SIDS INITIAL ASSESSMENT REPORT
For 16th SIAM
Paris, France
May 27-30, 2003

Category Name: n-Butyric Acid/n-Butyric Anhydride Category

Category Members: n-Butyric Acid, CAS No. 107-92-6
n-Butyric Anhydride, CAS No. 106-31-0

Sponsor Country: United States

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Testing: **No testing:** **(x)**
Testing **( )**

Comments: Based on the metabolic series approach, data for n-butyl acetate (CAS# 123-86-4) and n-butyl alcohol (CAS# 71-36-3) are used to represent the mammalian toxicity of n-butyric acid. Both these chemicals were presented and data sets approved at SIAM 13. In addition, data from propionic acid (CAS# 79-09-4), isobutyric acid (CAS# 79-31-2) and pentanoic acid (CAS# 109-52-4) are used as analogs for n-butyric acid to assist in the presentation of data for the acute aquatic toxicity.

Deadline for Circulation:

Date of Circulation: Revised November 2006

1.0 IDENTITY OF CATEGORY MEMBERS

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) and are listed in Table 1. 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-butyric acid have been demonstrated following administration of the metabolic precursors of n-butyric acid (n-butyl acetate 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# 123-86-4) and/or n-butanol (71-36-3) are used to either address or supplement the respective systemic toxicity endpoints for n-butyric acid since they are likely to share toxicologic characteristics with the sponsored chemicals. Both 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 n-butyric acid. The n-butyric acid data are also supplemented with data from structural analogs, alleviating the need for additional testing on n-butyric acid. As a result, available data from propionic (CAS# 79-09-4), isobutyric (CAS# 79-31-2) and pentanoic (CAS# 109-52-4) acids have been used to assist in addressing the acute aquatic toxicity of n-butyric acid.

Data for n-butyl acetate and n-butanol have been previously reviewed under the OECD SIDS Program at SIAM 13 and are presented in this SIAR, consistent with that of the previous data sets.

Table 1. Members of the n-Butyric Acid/n-Butyric Anhydride Category

Chemical Name	**n-Butyric Acid**	**n-Butyric Anhydride**
IUPAC Name	Butyric Acid	Butyric Anhydride
CAS Number	107-92-6	106-31-0
Molecular Formula	$C_4 H_8 O_2$	$C_8 H_{14} O_3$
Structural Formula	HO-C(=O)-CH2-CH2-CH3	CH3-CH2-CH2-C(=O)-O-C(=O)-CH2-CH2-CH3
Synonyms	Ethylacetic Acid Butanoic Acid Propylformic Acid 1-Propanecarboxylic Acid Butyrate	n-Butyric Anhydride Butanoic Acid, Anhydride Butanoic Anhydride
Composition	>99% n-Butyric Acid (CAS No. 107-92-6)	>99% n-Butyric Anhydride (CAS No. 106-31-0)

1.1 Metabolic Series and Analog Justification

Description of Hydrolysis Studies that Provide a Basis for the Category

The abiotic hydrolytic degradation of n-butyric anhydride was investigated in various aquatic environments (Isaacs and Hoffman, 2002). The EPA and OECD testing guidelines for abiotic degradation (hydrolysis) were expanded to include distilled deionized water, aquatic culture water, distilled deionized water buffered to a pH of 4, 7, or 9, and aquatic culture water buffered to a pH of 4, 7, or 9. The study was conducted at a temperature of 22 °C. A gas chromatograph equipped with a flame ionization detector (GC/FID) was used for quantitation of the loss of n-butyric anhydride and appearance of n-butyric acid. A mass-balance calculation was performed. The pH of the receiving aquatic solution was the most important predictor of the rate of hydrolysis. Solutions with a buffered pH of 4 or those that rapidly reached a pH of 4 following the addition of the anhydride (the distilled deionized water and aquatic culture water solutions) had a T½ of 17-18 minutes. The T½ for anhydride in the pH 7 buffered distilled deionized water and aquatic culture water solutions were 7 minutes while the T½ for the pH 9 buffered solutions was 2 minutes (Isaacs and Hoffman, 2002). The analytical method dictated at least 2 minutes between the addition of the anhydride and the analysis, at which point the hydrolysis was 20-80% complete (depending on the pH of the receiving solution). The mass balance calculations indicated that all of the loss of n-butyric anhydride was due to simple hydrolysis and not due to other factors.

Use of n-butyric acid and anhydride data:

These chemicals form a category because n-butyric anhydride rapidly hydrolyzes in the presence of water to form n-butyric acid. Examples of available aqueous environments for this reaction include airborne moisture, sweat, surfactant (within the respiratory airways), gastric fluids, and the aquatic environment. The hydrolysis of n-butyric anhydride upon contact with buffered distilled water (pH 7) is rapid, with a T½ of 7 minutes (Isaacs and Hoffman, 2002). The hydrolysis is faster with a more alkaline pH and is slower at acidic pH values. The T½ for hydrolysis in rat serum (buffered to a pH of 7.4) was 0.31 minutes (Isaacs and Hoffman, 2002), indicating a very rapid hydrolysis should the anhydride ever come in contact with the systemic circulation. Since the presence of water is ubiquitous to all life forms, n-butyric anhydride would be expected to hydrolyze to n-butyric acid under typical mammalian and environmental toxicity test conditions. Accordingly, systemic toxicity data from n-butyric acid toxicity may be used to read-across for n-butyric anhydride.

Use of n-butyl acetate and n-butanol data:

Exposure to either n-butyl acetate or n-butanol results in increased blood and tissue levels of n-butyric acid as a result of the metabolism of these two materials. Note that n-butanol and n-butyl acetate exposure may result in a greater amount of n-butyric acid in the mammalian systems than is possible by direct exposure because the corrosive properties of butyric acid preclude the use of higher concentrations during testing. The use of data for metabolic precursors is based on the "metabolic series" approach (See Appendix 1) that has been demonstrated and verified experimentally for the n-butyl acetate series. A data matrix is located in Appendix 2.

Use of Structural Analogs: (For Acute Aquatic Toxicity)

Due to the rapid hydrolysis of n-butyric anhydride in water to n-butyric acid (half-life of 2 minutes at environmentally relevant pH values), data from n-butyric acid or an analogous acid can be used to address the biodegradation and ecotoxicity endpoints. When data for n-butyric acid did not meet current OECD requirements, data from analogous compounds were used. Based on structural similarities and carbon chain length, data for propionic acid (CAS# 79-09-4), pentanoic acid (CAS# 109-52-4), and isobutyric acid (CAS# 79-31-2) are all considered suitable to serve as analog compounds for n-butyric acid. A data matrix is located in Appendix 2.

1.2 Physicochemical Properties

The physicochemical properties of n-butyric acid and n-butyric anhydride are described in Table 2. Included in this table is the hydrolysis data for n-butyric anhydride that forms the basis for this category. The available physicochemical data are adequate to the properties of these two materials.

Table 2. Physical and Chemical Properties of Category Members

Category Member	n-Butyric Acid	n-Butyric Anhydride
CAS No.	107-92-6	106-31-0
Physical form of marketed product	Liquid	Liquid
Melting point (^{o}C)	-7.9	–75
Boiling point (^{o}C)	165.5	195
Density (g/cm^3)	0.959	0.9668
Vapor pressure (hPa)	2.2 @25˚C	0.377 @ 25˚C
Partition coefficient (Log K_{ow})	0.79	1.39 (estimated)
Water solubility (mg/l)	miscible (1,000,000 mg/L @ 25ºC)	4561 @ 25˚C*
Flash point (^{o}C)	75	82
Stability in Water	Stable due to lack of hydrolyzable functional groups; based on its preferred pKa of 4.82, n-butyric acid is expected to undergo considerable dissociation at ambient pH values of 4 to 9	Readily hydrolyzes to butyric acid t½ unbuffered water = 17 min t½ pH 4 water = 17 min t½ pH 7 water = 7 min t½ pH 9 water = 2 min

*Estimated from the calculated partition coefficient value and therefore, may be somewhat uncertain.

2.0 GENERAL INFORMATION ON EXPOSURE

Manufacture

n-Butyric acid is manufactured in enclosed, continuous equipment by the catalyzed air oxidation of butyraldehyde. It is purified by distillation and stored and transported in tanks, tank cars and trucks. The Chemical and Economic Handbook (CEH, 1999) reported that in the United States about 11.3-12.3 thousand metric tons of n-butyraldehyde is consumed annually in the manufacture of n-butyric acid. It is also co-produced (about 4.5 thousand metric tons) along with acetic acid from the liquid phase oxidation of n-butane to acetic acid (SRI, 1999). Global production was estimated to be no more than 37 thousand metric tons with approximately 17 thousand metric tons produced in the US and 20 thousand metric tons coming from Western Europe (CEH, 1997). Smaller amounts of n-butyric acid are produced in Japan and elsewhere. According to the Environmental Protection Agency's 1998 Inventory Update Rule report, two U.S. companies imported or manufactured between 45 thousand to 227 thousand metric tons of n-butyric acid in 1998.

Total production of n-butyric anhydride in the United States is by a single manufacturer and is estimated in the range of 34 - 68 thousand metric tons. n-Butyric anhydride is manufactured in enclosed continuous process equipment by the dehydration of n-butyric acid. The product is purified by distillation and stored in tanks**.** It is transferred externally via trucks and drums for use on site and external sale. Public information on possible manufacturers of n-butyric anhydride outside of the United States has not been identified and is not readily available.

Uses

Most n-butyric acid is consumed in the manufacture of cellulose acetate butyrate or CAB (CEH, 1999). CAB sheet is used for thermoformed sign faces, blister packaging, and goggles and face shields, while molded CAB is used to make pen barrels, eyeglass frames and screwdriver handles. CAB is a component in acrylic enamel for automotive original equipment manufacturing coatings (CEH, 1999). In Western Europe n-butyric acid is used to make butyroperoxides and herbicides (CEH, 1999). n-Butyric acid is also used as an intermediate for pharmaceuticals, emulsifiers and disinfectants, and a leather tanning agent and a sweetening agent in gasolines (SRI, 1999). It is used in the synthesis of butyrate ester perfume (Hawley, 1981), in the manufacture of esters (Reimenschneider, 1986), some of which serve as the bases of artificial flavoring ingredients of certain liquors, soda-water syrups, candies (Budavari, 1989). Another use is as a food additive in butter, cheese, butterscotch, caramel, fruit and nut flavors (Furia, 1972). n-Butyric acid is used in the preservation of high moisture wheat grains against fungal deterioration in India (Ghosh, 1985).

The major use of n-butyric anhydride is as an industrial intermediate in the manufacture of cellulose esters, such as cellulose acetate butyrate (CAB). About 24 – 48 thousand metric tons (>70% of total production) are used annually for this purpose. More minor uses reported are in the production of drugs and tanning agents (Patty, 1963), as a chemical intermediate for perfumes (e.g., geranyl butyrate) (SRI, 1999) and for the manufacture of sodium tyropanoate (oral cholecystographic) (SRI, 1999).

2.1 Environmental Exposure and Fate

n-Butyric anhydride rapidly hydrolyzes (half-lives in minutes) in water at ambient pH values. The formation by-product of n-butyric anhydride is n-butyric acid. Thus, physical properties and environmental fate data are presented for n-butyric acid.

An estimated Henry's constant of $5.35x10^{-7}$ atm-m^3 /mole has been reported for n-butyric acid. In addition, a Henry's law constant of $3.4 x10^{-6}$ atm-m^3/mole has been calculated for n-butyric acid from its physical properties (EPIWIN, 2000). This Henry's law constant was calculated using a vapor pressure of 2.2 hPa (1.65 mm Hg) @ 25 ºC, an aqueous solubility of 56,200 mg/L, and its molecular weight of 88.11 g/mol. In general, chemicals with a Henry's law constant greater than $1.0x10^{-5}$ atm-m^3/mole are considered volatile chemicals (Lyman, et al., 1982). By this measure, n-butyric acid is not considered to be a volatile chemical. n-Butyric acid is not expected to accumulate in organisms or adsorb onto soil or sediment, given its low BCFs (2.3 – 3.16 L/kg wet weight) calculated from a log K_{ow} of 0.79 and measured soil partition coefficients (14.7 to 27.6 L/kg dry weight).

2.1.1 Photodegradation

n-Butyric anhydride and n-butyric acid are readily removed via atmospheric photo-oxidation processes. Using the EPA-developed model AOPWIN (v 1.90), secondary rate constants for hydroxyl radical mediated atmospheric photo-oxidation were calculated to be 3.35 to 3.45 x 10^{-12} cm^3/molecule-sec for the anhydride and 2.4 to 2.7 x 10^{-12} cm^3/molecule-sec for the acid. Using the standard assumptions of 1.5 x 10^6 hydroxyl radicals per cubic centimeter, and 12 hr/day of daylight, pseudo first-order half-lives of 3.1 to 3.2 days and 3.96 to 4.46 days were calculated for the anhydride and acid, respectively. Upon contact with water vapor in the atmosphere, n-butyric anhydride would rapidly convert to the acid. The acid would then ionize to the dissociated form due to its pKa of 4.66-4.82.

2.1.2 Stability in Water

n-Butyric anhydride rapidly hydrolyses in water at ambient pH values. Hydrolysis half-lives at 22 °C were measured in buffered aquatic culture water and buffered distilled deionized water (Isaacs and Hoffman, 2002). At pH values of 4, 7, and 9 in both distilled deionized water and buffered aquatic culture water, half-lives of 17, 7, and 2 minutes, respectively were reported. n-Butyric acid is not expected to hydrolyze due to a lack of hydrolysable groups. Due to its pKa of 4.66-4.82, n-butyric acid is expected to undergo considerable ionization at ambient pH values (i.e., pH 5-9).

2.1.3 Stability in Soil

No hydrolysis data specific for soils are available for n-butyric anhydride. Since n-butyric anhydride hydrolyzes so rapidly to n-butyric acid when released into water, it would be expected to hydrolyze rapidly in moist soil.

n-Butyric acid is not expected adsorb onto soil or sediment, given its measured soil partition coefficients (14.7 to 27.6 L/kg dry weight).

2.1.4 Volatilization

n-Butyric anhydride has a low vapor pressure (0.377 hPa @ 25 ºC) and therefore has a limited volatilization potential. n-Butyric acid has a calculated Henry's law constant of 3.4×10^{-6} atm-m^3 /mole with a reported measured value of 5.35×10^{-7} atm-m^3 /mole. In general, chemicals with a Henry's law constant greater than 1.0×10^{-5} atm-m^3 /mole are considered volatile chemicals (Lyman, et al., 1982). By this measure, n-butyric acid is not considered to be a volatile chemical.

2.1.5 Transport and Distribution

Level I distribution modeling of n-butyric anhydride suggests that nearly all would remain in water (97.7%), with 0.118% in air, 2.12% in soil and <0.1% in sediment (Trent University, 2003). Level I distribution modeling calculates the instantaneous distribution of any amount of a chemical in a closed modeled environment. The n-butyric anhydride within the water compartment would hydrolyze to n-butyric acid. Level III distribution modeling of n-butyric acid showed that most of the n-butyric acid released to the environment would partition primarily into the water and soil (37.2% and 57.0%, respectively), with most of the remaining into the air (5.67%) and little (<0.1%) in sediment. Level III modeling assumed equal amounts of n-butyric acid were released to air, water, and soil (EPIWIN, 2000).

2.1.6 Biodegradation

Biodegradation is an important removal process for n-butyric acid. The biodegradation of n-butyric acid was determined by measuring consumption of biochemical oxygen demand (BOD) using a respirometer method (modified MITI, 301C). n-Butyric acid biodegraded by 72% in 5.8 days, following a 5-day lag period. n-Butyric acid is considered readily biodegradable. n-Butyric anhydride is expected to hydrolyze to n-butyric acid in the environment.

2.1.7 Bioaccumulation

n-Butyric acid is not expected to accumulate in organisms given its low calculated BCFs that were calculated from a log K_{ow} of 0.79 (2.3 to 3.1 L/kg wet weight) (EPIWIN, 2000).

2.2 Exposure to Humans

The probable routes of exposure to n-butyric acid are by inhalation or dermal contact during its manufacture or use. General population exposure may occur by inhalation or dermal contact if commercial products containing this compound are used in the home. Ingestion is a probable route of exposure as a result of its presence in foods (Coleman, 1981; Harper, 1986).

Potential occupational exposure to n-butyric anhydride would probably be via inhalation and dermal absorption (Eastman Chemical Company unpublished data - 2001).

2.2.1 Workplace Exposure

Workplace exposure is limited by the enclosed nature of its production processes. There are two manufacturers of n-butyric acid in the United States and three in Western Europe. Much of the n-butyric acid made by these producers is consumed on site as an industrial intermediate to manufacture other chemicals, again using enclosed processes and equipment.

n-Butyric anhydride is produced in the U.S. by a single manufacturer. About 100 workers are estimated to be associated with manufacture and use at this site, and thereby potentially exposed. Exposure to n-butyric anhydride in the workplace is also limited by the enclosed nature of the manufacturing process and the use of engineering controls and personal protective equipment. Vapor collection systems ensure minimum exposure during product sampling and loading. Personal protective equipment (goggles, rubber gloves) are required whenever taking or handling samples. Respirators are provided and required in the event of accidental discharges and exposure to significant concentrations during abnormal or emergency situations. For the same reasons, exposure is limited in its use as an industrial intermediate to manufacture other substances, such as cellulose acetate butyrate. n-Butyric anhydride is corrosive and irritating to the eyes, skin, and lung. These properties reinforce workplace hygiene practices used to limit exposure. Detailed information regarding personal protective equipment used in customer plants where n-butyric anhydride is converted to other products is not readily available. However, based on the strongly irritative and corrosive nature of n-butyric anhydride, and based on the warnings and handling precautions given on container labels and the material safety data sheet, it is likely that vapor concentrations are controlled to a very low level outside of the equipment, and that personal protective equipment similar to that used at the manufacturing site is employed at use sites when exposure may occur.

2.2.2 Commercial Product Exposure

The major consumer use of n-butyric acid is as an approved additive in various foods, in compliance with the U.S. Federal Food, Drug, and Cosmetic Act (21 CFR §582.60). Since n-butyric anhydride is used solely as a reactive industrial intermediate, it is not used in consumer products. n-Butyric anhydride is reactive and hydrolyzes to n-butyric acid on contact with water or water vapor. Any small concentration of residual n-butyric anhydride remaining unconverted in producing other products, such as cellulose acetate butyrate, does not remain unchanged for an appreciable length of time. Further processing of cellulose acetate butyrate (CAB) at elevated temperatures in the presence of water and sulfuric acid before it is used to make final products such as plastic sheeting or other plastic articles, further assures that negligible residual n-butyric anhydride remains unreacted. Technical personnel in CAB manufacture and processing at Eastman Chemical Company believe that the presence of <0.03% n-butyric anhydride in CAB represents a conservative, worst case.

2.2.3 Environmental Exposure

n-Butyric acid is regulated in the United States as a hazardous substance under CERCLA, under which its reportable quantity (when there is an environmental release) is 2270 kg (40 CFR §302.4). n-Butyric acid is regulated under the Clean Air Act as a volatile organic chemical (VOC; 40 CFR

§60.489) and therefore actions are taken to minimize equipment leaks in the Synthetic Organic Chemical Manufacturing Industry (SOCMI). It is designated as a hazardous substance under section 311(b)(2)(A) of the Federal Water Pollution Control Act and further regulated by the Clean Water Act Amendments of 1977 and 1978 (40 CFR §116.4).

General population exposure to n-butyric acid in the environment is caused by both its artificial and natural presence. It may be released to the environment as a fugitive emission during its production and use, and in the exhaust of motor vehicles (SRC, 1999). n-Butyric acid has been quantitatively identified in the Ohio River, Little Miami River, and Tanner's Creek, where the concentration ranged from 0.1-0.3, 0.4-0.5, and 0.5 µg/l respectively (Murtauch, 1965). Concentrations in ground water ranging from 12.87 mg/l at 6 m depth and 0.17 mg/l at 18 m depth have been determined about 170 m from a closed wood preserving facility in Pensacola FL (Goerlitz, 1985). n-Butyric acid was detected in the sediment of Loch Eil, Scotland, at a concentration ranging from trace to 160 µg/g dry weight (Miller, 1979), and detected at a concentration of 0.273 mg/g in the sediment of Lake Biwa, Japan in 1981 (Maeda, 1986). The concentration of n-butyric acid in Los Angeles, CA air in July and September 1984 ranged from 0.014-0.083 ppb (8 samples) (Kawamura, 1985).

n-Butyric acid is found naturally in vegetable oils and in animal fluids, such as sweat, tissue fluids and milk fat. It is an important metabolite in the breakdown of carbohydrates, fats and proteins (Reimenschneider, 1986). It may arise from natural fermentive processes occurring in sediment (Miller, 1979). n-Butyric acid is present in butter as an ester to the extent of 4-5% (Budavari, 1989). It has been found in essential oils of citronella Ceylon, eucalyptus globules, nutmeg, hops, Spanish anise and strawberry aroma. (Fenaroli, 1975.)

n-Butyric anhydride may be released to the environment as a result of its manufacture and use. Actual environmental release is expected to be limited, based on a single manufacturer in the United States, and the use of enclosed processes for manufacture and conversion to other chemicals. Because of its reactive nature and rapid hydrolysis in aqueous media, it is highly unlikely that n-butyric anhydride will remain unchanged for significant periods in the environment, and result in general population exposure.

3.0 HUMAN HEALTH HAZARDS

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. See Appendix 2.

In addition, increased blood levels of n-butyric acid have been demonstrated following administration of the metabolic precursors of n-butyric acid (n-butyl acetate 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 system exposure to n-butyric acid.

Therefore, data from n-butyl acetate (CAS# 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 n-butyl acetate and n-butanol data sets were accepted at SIAM 13.

Metabolic Series Approach for Specific Health Effects Endpoints for n-Butyric Acid

The results of selected studies with n-butyl acetate and n-butanol have been used to identify the hazards associated with exposure to n-butyric acid for certain, specific health effects endpoints. This use of n-butyl acetate and n-butanol, which are metabolic precursors of n-butyric acid, has now become known, in general, as the "metabolic series approach." This relatively new approach to hazard evaluation (Barton, 2000) is intended to facilitate the maximal use of toxicity data.

n-Butyl acetate is the ester of n-butanol and acetic acid. n-Butyl acetate and n-butanol are part of a metabolic series that includes n-butyl acetate and its primary metabolites, n-butanol, butyraldehyde, and n-butyric acid. n-Butyl acetate is the parent, or immediate precursor, of n-butanol. In an *in vivo* toxicokinetics study in rats using radiolabeled n-butyl acetate administered intravenously, hydrolysis of n-butyl acetate to n-butanol in blood and brain was 99 percent complete within 2.7 minutes (Deisinger and English, 2001). n-Butanol is rapidly metabolized to n-butyric acid (via butyraldehyde). n-Butyric acid (also a natural component of blood) was found in increased levels 30 seconds following intravenous administration of either n-butyl acetate or n-butanol. Furthermore, following intravenous dose administration, n-butyric acid is the major blood metabolite of both of these materials (within 2.5 minutes.). Because n-butyl acetate and n-butanol are rapidly metabolized to form n-butyric acid, organisms exposed to n-butyl acetate or n-butanol can experience appreciable tissue concentrations of n-butyric acid. In this way, information from toxicity studies for n-butyl acetate and n-butanol inherently provides information on the toxicity of n-butyric acid. In this same study, intravenous injection of n-butyric acid was examined and the T½ for clearance of n-butyric acid was less than 60 seconds.

The potential increased blood levels of n-butyric acid found following n-butyl acetate and n-butanol exposure may in fact be greater than what would be attainable following direct exposure to n-butyric acid because the corrosive properties of the acid would preclude administration of appreciable amounts. Direct administration onto the skin or into the stomach would result in corrosion of the epithelial surfaces. Therefore, the increased systemic blood concentrations found following n-n-butyl acetate or n-butanol administration represents the best way to evaluate the toxicity hazard associated with systemic exposure to n-butyric acid.

The use of n-butyl acetate and n-butanol results to identify hazards associated with exposure to n-butyric acid does have some limitations, however. It should be noted that the metabolic series approach is only appropriate for endpoints directly related to the systemic blood levels of the series members (i.e. the parent compound and its metabolites). It is not relevant for all routes of exposure, for site-of-contact effects, or for endpoints dependent upon the physical-chemical properties of the material. Thus, it would be inappropriate to use surrogate n-butyl acetate or n-butanol data for n-butyric acid skin irritation, eye irritation, skin sensitization, certain *in vitro* mutagenicity studies, dermal studies of any type, aquatic studies, or any other environmental studies. These types of surrogate data are inappropriate because studies have not yet been conducted to confirm the rapid metabolism of n-butyl acetate and n-butanol to n-butyric acid under specialized exposure conditions

such as skin contact, eye contact, *in vitro* genetic toxicity, in fish, or in other non-mammalian species. The endpoints addressed with the use of data on n-butyl acetate and n-butanol include Repeated Dose Toxicity, Reproductive/Developmental Toxicity, *in vivo* Genetic Toxicity, Neurotoxicity, and Toxicokinetics and Metabolism.

The toxicology of n-butyric acid was reviewed at SIAM 13. Only those data that are considered most relevant to the assessment of potential human health hazards are summarized here. The *in vivo* metabolism studies with n-butyl acetate and n-butanol (Deisinger and English, 2001) are summarized below under Section 3.1 Pharmacokinetics and Metabolism. Surrogate data from n-butyl acetate and n-butanol studies relevant to the hazard assessment of n-butyric acid are summarized and/or referenced under their appropriate endpoint headings.

Comments on the Spontaneous Hydrolysis of n-Butyric Anhydride to n-Butyric Acid

n-Butyric anhydride is reactive upon contact with water (Isaacs and Hoffman, 2002) and is expected to hydrolyze under normal conditions of exposure. Inhaled n-butyric anhydride would be expected to hydrolyze in the humidified air, mucous, and surfactant layers within the respiratory tract. Ingested n-butyric anhydride would also be expected to hydrolyze in the aqueous environment within the digestive tract. Therefore, oral or inhalation exposure to n-butyric anhydride would be expected to result in the formation of n-butyric acid available for systemic absorption.

Hydrolysis following dermal exposure would be dependent upon the presence of moisture (e.g. sweat) at the site of contact. There are no dermal LD_{50} values available for n-butyric anhydride. Anhydrides applied to skin in a moist atmosphere would be expected to hydrolyze to the corresponding acids. The presence of sweat on the skin would provide adequate moisture for the hydrolysis to occur and would be a worst-case scenario. Studies with anhydrides on dry skin under conditions presumed to minimize the hydrolysis reaction (occluded patch testing) would provide a best-case scenario. In order to be conservative, hydrolysis is presumed to occur and therefore, the acute dermal toxicity value for n-butyric acid is used as the appropriate value for n-butyric anhydride. Skin and eye irritation data from review papers indicate that n-butyric anhydride is a skin and eye irritant and is classified by the Department of Transportation (US DOT) as corrosive. This data and conclusion is supported by the data from the hydrolysis product (n-butyric acid) which is also a strong skin and eye irritant.

Since n-butyric acid is formed following exposure to n-butyric anhydride, the data set used to evaluate hazards associated with the systemic toxicity of n-butyric acid are also used to identify the hazards associated with n-butyric anhydride.

3.1 Pharmacokinetics and Metabolism

In order to confirm the rapid metabolism of n-butyl acetate and n-butanol, an *in vivo* toxicokinetics study was conducted in rats with intravenously administered n-butyl acetate and n-butanol (Deisinger and English, 2001). n-Butyl acetate and n-butanol were administered via indwelling femoral vein catheter to 5 male rats at a mean dose of 0.28 mmol/kg body weight. Gas chromatography with mass spectroscopy selected ion-monitoring analysis (with internal standard) of whole blood following this dose revealed rapid systemic distribution of the materials and rapid

metabolism and elimination from whole blood. n-Butyric acid was detected at the initial 30 second time point with peak n-butyric acid concentrations found at approximately 1 minute following n-butyl acetate injection and at approximately 1.5 minutes following the n-butanol injection. The n-butyric acid levels were 36-fold higher than background following n-butanol administration and 69-fold higher than background following n-butyl acetate administration. The rapid metabolism of both n-butyl acetate and n-butanol to n-butyric acid indicates that these materials may be considered as surrogate for dosing with n-butyric acid in examining systemic effects. In addition, intravenous injection of n-butyric acid was examined in this same study and the T½ for clearance of n-butyric acid was less than 60 seconds, demonstrating the rapid metabolism and clearance of this material.

n-Butyric anhydride has a T½ of 7 and 2 minutes in a water solution buffered to 7 and 9, respectively (Isaacs and Hoffman, 2002). Therefore, the T½ at physiological pH (7.4) would be expected to be somewhere between 2 and 7 minutes. Experiments conducted in rat serum (diluted 25% with physiological saline) demonstrated a T½ of 0.31 minutes (Eastman Kodak, 2002). Therefore, n-butyric anhydride would be expected to hydrolyze extremely quickly under the rare circumstance that n-butyric anhydride would reach the systemic circulation.

3.2 Acute Toxicity

n-Butyric Acid

The acute toxicity data for n-butyric acid are summarized in Table 3. These data suggest that n-butyric acid is only slightly toxic to experimental animals via the oral and inhalation routes of exposure but is moderately toxic via the dermal exposure route.

Table 3 Acute Toxicity of n-Butyric Acid in Experimental Animals

Species	Sex	Route	Type	Value	References
Rat	NS	Oral	LD_{50}	2940 mg/kg	Smyth, et al., 1951
Rat	female	Oral*	LD_{50}	8790 mg/kg	Smyth et al., 1954
Rabbit	NS	Oral	LD_{lo}	3600 mg/kg	IITI, 1982
Rabbit	male	Dermal*	LD_{50}	6077 mg/kg	Smyth et al., 1954
Rat	NS	Inhalation*	LC_0 (8 hrs)	Saturated vapor (no deaths)	Smyth, et al., 1951
Rabbit	NS	Inhalation	LC_0 (90 min.)	>40000 mg/m^3; noted clinical signs included lethargy and dyspnea; bronchial and capillary dilation and emphysema.evident at necropsy	Danishevskii and. Monastyrskaya. 1960 *cited in:* Patty's Indust. Hyg. & Toxicol., 1981

* = Key Study, NS = Not Specified, LD = Lethal Dose, LC = Lethal Concentration

n-Butyric Anhydride

The acute toxicity data for n-butyric anhydride are summarized in Table 4. These data suggest that n-butyric anhydride is only slightly toxic to experimental animals via the oral and inhalation routes of exposure but is moderately toxic via the dermal exposure route.

Table 4 Acute Toxicity of n-Butyric anhydride in Experimental Animals

Species	Sex	Route	Type	Value	References
Rat	female	Oral*#	LD_{50}	8790 mg/kg	Smyth et al., 1954
Mouse	NS	Oral	LD_{lo}	1000 mg/kg; noted clinical signs included general depressed activity and changes to the liver, kidney, ureter and bladder.	Tox. New Ind. Chem. Subs. 1962
Rabbit	NS	Dermal*[#]	LD_{50}	6077 mg/kg	Smyth et al., 1954
Rat	NS	Inhalation*	LC_{lo}	50 mg/m^3	Tox. New Ind. Chem. Subs. 1962
Mouse	NS	Inhalation	LC_{lo}	50 mg/m^3	Tox. New Ind. Chem. Subs. 1962

* = Key Study, NS = Not Specified, LD = Lethal Dose, LC = Lethal Concentration [#] = Data for n-butyric acid

The n-butyric acid oral LD_{50} value of 8790 mg/kg bw in rats and the dermal LD_{50} values of 8790 and6077 mg/kg for rabbits, are used since n-butyric anhydride is expected to hydrolyze to form n-butyric acid upon contact with water when ingested or upon contact with skin (e.g. sweat). Therefore, the dermal LD_{50} value for n-butyric acid identifies a "worst-case" scenario and is a conservative value. n-Butyric anhydride inhaled into the lung would be expected to undergo an exothermic hydrolysis reaction with the humidified air, mucous, and surfactant layers within the respiratory tract.

Corrosivity/Irritation/Sensitization

Data from studies using experimental animals (Smyth et al., 1954; Patty's, 1981 and Grant, 1974) indicate that n-butyric acid is a moderately strong irritant to skin, whereas it is severely irritating to eyes. No relevant data were found for the skin sensitization endpoint for butyric acid.

Skin and eye irritation data from review papers indicate that n-butyric anhydride is a skin and eye irritant and is classified by the Department of Transportation (US DOT) as corrosive. This data and conclusion is supported by the fact that the hydrolysis product (n-butyric acid) is also a strong skin and eye irritant. No relevant data were found for the skin sensitization endpoint for butyric anhydride.

Undiluted butyric acid can produce severe skin and eye irritation. Butyric anhydride is considered a corrosive material. Accordingly, both butyric acid and butyric anhydride should be considered respiratory irritants. Symptoms of respiratory irritation may be delayed upon inhalation of butyric anhydride, and inhalation of vapor or aerosol may cause pulmonary edema.

3.3 Repeated-Dose Toxicity

Two definitive *n-butyl acetate* studies were conducted that are considered to be key studies for this endpoint. Both were 13-week inhalation studies with Spraque-Dawley rats exposed to 500 (2376 mg/m^3), 1500 (7128 mg/m^3) and 3000 ppm (14256 mg/m^3) (David et al., 1998 and David et al., 2001). In David et al, 2001, rats exposed to the 1500 (7128 mg/m^3)and 3000 ppm (14256 mg/m^3) dose groups had decreased body weight and feed consumption, increased testes weights, increased adrenal weights and signs of localized necrosis of olfactory epithelium. Minimal, transient narcosis and sedation effects were also observed in rats exposed to 1500 (7128 mg/m^3) and 3000 ppm (14256 mg/m^3) n-butyl acetate during exposure only, but no cumulative effect on activity during the 13-week exposure was observed. In addition at only the highest dose of 3000 ppm (14256 mg/m^3), reduced spleen weights and increased lung weights were noted (David *et a*l., 2001).

In the earlier studies using *n*-butyl acetate (David et al, 1998), rats developed central nervous system effects (reduced activity) during exposure, with rapid recovery once the exposure is ended. Daily, repeated exposure did not exacerbate the effect. Reduced body weights, reduced body weight gains, and decreased feed consumption were noted in animals exposed to $\geq$1500 ppm (7128 mg/m^3). Detailed evaluation of central and peripheral nervous system function (motor activity, functional observational battery, scheduled-controlled operant behavior) in these same studies demonstrated a lack of cumulative neurotoxicity following repeated (90-days) exposures. Signs of degeneration of the olfactory epithelium following exposures of $\geq$1500 ppm (7128 mg/m^3) represent a common lesion in rats exposed to acetate esters of alcohols. The degeneration of the olfactory epithelium within the nose is a common lesion in rats exposed by inhalation to acetate esters of short-chain alcohols due to the liberation of acetic acid in these cells from the hydrolysis of the ester linkage. Since rats are obligate nose-breathers, the delivered dose to this portion of the nose is higher in rats than humans and the significance of this lesion in human health is questionable. Acute central nervous system depression during the inhalation exposure was noted at concentrations $\geq$ 750 ppm (3564 mg/m^3). The NOAEL for systemic toxicity from these studies was 500 ppm (2378 mg/m^3, based on reduced body weights) and a NOAEL of 3000 ppm (14256 mg/m^3; highest dose tested) was reported for post-exposure neurotoxicity.

One 13-week oral toxicity study in rats using dose levels of *n-butanol* up to 500 mg/kg bw/-day by gavage reported a NOAEL of 125 mg/kg/day and a LOAEL of 500 mg/kg bw/-day based on transient post-dose ataxia and hypo activity (Tox. Res. Lab., 1986). A seven-day dietary study with *n-butyric acid* (4% in the diet) resulted in changes to the non-glandular portion of the stomach indicative of severe irritation (Harrison, et al., 1991). The repeated-dose toxicity data are summarized in Table 5.

Table 5 Repeated-dose Toxicity

Test Substance	Species	Dose Levels	Route/ Duration	NOAEL/ LOAEL	Reference
n-butyl acetate	Rat (M/F)	0, 500, 1500 3000 ppm (0, 2376, 7128 and 14256 mg/m^3)	Inhalation/13 weeks	500 ppm /1500 ppm	David et al., 2001
n-butyl acetate	Rat (M/F)	0, 500, 1500, 3000 ppm (0, 2376, 7128 and 14256 mg/m^3)	Inhalation/13 weeks	500 ppm /1500 ppm (reduced body weight) 3000 ppm (neurotox)	David et al., 1998
n-butyric acid	Rat/Mice/ Hamsters (M/F)	0, 4% (mice – 5200 mg/kg bw-day rats – 2000 mg/kg bw-day; hamsters – 3320 mg/kg bw-day)*	Dietary/ 7 days	NA/ 4%	Harrison et al., 1991
n-butanol	Rat (M/F)	0, 30, 125, 500 mg/kg bw/day	Gavage/ 90 days	125 m/k/d 500 m/k/d	Tox. Res. Lab. 1986

*estimated dose per day based on 1986 USEPA conversion factors of 0.13 for mice, 0.05 for rats, and 0.083 for hamsters.

3.4 Genotoxicity

In Vitro

The dataset used to identify hazards for *n*-butyric acid were also used to identify mutagenicity hazards associated with n-butyric anhydride exposure. *n*-Butyric acid was not mutagenic in five tester strains of bacteria when tested up to 10 mg/plate, *(Salmonella typhimurium*) in the presence and absence of metabolic activation (Ishidate, et al., 1984; Fujita, et al., 1992). No mutagenic effects were observed in experiments with *n*-butyric acid on cultured Chinese hamster lung (CHL) cells at concentrations up to 1 mg/milliliter (Ishidate, et al., 1984).

In Vivo

The dataset used to identify hazards for n-butyric acid were also used to identify in vivo mutagenicity hazards associated with n-butyric anhydride exposure. The most robust test for genetic toxicity was the oral *in vivo* mouse micronucleus test conducted with *n-butanol* by the BASF Corporation (Engelhardt and Hoffman, 1998). *n*-Butanol was administered once orally to male and female NMRI mice at doses up to 2,000 mg/kg body weight. Positive and negative controls all produced appropriate responses. *n*-Butanol did not produce any chromosome-damaging

(clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (no spindle poison effect).

Table 8 Genotoxicity

Test Substance	Method	Species	Dose Levels	Results	Reference
In Vitro					
n-butyric acid	Ames Assay; with and w/out activation	Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 10 mg/plate	Negative	Ishidate, et al., 1984
n-butyric acid	Ames Assay; w/out activation (only)	Salmonella typhimurium TA97, TA102	Up to 10 mg/plate	Negative	Fujita, et al., 1992
n-butyric acid	Cytogenetics Assay; w/out activation (only)	Hamster (cultured CHL cells)	Up to 1 mg/ml	Negative	Ishidate, et al., 1984
In Vivo					
n-butanol	Mouse Micronucleus Assay	Mice; NMRI (M,F)	Oral; single dose up to 2000 mg/kg	Negative	Engelhardt &Hoffman 1998

3.5 Carcinogenicity

No reliable data are available.

3.6 Reproductive Toxicity

In a study reported by Nelson *et a*l. (1989a), male rats (18/group) were exposed to *n-butanol* via inhalation at 3000 (9096 mg/m^3) or 6000 ppm (18192 mg/m^3) levels for 6 weeks prior to mating with unexposed females. These females remained unexposed throughout gestation. Exposure of the male rats to n-butanol prior to breeding had no effect on any of the reproductive parameters. In a separate experiment reported in the same literature article, pregnant females (15/group) were exposed throughout gestation to either 3000 (9096 mg/m^3) or 6000 ppm (18192 mg/m^3) *n-butanol* without any effect on pregnancy rate. Supporting developmental toxicity data with *n-butyl acetate* showed no changes in reproductive performance in female rats exposed to 1500 ppm (7128 mg/m^3, only dose tested) for three weeks prior to mating with unexposed males and continuing throughout gestation. (Hackett et al.,1982).

In David et al., 2001, male rats were exposed via inhalation to 0, 500, 1500, or 3000 ppm (0, 2376, 7128 and 14256 mg/m^3) of *n-butyl acetate* (6 hrs/day) for at least 65 exposures over 14 weeks. An increase in relative testes weights was seen in the 1500 and 3000 ppm (7128 and 14256 mg/m^3) that represented a "tissue sparing" effect due to the reduced body weight gain in these groups. Further

investigation of epididymal and testicular sperm counts and testes histopathology did not indicate testicular toxicity. Therefore, in this study, the NOAEL following repeated inhalation exposure was 3000 ppm (14256 mg/m^3, highest dose tested).

Table 6 Reproductive Toxicity

Test Substance	Species	Dose Levels	Route/ Duration	NOAEL	Reference
n-butanol	Rat (M) (mated to unexposed females)	0, 3000, 6000 ppm (0, 9096, 18,192 mg/m^3)	Inhalation/ 6 weeks prior to mating	6000 ppm (male reproductive function)	Nelson et al., 1989
n-butanol	Rat (F) (exposed only during gestation)	0, 3000, 6000 ppm (0, 9096, 18,192 mg/m^3)	Inhalation/ 3 weeks	6000 ppm (female reproductive function)	Nelson, et al., 1989
n-butyl acetate	Rat (F) (exposed for 3 weeks premating and throughout gestation)	0, 1500 ppm (0, 7128 mg/m^3)	Inhalation/ 6-7 weeks	1500 ppm (female reproductive function)	Hackett, et al., 1982
n-butyl acetate	Rat (M/F)	0, 500, 1500, 3000 ppm (0, 2376, 7128 and 14256 mg/m^3)	Inhalation/ 13 weeks	3000 ppm (sperm counts, histopathology)	David, et al., 2001

3.7 Developmental Toxicity

The most robust studies available for developmental effects were conducted by Nelson *et al*., (1989a, 1989b) using n-butanol.

In a definitive developmental study (Nelson et al., 1989a), groups of 15 pregnant female Sprague-Dawley rats were exposed via inhalation to 0, 3500, 6000 or 8000 ppm (0, 10612, 18192, 24256 mg/m^3) *n-butanol* for 7 hours/day during gestation (days 1-19.) In the treated groups, the only effect noted consisted of a very slight decrease in fetal body weights at the 6000 (18192 mg/m^3) and 8000 ppm (24256 mg/m^3) doses. Maternal effects included decreased feed consumption, narcosis and mortality in the 8000 ppm (24256 mg/m^3) group. In addition, decreased feed consumption was observed in the 6000 ppm (18192 mg/m^3) group. The NOAEL for both maternal and fetal effects was 3500 ppm (10612 mg/m^3). In a developmental neurotoxicity study with *n-butanol* (Nelson et al, 1989b), male and female rats were exposed via inhalation to 0, 3000 and 6000 ppm (0, 10612 and 18192 mg/m^3). Males were exposed for six weeks prior to mating with unexposed females and females were exposed only during gestation (days 1-20) for three weeks. The NOAEL for developmental neurotoxicity was determined to be 6000 ppm (18192 mg/m^3, highest dose tested) for both male and female rats.

Supporting data are available from studies conducted with *n-butyl acetate*. In Hackett et al. (1982), decreases in maternal body weight and food consumption, and reductions in fetal size were observed when Sprague-Dawley rats were exposed prior to mating and during gestation to a single high concentration of 1500 ppm (7128 mg/m^3) *n-butyl acetate*. In New Zealand white rabbits exposed during gestation to the same single concentration of *n-butyl acetate* (1500 ppm or 7128 mg/m^3), no signs of maternal toxicity, changes in reproductive performance, or major malformations in the offspring were observed.

Table 7 Developmental Toxicity

Test Substance	Species	Dose Levels	Route/ Duration	NOAEL	Reference
n-butanol	Rat (M) (mated to unexposed females)	0, 3000, 6000 ppm (0, 9096, 18,192mg/ m^3)	Inhalation/ 6 weeks prior to mating	6000 ppm (developmental neurotoxicity)	Nelson et al., 1989a
n-butanol	Rat (F)	0, 3000, 6000 ppm (0, 9096, 18192 mg/m^3)	Inhalation/ (exposed during gestation)	6000 ppm (developmental neurotoxicity)	Nelson, et al., 1989a
n-butanol	Rat (F)	0, 3500, 6000, 8000 ppm (0, 10612, 18192, 24256 mg/m^3)	Inhalation/ (exposed throughout gestation)	3500 ppm	Nelson, et al., 1989b
n-butyl acetate	Rat (F)	0, 1500 ppm (0, 7128 mg/m^3)	Inhalation/4 grps; control; exposed for 3 weeks premating and from day 1-16 of gestation; days 1-16 and day 7-16 of gestation	1500 ppm (only concentration tested)	Hackett, et al., 1982
n-butyl acetate	New Zealand White rabbit	0, 1500 ppm (0, 7128 mg/m^3)	Inhalation/ 3grps; control; days 7 –19 and days 1-19 of gestation.	1500 ppm (only concentration tested)	Hackett et al., 1982

4.0 HAZARD TO THE ENVIRONMENT

4.1 Analog Justification

No data are available for n-butyric anhydride, as n-butyric anhydride rapidly hydrolyzes in the presence of water to n-butyric acid. As a result, data from n-butyric acid are used to address the acute aquatic toxicity of n-butyric anhydride. When data for n-butyric acid did not meet current OECD requirements, data from analogous compounds were used. Based on similarities of chemical structure, carbon chain length, molecular weight, functionality, and chemical-physical properties, the collective use of test results forpropionic acid, pentanoic acid, and isobutyric acid should provide a suitable data set for estimating the aquatic toxicity of n-butyric acid. All four chemicals are low molecular weight alkyl-carboxylic acids with only one functional (acid) group. They are all water soluble over the concentration range studied. The compounds are essentially identical in their acidity having pKa values within the range of 4.82 to 4.87. Thus, when dissolved in water at identical molar concentrations, each acid will produce the same concentration of hydrogen (H^+) ions. Similarly, at any given pH, each of the four acids would be identically distributed between the acid form and its conjugate base.

Using an average pKa of 4.85 for all four acids, then at pH 4.85 there are equal amounts of the acid and conjugate base form. As pH increases, the relative amount of the test substance in the acid form decreases. By pH 7, more than 99% of each acid will be in the form of its conjugate base. These data apply to all four of the alkly acids: propionic, iso-butyric, pentanoic, and n-butyric.
A data matrix is located in Appendix 2.

4.2 Aquatic Effects

Valid acute aquatic toxicity data are available for n-butyric acid in fish, aquatic invertebrate, and green algae. The fish test used Medaka (*Oryzias latipes*; red killifish) in a static renewal exposure system (Onitsuka et al., 1989). The authors reported a 48-hour LC_{50} value of 90 mg/L for n-butyric acid in a buffered freshwater solution. The second study used the pelagic invertebrate *Daphnia magna* and was conducted using method DIN 38412 in buffered and unbuffered solutions (Bringmann and Kuhn, 1982). The 24-hour EC_{50} values of 1,950 mg/L (buffered, 95% CI 1318-2884) and 55 mg/L (un-buffered, 95% CI 45-67) for n-butyric acid were reported. An 8-day growth rate study using the green alga *Scenedesmus quadricauda* was conducted in a closed, static system (Bringmann and Kuhn, 1980), however, this study was deemed invalid because the exponential growth interval for a static system was exceeded.

Due to non-OECD guideline study duration and the lack of experimental details available in the acute ecotoxicity studies for n-butyric acid conducted in fish, aquatic invertebrate and algae, data from appropriate structural analog(s) are presented to assist in addressing the SIDS required endpoints. Supporting data are available and used as follows: fish, data from pentanoic and propionic acid; aquatic invertebrates, data from propionic and isobutyric acid; and algae, data from propionic acid. All representative data are presented in Table 9.

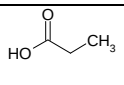
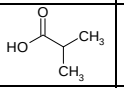
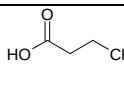
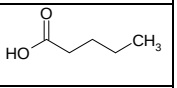
Table 9 Ecotoxicity data for n-butyric acid and analogs

Endpoint	**n-butyric acid**	**n-Propionic acid**	**Isobutyric acid**	**n-Pentanoic acid**
Fish	*Oryzias latipes* 48-h LC50 = 90 mg/L*	*Pimephales promelas* 96-h LC50 = 51.8 mg/L		*P. promelas* 96-h LC50 = 77 mg/L
Aquatic Invertebrate	*D. magna* 24-h EC50 = 1950 mg/L 24-h EC50 = 55 mg/L	*D. magna* 48-h EC50 = 22.7 mg/L	*D. magna* 48-h EC50 = 51.25 mg/L	---
Algae		*Scenedesmus subspicatus* 96-h EC50 = 42.9 mg/L	---	---

*Buffered solution

Thus the toxicity of n-butyric acid, in an unbuffered test system, to fish, invertebrates and green algae is expected to range between 22.7 and 77 mg/L based on analog data. The effect of pH was not specifically evaluated in any of these studies. One study with Daphnia magna was conducted in buffered and unbuffered solutions; the 24-hr LC50 in unbuffered solution was significantly lower than that observed in buffered solution (see Table 9). However, without additional experimental data using unbuffered test medium and buffered test medium in studies conducted in parallel, no assessment can be reliably made of the possible effects of pH on test organisms.

Table 10 Ecotoxicity data for n-butyric acid and analogs

Parameter	Propionic	Isobutanoic	Butanoic	Pentanoic
CAS	79-09-4	79-31-2	107-92-6	109-52-4
Molform	C3 H6 O2	C4 H8 O2	C4 H8 O2	C5 H10 O2
MW	74.08	88.11	88.11	102.13
Mol.structure				
MP (ºC)	20.7	-46	-7.9	-34
BP (ºC)	141.1	154.4	165.5	186.1
VP (Pa)	470.5	241.3	219.9	26.1
WSOL, mg/l)	1000000	167000	1000000	24000
pKa	4.87 @ 20ºC	4.84 @ 25ºC	4.82 @25ºC	4.84 @ 20ºC
log Kow	0.33	0.94	0.79	1.39
Experimental				
EC_{50} data:				
Fish (96h), mg/l	51.8		[(48h): 90*]	77
Daphnia (48h) ,mg/l	22.7	51.25	[(24h): 55]	
Algae (96h), mg/l	42.9			
EcoSAR_acute estimation, may be unreliable due to ionization				
Fish (96h), mg/l	11870	5688	4890	1962
Daphnia (48h), mg/l	11530	5688	4910	2040
Algae (96h), mg/l	6644	3357	2910	1243

*Test conducted in a buffered solution.
The conclusion in the SIAR that the acute aquatic toxicity is expected to range between 23 and 77 mg/l is supported (source: DK-EPA)

4.3 Terrestrial Effects

No data are available for this endpoint.

4.4 Toxicity to Microorganisms/Bacteria

One study is available in *Microcystis aeruginosa.* However, the data were considered unreliable for presentation in the SIAR.

5.0 CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

n-Butyric Anhydride

A single producer in the United States manufactures n-butyric anhydride. It is used solely as a reactive industrial intermediate for conversion to other chemicals, such as cellulose acetate butyrate. Enclosed processes and engineering controls are employed for manufacture and use, limiting workplace exposure. n-Butyric anhydride is not used in consumer products. Because of its reactivity in aqueous media, its presence in the environment, when released is short-lived. For this reason, general population exposure is not anticipated.

n-Butyric anhydride rapidly hydrolyzes in the presence of water to form n-butyric acid and data used to identify hazards for n-butyric acid were used to identify hazards for n-butyric anhydride exposure. n-Butyric anhydride was only slightly toxic to experimental animals following acute oral or inhalation exposure. Dermal toxicity hazards used n-butyric acid data since hydrolysis is expected in the presence of moisture (e.g. sweat). The same data used to identify subchronic toxicity; reproductive and developmental toxicity and mutagenicity hazards for n-butyric acid were used for n-butyric anhydride. Subchronic exposure to n-butyl acetate produced transient hypoactivity (during exposure only) at 1,500 and 3,000 ppm along with decreased body weight and food consumption, but no post exposure neurotoxicity even at 3,000 ppm. In several studies, exposure to n-butyl acetate and n-butanol did not result in reproductive toxicity. n-Butanol produced signs of developmental toxicity (slight decreases in fetal body weight and body size) at high concentrations. Several *in vitro* tests with n-butyric acid and an *in vivo* micronucleus test with n-butanol indicate that n-butyric acid (and hence n-butyric anhydride) is not genotoxic. n-Butyric acid is a moderately strong irritant to skin, but it is a severe eye irritant and n-butyric anhydride is expected to have similar properties. No data are available on skin or respiratory sensitization.

The available physicochemical data are adequate to describe the properties of n-butyric anhydride. n-Butyric anhydride is not environmentally persistent or likely to bioaccumulate. The aquatic toxicity data for n-butyric acid was used to identify hazards associated with release of n-butyric anhydride to this media as rapid hydrolysis of the anhydride to the acid occurs at environmentally relevant pH values. The aquatic toxicity of n-butyric acid (and hence, n-butyric anhydride) is low.

n-Butyric Acid

Workplace exposure to n-butyric acid during manufacture and use as an intermediate is limited by the use of closed processes, the use of protective clothing and by the compound's limited volatility. n-Butyric acid is not used in consumer products, but consumers ingest foods that contain naturally occurring n-butyric acid. In addition, n-butyric acid is a normal component of intermediary mammalian metabolism. n-Butyric acid does not persist or bioconcentrate in the environment, and is readily biodegradable in aqueous media, volatilizes from surface waters at a moderate rate, and readily undergoes photodegradation in the atmosphere. For these reasons, environmental exposure to n-butyric acid is limited.

n-Butyric acid was only slightly toxic to experimental animals following acute oral or inhalation exposure but was moderately toxic by the dermal route. Subchronic exposure to n-butyl acetate produced transient hypoactivity (during exposure only) at 1,500 and 3,000 ppm along with decreased body weight and food consumption, but no post exposure neurotoxicity even at 3,000 ppm. Several studies indicate that n-butyl acetate and n-butanol (exposures expected to produce appreciable systemic n-butyric acid levels) are not reproductive toxicants. n-Butanol produced signs of developmental toxicity (slight decreases in fetal body weight and body size) at high concentrations.Several *in vitro* tests with n-butyric acid and an *in vivo* micronucleus test with n-butanol indicate that n-butyric acid is not genotoxic. n-Butyric acid is a moderately strong irritant to skin, but it is a severe eye irritant.

The data collected were considered adequate for hazard identification for the purposes of the OECD SIDS program.. The available physicochemical data were also considered adequate to describe the properties of n-butyric acid. n-Butyric acid is not environmentally persistent or likely to bioaccumulate. Based on data from n-butyric acid and analogous compounds it can be concluded that the toxicity of n-butyric acid (in unbuffered test systems) to fish, invertebrates and green algae is expected to range between 22.7 and 77 mg/L.

5.2 Recommendations

The data collected were considered adequate for hazard identification for the purposes of the OECD SIDS program. n-Butyric Acid and n-Butyric Anhydride possess severe dermal and eye irritation properties. In addition, they are indicated to be a moderate hazard in the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low. Therefore, the chemicals are currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. n-Butyric anhydride and n-butyric acid are currently recommended for low priority for further work.

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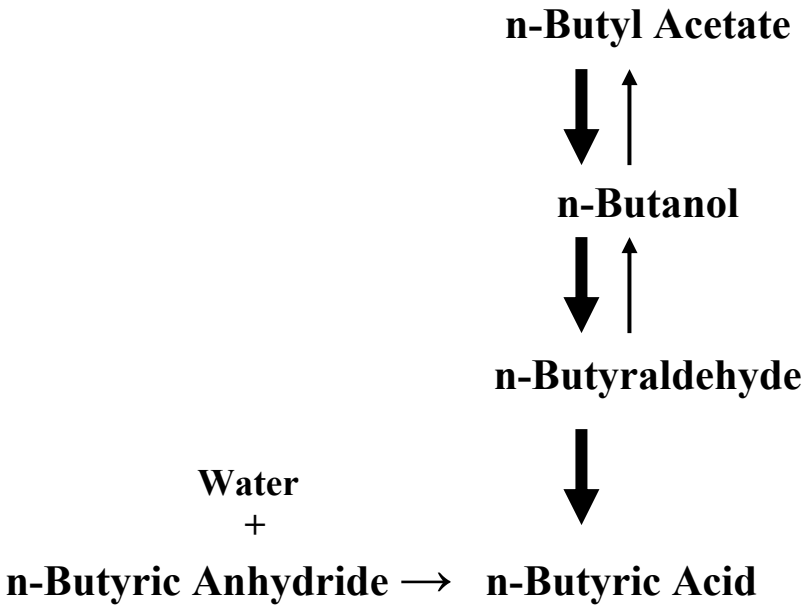
Appendix 1

METABOLIC SERIES APPROACH



OVERVIEW

The hydrolysis of the acetate ester to the primary alcohol is catalyzed by esterases and proteases found in mammalian tissues and gastric fluids. The metabolism of the primary alcohol to the aldehyde is primarily by alcohol dehydrogenase with some contribution from catalases and P450 isozymes; under certain physiological conditions this reaction is reversible. The metabolism of the aldehyde to the acid is by aldehyde dehydrogenase and is irreversible under physiological conditions. The anhydride spontaneously hydrolyzes in the presence of water to form the acid. The reaction is nonenzymatic and is thermodynamically favored.

APPENDIX 2

MAMMALIAN TOXICITY DATA MATRIX

	n-Butyl Acetate	n-Butanol	**n-Butryic Acid**	**n-Butyric Anhydride**
Acute Toxicity	N/R	N/R	AD	AD
Repeated Dose	AD	AD	Metabolic Series	Metabolic Series
Reproductive Toxicity	AD	AD	Metabolic Series	Metabolic Series
Developmental Toxicity	AD	AD	Metabolic Series	Metabolic Series
In vitro Genotoxicity	N/R	N/R	AD	Metabolic Series
In vivo Genotoxicity	N/R	AD	Metabolic Series	Metabolic Series

AD = Adequate data available to meet the endpoint
N/R = Not required; as sufficient data is available for the sponsored chemicals
Metabolic Series approach, see Appendix 1

ACUTE AQUATIC TOXICITY DATA MATRIX

	Propionic Acid	Isobutyric Acid	Pentanoic Acid	**n-Butyric acid**	**n-Butyric Anhydride**
Fish	AD	-----	AD	AN	N/R*
Aquatic Invertebrate	AD	AD	-----	AN	N/R*
Algae	AD	----	-----	AN	N/R*

AD = Adequate data available to meet the endpoint
AN = Analog data to be used
N/R* = Data to be considered sufficient based on rapid hydrolysis to n-butyric acid.
Metabolic Series approach, see Appendix 1