SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-31-2 97-72-3
Chemical Name	Isobutyric Acid (CAS No. 79-31-2) Isobutyric Anhydride (CAS No. 97-72-3)
Structural Formula	Isobutyric Acid $HO-C(=O)-CH(CH_3)-CH_3$ Isobutyric Anhydride $CH_3-CH(CH_3)-C(=O)-O-C(=O)-(CH_3)-CH-CH_3$

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category members isobutyric acid (CAS No. 79-31-2), and isobutyric anhydride (CAS No. 97-72-3) are closely related since the anhydride rapidly hydrolyzes in the presence of water to form the acid. Since testing of the anhydride is in reality testing of the acid form, these materials share toxicity characteristics and form the basis of the category. As a result, the metabolic series approach can be used to address the non-acute health endpoints.

Increased blood levels of isobutyric acid have been demonstrated following administration of isobutanol, a metabolic precursor of isobutyric acid. Hazard identification studies using isobutanol exposures have been used to identify the hazards associated with systemic exposure to isobutyric acid. Therefore, isobutanol (78-83-1) is used as an analog to either address or supplement the respective systemic toxicity endpoints for isobutyric acid.

Based on hydrolysis data, the acute aquatic toxicity endpoints of both isobutyric acid and isobutyric anhydride have been addressed using data from structural analogs, alleviating the need for additional testing on isobutyric acid. As a result, available data from propionic acid (CAS No. 79-09-4) and pentanoic acid (CAS No. 109-52-4) have been used to address the acute aquatic toxicity of isobutyric acid. In addition, data from propionic acid (CAS No. 79-09-4), n-butyric acid (CAS No. 107-92-6) and pentanoic acid (CAS No. 109-52-4) have been used to address the biodegradability of isobutyric acid.

Human Health

The acute oral and dermal LD_{50} values for isobutyric acid are >500 mg/kg/bw (rat) and >200 mg/kg/bw (rabbit), respectively. The oral and dermal LD_{50} for isobutyric acid is used for isobutyric anhydride. Data are available for the anhydride via the inhalation route indicating a low toxicity with an LC_{50} value of >5.1 mg/L.

Both the acid and anhydride forms are considered moderate to severe eye irritants. Isobutyric acid is a moderate to severe skin irritant and is corrosive to skin. Isobutyric anhydride is not a skin irritant unless it comes in contact with water and hyrolyses to isobutyric acid (a moderate to severe skin irritant). Based on clinical signs observed in the LC50 study (e.g. rales, nasal secretions, weight loss) airborne isobutyric acid or isobutyric anhydride can cause irritation of the upper respiratory tract. Repeated inhalation exposures would likely exacerbate the irritative effects. Although reported as a non-sensitizer, sensitization data are not available.

Repeated exposures to moderate to high concentrations of isobutanol (the metabolic precursor of isobutyric acid) are well tolerated in rats. In a 90-day inhalation study, rats were exposed to isobutanol at 0, 250, 1000, and 2500 ppm. A reduced response to an external stimulus was noted in the exposed animals. Repeated exposures did not exacerbate these transient effects. There was no evidence of neurotoxicity based on functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. Slight increases in red blood cell count, hematocrit, and hemoglobin parameters were reported in the 2500 ppm female rats. A 13-week oral gavage study was conducted with isobutanol with dose levels of 0, 100, 316, and 1000 mg/kg. Hypoactivity, ataxia, and salivation were noted in the 1000 mg/kg dose groups after dosing. In addition slight decreases in body weight gain and feed consumption was noted in the first two weeks of the 13-week study in the 1000 mg/kg dose group. The 100 and 316 mg/kg dose groups were unaffected.

The developmental/reproductive toxicity for isobutyric anhydride and isobutyric acid have been met for the purposes of the OECD SIDS program. An inhalation two-generation reproductive toxicity study conducted with isobutanol (up to 2500 ppm) 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 to 10 mg/L isobutanol during gestation.

Isobutyric acid is not mutagenic in bacteria *(Salmonella typhimurium*, *Bacillus subtilis*, or *Escherichia coli*). An *in vivo* mouse micronucleus test conducted with isobutanol administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight did not produce any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (spindle poison effect).

Environment

The preferred physical property values for isobutyric anhydride are: melting point –53.5 ^{0}C, boiling point 181.5 ^{0}C, density 0.9535 g/m^3, vapor pressure 5 hPa (at 50^{0}C) and 1.20 hPa (at 25°C), log Kow 1.24, aqueous solubility 16030 mg/L. The preferred physical property values for isobutyric acid are: melting point -47 ^{0}C, boiling point 153-155 ^{0}C, density 0.95 g/m^3, vapor pressure 19.6 hPa, log Kow 0.94, aqueous solubility 167,000 mg/L, Henry's law constant 8.85x10^{-7} atm-m^3/mol, and pKa 4.84-4.86. These compounds are liquid at 25°C and are very water-soluble. Under environmental conditions, based on its pKa, the acid is expected to exist primarily in its dissociated form. Neither compound is expected to be volatile.

Calculated atmospheric photo-oxidation half-lives were 5.7 days for isobutyric anhydride and 4.6 days for isobutyric acid. Isobutyric anhydride is unstable in water with half-lives of 2 - 17 minutes at environmentally relevant pH values pH 4 to 9 (23°C). Isobutyric acid is the hydrolysis by-product.

Level III fugacity modeling results indicate that isobutyric acid (which is representative of isobutyric anhydride) will primarily partition to soil (45.3%) and water (45.7%).

Biodegradation testing cannot be performed for isobutyric anhydride. Isobutyric acid rapidly biodegrades under anaerobic conditions (100% in 3 days). Manometric respirometry studies conducted for 30 days for the analog compounds propionic, n-butyric, and pentanoic acids showed biodegradation of 74, 58, and 72% ThOD, respectively. In addition, a modified MITI test (OECD 301C) with n-butyric acid reported 72% ThOD in 5.8 days. Collectively, these data with analog compounds support the conclusion that isobutyric acid is rapidly biodegradable. This conclusion is further supported by unverifiable BOD5 test with isobutyric acid. Fish bioconcentration factors of <2 to 3.16 were calculated for isobutyric acid. Based on the reactive nature of isobutyric anhydride, its tendency to hydrolyze in aqueous media, and the low log Kow value of the acid (0.94) one can conclude that isobutyric acid is not expected to bioaccumulate.

Aquatic toxicity data are only presented for isobutyric acid, due to the rapid hydrolysis of isobutyric anhydride in water. Since there is only aquatic invertebrate data available for isobutyric acid, data for analogous compounds are presented as well. The analogous compounds used were propionic acid ($C_3H_6O_2$, pKa 4.88) and pentanoic (valeric) acid ($C_5H_{10}O_2$, pKa 4.84). In fish *(Pimephales promelas*) the 96-hour LC_{50} values are 51.8 and 77 mg/L for propionic acid and pentanoic acid, respectively. Isobutyric acid was tested in Daphnia magna with the 48-hour EC_{50s} value of

51.25 mg/L. In green algae (*Scenedesmus subspicatus*) the 96-hour EC_{50} value is 42.9 mg/L for propionic acid and using *Selenastrum capricornutum*, a 96-h EC50 of 10.7 mg/L was reported for pentanoic acid. The pH was not controlled in any study after test initiation. In all studies, at least at higher concentrations, pH in the test medium was reduced to as low as 4.4 to 5.8 during the test. However, since pH was not a controlled variable in any test, effects on toxicity attributable to pH fluctuations cannot be discerned. Furthermore, with a pKa of 4.84-4.86, it is not likely that the acute aquatic toxicity of butyric acid will be dependent upon pH at environmentally relevant pH values (6 to 8). The toxicity of isobutyric acid (unbuffered) to fish, invertebrates and green algae is expected to range between 10.7 and 77 mg/L based on data for isobutyric acid and its analogs.

Exposure

Both isobutyric anhydride and isobutyric acid are manufactured in closed-systems in the sponsor country, and transported in tank cars, thus releases to the environment are anticipated to be minimal. Exposure of workers in processing facilities is likely to be limited by recommended personal protective equipment, its very distinct disagreeable odor, and because of the strong irritative properties of isobutyric anhydride. General population exposure is not anticipated, as isobutyric anhydride is not used in consumer products. Most isobutyric acid manufactured is consumed as an industrial intermediate in the production of other chemicals, such as isobutyronitrile and sucrose acetate isobutyrate. The major consumer use of isobutyric acid is as an approved additive in various foods, but in terms of total pounds manufactured, this is a very low percentage use. General population exposure to isobutyric acid may occur via its artificial and natural presence in foods. Environmental sources include fugitive emissions during its production and use, the exhaust of motor vehicles, and in vegetable oils and animal fluids. Isobutyric acid is an important metabolite in the breakdown of carbohydrates, fats and proteins. Isobutyric acid may arise from natural fermentation processes occurring in sediment and is a natural component of fruits, grains, and essential oils.

RECOMMENDATION

The Isobutyric Acid/Isobutyric Anhydride Category is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

These chemicals possess properties indicating a hazard for human heath (dermal, respiratory, and eye irritation) and the environment. Although these hazards do not warrant further work as they are related to transient effects or acute toxicity which may become evident only at high exposure levels, they should nevertheless be noted by chemical safety professionals and users.