121.1164).

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

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

Environment: The chemical possesses properties indicating a hazard for the environment (fish and algae). However, the chemical is of low priority for further work due to ready biodegradability and limited potential for bioaccumulation.