SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-92-6 106-31-0
Chemical Name	n-Butyric Acid (CAS No. 107-92-6) n-Butyric Anhydride (CAS No. 106-31-0)
Structural Formula	n-Butyric Acid HOC(=O)-CH2-CH2-CH3 n-Butyric Anhydride CH3-CH2-CH2-C(=O)-O-C(=O)-CH2-CH2-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The n-Butyric Acid/n-Butyric Anhydride Category consists of two sponsored chemicals: n-butyric acid (CAS No. 107-92-6), and n-butyric anhydride (CAS No. 106-31-0.) The category members 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.

In addition, increased blood levels of n-butryic acid have been demonstrated following administration of the metabolic precursors of butyric acid (n-butyl actetate and n-butanol.) Since the increased blood levels of n-butyric acid following n-butyl acetate and n-butanol have been demonstrated experimentally, hazard identification studies using either n-butyl acetate or n-butanol exposures have been used to identify the hazards associated with systemic exposure to n-butyric acid. Therefore, data from n-butyl acetate (CAS No. 123-86-4) and/or n-butanol (71-36-3) are used as analogs to either address or supplement the respective systemic toxicity endpoints for n-butyric acid. Both the n-butyl acetate and n-butanol data sets were accepted at SIAM 13.

Based on hydrolysis data, the acute aquatic toxicity endpoints of both n-butyric acid and n-butyric anhydride have been addressed using data from structural analogs, alleviating the need for additional testing on n-butyric acid. As a result, available data from propionic (CAS No. 79-09-4), isobutyric (CAS No. 79-31-2) and pentanoic (CAS No. 109-52-4) acids have been used to assist in addressing the acute aquatic toxicity of butyric acid.

Human Health

The acute oral and dermal LD50 values for n-butyric acid are 2,940 mg/kg (rat) and 530 mg/kg (rabbit), respectively. The oral LD50 is representative of n-butyric anhydride. Data are available via the inhalation route indicating a low toxicity at saturated vapor concentration (no deaths). Both the acid and anhydride forms are considered skin and eye irritants. No data are available for dermal or respiratory sensitization. In general, some anhydrides are known respiratory sensitizers. However, butyric anhydride is not structurally similar to these anhydrides and is expected to quickly hydrolyze to the acid.

Repeated exposures to moderate to high concentrations of n-butyl acetate and n-butanol (the metabolic precursors of n-butyric acid) are well tolerated in rats. In a 90-day inhalation study, rats were exposed to n-butyl acetate at 0, 500, 1500, and 3000 ppm. Rats exposed at 1500 and 3000 ppm had minimal transient narcosis and sedation. Repeated exposures did not exacerbate these transient effects. Effects noted at these same exposure concentrations included reduced body weight gain and decreased feed consumption. There was no evidence of neurotoxicity based on

functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. Based on decreased body weight gain, the NOAEL for systemic effects is 500 ppm and a NOAEL for post-exposure neurotoxicity is 3000 ppm (highest dose tested).

The developmental/reproductive toxicity for butyric anhydride and butyric acid has been met for the purposes of the OECD SIDS program. The various studies that support this make it difficult to choose a single hazard value for reproductive effects (see SIAR for details on acceptable repeated dose studies assessing reproductive organs and two separate studies examining reproductive effects of either males or females). No adverse developmental effects were noted in rats exposed to 3500 ppm n-butanol or rats and rabbits exposed to 1500 ppm n-butyl acetate.

N-butyric acid is not mutagenic in bacteria *(Salmonella typhimuriu*m) or cultured Chinese hamster lung (CHL) cells. An *in vivo* mouse micronucleus test conducted with n-butanol 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 n-butyric anhydride are: melting point –75 ^{0}C, boiling point 195 ^{0}C, density 0.96 g/m^3, vapor pressure 0.377 hPa, log Kow 1.39, aqueous solubility 4561 mg/L (estimated from Log Kow). The preferred physical property values for n-butyric acid are: melting point -7.9 ^{0}C, boiling point 165.5 ^{0}C, density 0.96 g/m^3, vapor pressure 2.20 hPa, log Kow 0.79, aqueous solubility 56,400 mg/L, Henry's constant 5.35E-7 atm-m^3/mol, and pKa 4.82. 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 3.1 to 3.2 days for butyric anhydride and 3.96 to 4.46 days for n-butyric acid. Butyric anhydride is unstable in water with half-lives of 2 - 17 minutes at environmentally relevant pH values pH 4 to 9 (22°C). n-Butyric acid is the hydrolysis by-product. Level III fugacity modeling results indicate that n-butyric acid (which is representative of n-butyric anhydride) will primarily partition to the soil (57.0%) and water (37.2%) compartments. Biodegradation testing cannot be performed for butyric anhydride. n-Butyric acid was readily biodegradable (72% in 5.8 days) in an OECD 301C modified MITI test. Fish bioconcentration factors of 2.3 to 3.16 were calculated for n-butyric acid.

Aquatic toxicity data are only available for n-butyric acid, due to the rapid hydrolysis of butyric anhydride in water. Since the duration of the butyric acid studies was either shorter or longer than current OECD guidelines and because of uncertainties in study details, data for analogous compounds are presented. The analogous compounds used were propionic acid ($C_3H_6O_2$, pKa 4.88), isobutyric acid ($C_4H_8O_2$, pKa 4.86), and pentanoic (valeric) acid ($C_5H_{10}O_2$, pKa 4.84). In fish *(Pimephales promelas*), the 96-hour LC50 values are 51.8 and 77 mg/L for propionic acid and pentanoic acid, respectively. In *Daphnia magna* the 48-hour EC50s values are 22.7 and 51.25 mg/L for propionic acid and isobutyric acid, respectively. In green algae (*Scenedesmus subspicatus*) the 96-hour EC50 value is 42.9 mg/L for propionic 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 4.82, the acute aquatic toxicity of butyric acid may be partly due to pH effects. The toxicity of n-butyric acid (unbuffered) to fish, invertebrates and green algae is expected to range between 22.7 and 77 mg/L based on analog data.

Exposure

Both n-butyric anhydride and n-butyric 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. Should n-butyric acid or n-butyric anhyride become airborne, irritation of the upper respiratory tract in workers can occur. Based on the reactive nature of n-butyric anhydride, its tendency to hydrolyze in aqueous media, and the biodegradability of the breakdown products it does not accumulate in the environment. General population exposure is not anticipated, as n-butyric anhydride is not used in consumer products. Most n-butyric acid manufactured is consumed as an industrial intermediate in the production of other chemicals, such as cellulose acetate butyrate. The major consumer use of n-

butyric acid is as an approved additive in various foods, but in terms of total pounds manufactured, this is a very low percentage use. Other uses of n-butyric acid are as a tanning agent and a fungicide, which could result in exposure. General population exposure to n-butyric 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. N-butyric acid is an important metabolite in the breakdown of carbohydrates, fats and proteins. N-butyric acid may arise from natural fermentation processes occurring in sediment and is present in butter as an ester to the extent of 4-5%. N-butyric acid is a natural component of essential oils of citronella Ceylon, eucalyptus globules, nutmeg, hops, Spanish anise and strawberry aroma.

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

Human Health: These chemicals possess properties indicating a hazard for human heath (dermal and eye irritation). Although these hazards do not warrant further work, they should nevertheless be noted by chemical safety professionals and users.

Environment: These chemicals have properties indicating a hazard for the environment (acute aquatic EC/LC50s between 1 and 100 mg/L based on analog data). However, the chemicals are of low priority for further work for the environment because of the rapid biodegradation and limited potential for bioaccumulation.