FOREWORD INTRODUCTION

n-Butyl Alcohol

CAS N°: 71-36-3

SIDS Initial Assessment Report

For

SIAM 13

Bern, Switzerland, 6 - 9November, 2001

1. Chemical Name: n-Butyl Alcohol

2. CAS Number: 71-36-3

3. Sponsor Country: United States of America

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5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium
- Process used

6. Sponsorship History The work and review process undertaken for this chemical was done by the American Chemistry Council's Oxo Process Panel and the United States Environmental Protection Agency. Members of the Oxo Process Panel conducted a comprehensive literature search. Documents were prepared and reviewed by industry prior to submission to sponsor country. Sponsor country conducted reviews of submitted data and offered comments to industry. Industry prepared and resubmitted documents for consideration at SIAM 13.

- How was the chemical or category brought into the OECD HPV Chemicals

Programme ?

7. Review Process Prior to the SIAM:

8. Quality check process:

9. Date of Submission: September 14, 2001

10. Date of last Update: June 2004

11. Comments: Testing: No testing (X)

Testing ( )

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71-36-3
Chemical Name	n-butyl alcohol
Structural Formula	CH_3-CH_2-CH_2-CH_2OH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Data from butyl acetate (BAc) toxicity studies have been included in the assessment of n-butanol (BA). Data from BAc is useful when assessing the hazards associated with the systemic toxicity of BA exposure due to the rapid and complete hydrolysis of BAc to BA *in vivo*. Exposure to BAc via dermal, inhalation, and water or dietary administration results in the rapid appearance of BA in the systemic circulation. Since exposure to either BAc or BA results in systemic exposure to BA, systemic toxicity data from studies that administer BAc are useful in identifying hazards associated with BA exposure. Endpoints of BAc toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from BA data due to the difference in physical-chemical properties of the two materials.

Human Health

n-Butyl alcohol (BA) was only slightly toxic to experimental animals following acute oral, dermal, or inhalation exposure. The acute oral LD_{50} values for female rats ranged from 790 to 4360 mg/kg. Different strains of rat were used in each of four studies, which may account for the variability. Oral LD_{50} values for mice, rabbits, hamsters, dogs, and male rats all fell within the same range. The rat inhalation LC_0 of 8000 ppm (24000 mg/m^3) indicates very low inhalation toxicity (no lethality at 8000 ppm). The rabbit dermal LD_{50} was 3402 mg/kg, indicating that BA can penetrate the skin, but not very readily. Animal experiments and human experience indicate that BA is, at most, moderately irritating to the skin, but it is a severe eye irritant. These effects are most likely due to BA's localized defatting and drying characteristics. Although no animal data are available, human studies and experience show that BA is not likely to be a skin sensitizer. A recent *in vivo* toxicokinetics study confirmed the rapid metabolism of n-butyl acetate (BAc) to BA. Hydrolysis of BAc in blood and brain was estimated to be 99 percent complete within 2.7 minutes (elimination $t_{½}$ = 0.41 minute). Thus, organisms exposed to BAc can experience appreciable tissue concentrations of BA. In this way, the results of toxicity studies with BAc can be used as supplemental, surrogate data to provide information on the toxicity of BA. A thirteen-week, subchronic exposure to BAc, the metabolic precursor of BA, produced transient hypoactivity (during exposure only) at 1500 and 3000 ppm (7185 and 14370 mg/m^3) along with decreased body weight and food consumption, but no post exposure neurotoxicity even at 3000 ppm. A concurrent subchronic neurotoxicity study under the same exposure conditions showed no evidence of cumulative neurotoxicity based upon functional observational battery endpoints, quantitative motor activity, neuropathology and scheduled-controlled operant behavior endpoints. A no observable effect level (NOAEL) of 500 ppm (2395 mg/m^3) was reported for systemic effects in rats, and a NOAEL of 3000 ppm (14370 mg/m^3) was reported for post exposure neurotoxicity in rats. Several studies indicate that BA is not a reproductive toxicant. Female rats exposed to 6000 ppm (18000 mg/m^3) BA throughout gestation and male rats exposed to 6000 ppm (18000 mg/m^3) BA for six weeks prior to mating showed no effects on fertility or pregnancy rate. Male rats given BA at 533 mg/kg/day for 5 days had no testicular toxicity. BA produced only mild fetotoxicity and developmental alterations at or near the maternally toxic (even lethal) dose of 8000 ppm (24000 mg/m^3) throughout gestation. An entire battery of negative *in vitro* tests and a negative *in vivo* micronucleus test indicate that BA is not genotoxic. The median odor threshold for BA (0.17 ppm) is well below the lowest nasal irritation threshold in humans (289 ppm), allowing warning of possible chemical exposure prior to nasal irritation occurring. Human studies are complicated by the odor characteristics of the material, as the odor threshold is well below the levels at which

irritation is observed.

Environment

BA's vapor pressure is 0.56 kPa at 20^0C, water solubility is 77 g/L at 20^0C and a Log K_{ow} is 0.88. Based on level III fugacity modeling, BA will partition 83.5% in air, 5.9% in soil, 10.6% in water, <0.1% in suspended solids, and <0.1% in biota and in sediment. BA degrades in air by reaction with hydroxyl radicals, having a half-life in air of 1.2 to 2.3 days. The volatilization half-life for BA in water is estimated to be 2.4 hours for streams, 3.9 hours for rivers and 126 days for lakes. BA exhibits low toxicity to fish, amphibians and aquatic invertebrates, plants, algae, bacteria and protozoans. However, some algal species are sensitive to BA. Acute toxicity to aquatic life may occur at concentrations greater than 500 mg/l. BA is classified as "readily biodegradable" under aerobic conditions. The octanol:water partitioning coefficient (log K_{ow}) for BA ranges from 0.88 to 0.97, and the calculated bioconcentration factor (BCF) is 3. These data indicate that BA has a low potential to bioaccumulate. BA is expected to migrate readily through soil to groundwater and not to sorb to soil particles.

Exposure

BA is used primarily as an industrial intermediate in the production of ethers and butyl ether acetates, pharmaceuticals, polymers and plastics. BA is used to a lesser extent as a solvent, reactant/diluent and component in consumer (nail polish formulations, rubber cement and safety glass) and industrial products. Production in the US is estimated at 784,000 tonnes, 575,000 tonnes in Western Europe and 225,000 tonnes in Japan. In regards to physical hazards of the chemical, it has a flammable range of 1.4 – 11.2 volume % in air (14,000 – 112,000 ppm) and a flash point of 98^0F (37^0C). In the US, due to the physical chemical properties of BA, workplace exposure during manufacture and use as industrial intermediate is limited by closed processing. For the same reasons, exposure is not anticipated during the formulation of butyl alcohol into various products as a solvent. Inhalation and dermal exposure can occur during industrial and commercial application of products containing butyl alcohol, such as lacquers and other coatings. Use in consumer products is limited, but is a possible source of exposure. Releases to the environment are primarily from solvent use. Butyl alcohol occurs naturally in foods.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 71-36-3
Chemical Name: n-Butyl Alcohol
Molecular Formula: CH_3-CH_2-CH_2-CH_2OH
Structural Formula: CH_3-CH_2-CH_2-CH_2OH
Molecular Weight: 74.12 g/mol
Synonyms: 1-butanol, butan-1-ol
n-butyl alcohol
butyl alcohol
butyl hydroxide
butyric alcohol
1-hydroxy butane
hydroxybutane
methylolpropane
NBA
normal primary butyl alcohol
BA
propylcarbinol
propyl methanol

1.2 Purity/Impurities/Additives

Purity 99.9%

Impurities 0.1% Isobutanol

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Physical Form of Marketed Product	Neat Liquid
Melting point	-89.9° C
Boiling point	117.6° C
Relative density	0.809 – 0.811 g/cm^3
Vapour pressure	0.56 kPa at 20° C
Water solubility	77 g/l at 20° C
Partition coefficient n-octanol/water (log value)	0.88
Odor Threshold	15 ppm (average)
Conversion Factor	1ppm = 3.03 mg/ m^3 at 25° C
Flashpoint	98° F (37° C)

n-Butyl alcohol (BA) is a liquid at standard temperature and pressure, with a boiling point of approximately 117.6º C and a melting point of approximately –89.9º C (Union Carbide Corporation, 1992a). It is less dense than water with a specific gravity of 0.8098 g/cm^3 at 20º C (Weast and Astle, 1985). The solubility limit in water is approximately 77 g/L at 20º C (Merck, 1983). This value indicates BA is very soluble in water.

The vapor density of BA is approximately 2.6-times that of air, with a vapor pressure of 0.56 kPa at 20º C (Union Carbide Corporation, 1992a). Given its solubility limits and its molecular weight of 74.14 g/mole, a Henry's law constant (at 25º C) can be calculated to be approximately 0.63 pascal-m^3 /mole (6.3x10 -6 atm-m^3 /mole). In general, chemicals with a Henry's law constant greater than 1.0x10 -5 atm-m^3 /mole, and a molecular weight less than 200 g/mole are considered volatile chemicals (US Environmental Protection Agency (USEPA), 1991). By this measure, BA is not considered to be a volatile chemical. BA does, however, meet the definition of a volatile organic compound (VOC), and does have appreciable volatility.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Manufacture

Butyl alcohol is manufactured by the catalyzed hydrogenation of butyraldehyde in enclosed systems, followed by distillation. About 784 thousand metric tons (1.7 billion pounds) of butyl alcohol was produced in the United States in 1997, estimated from the consumption of 1.725 billion pounds of butyraldehyde for this purpose (CEH Marketing Research Report Oxo Chemicals (1999) Chemical Economics Handbook-SRI International). Production in the United States in 2002 is projected to be 931 thousand metric tons (2.049 billion pounds). Based on butyraldehyde converted to butyl alcohol in Western Europe, 1997 production of butyl alcohol in this region was about 575 thousand metric tons (1.265 billion pounds), with 2002 production projected to be 610 thousand metric tons (1.342 billion pounds) (CEH-SRI). Similarly 1997 and 2002 production in Japan is estimated at 225 thousand metric tons (495 million pounds) in 1997 (CEH-SRI).

Use

Butyl alcohol is used predominately as an industrial intermediate. For example, it is used to make butyl acetate and other butyl esters; butyl ethers, such as ethylene glycol monobutyl ether, di- and triethylene glycol monobutyl ether, and the corresponding butyl ether acetates. It is used to manufacture dibutyl phthalate, pharmaceuticals, polymers, pyroxylin plastics, butyl xanthate and other butyl compounds. Butyl alcohol is used as a diluent/reactant in the manufacture of urea/formaldehyde and melamine/formaldehyde resins. When used as an industrial intermediate, butyl alcohol is consumed by chemical conversion to the desired product.

Butyl alcohol is used to a lesser extent as a solvent and in formulations to make, dyes, lacquers (including cellulose lacquers), resins and varnishes. It is a component in some nail polish formulations. It is used to make rubber cement, safety glass, rayon, waterproofed cloth, artificial leather, raincoats, motion picture and photographic film. It is used as a softener in the fabrication of cellulose nitrate plastics (Tabershaw et. al., 1944; Cogan and Grant, 1945; Sterner et al., 1949; Mellan, 1950; Doolittle, 1954). It is also used in the manufacture of pharmaceuticals, in microscopy (preparing paraffin imbedding materials), in veterinary medicine (as a bactericide), as a dehydrating agent, in perfumes, fruit essences, and as a flavoring agent in foods and beverages (Genium, 1993; Hall and Oser, 1965).

According to the CEH Marketing Research Report for Oxo Chemicals- SRI, consumption of butyl alcohol in the United States is as follows:

Uses	1997	2002
Acrylate/methacrylate Esters	595(a)	771(a)
Glycol Ethers	362	402
Butyl Acetate	220	245
Direct Solvent	125	128
Plasticizers	43	46
Other uses	69	74

Millions of pounds annually.

In the United States, butyl alcohol is approved by the Federal Food and Drug Administration (FDA) as an indirect food additive for use only as a component of adhesives (21 CFR 175.105). It is a food additive permitted by the FDA for direct addition to food for human consumption (21 CFR 172.515).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

BA is listed as a Toxic Release Inventory (TRI) chemical under EPCRA 313 in the United States. In the U.S., due to the physical chemical properties of BA, workplace exposure during manufacture and use as an industrial intermediate is limited by closed processing. For the same reasons, exposure is not anticipated during the formulation of butyl alcohol into various products as a solvent. BA is shipped in road and rail cars, and by ship. Any spillage during loading or handling would be recovered according to facility regulations. Some of the spillage may be directed to onsite wastewater treatment plants or may evaporate. Most environmental releases of n-butyl alcohol would occur through evaporation during its use as a solvent.

Release Data from the USEPA Toxics Release Inventory

Release data for the US from the most recent year available, 2001, was retrieved on May 1, 2004. The results are shown below. Combined releases directly to the environment, to air, water and soil (marked by asterisk), totaled 16, 905,396 pounds (7,684,271 kg). Of this amount, releases to air were 16,893,093 pounds (7,687,679 kg) or 99.75% of the total direct emissions to the environment were air. These numbers do not include emissions to air from consumer uses of products containing n-butanol as a solvent. Thus, for the purposes of distribution modeling, 100% of emissions were assumed to go to air.

*Total emissions to air:	16,893,093 pounds (7,678,679 kg)
*Surface water discharges:	40,175 pounds (18,261 kg)
Underground injection:	834,584 pounds (379,356 kg)
*Releases to land:	2,128 pounds (967 kg)
Total off site releases (e.g., to SPTs)	1,258,379 pounds (571,990 kg)

2.2.2 Photodegradation

BA vapors tend to degrade in air as a result of reactions with photochemically generated hydroxyl radicals.

Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 2000a). The estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson and co-workers that rely on structural features of the subject chemical. The model calculates a second-order half-life with units of cm^3/molecules-sec. Photo-degradation based on atmospheric photo-oxidation is based on the second order rate of reaction with hydroxyl radicals (HO⁄), ($k2_{phot}$ with units of cm^3/molecules-sec). Default AOPWIN assumptions for calculation of first-order half-lives include an HO⁄ concentration of 1.5 E^{+6} molecules/cm^3 and 12 hours of daylight per day. Pseudo-first order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2}$ = 0.693 / $k2_{phot}$ x HO⁄ x 12-hr / 24-hr.

ForBA , the $k2_{phot}$ value was calculated to be 6.89 E^{-12} cm^3/molecules-sec and the resulting half-life was $t_{1/2}$ = 1.552 days or 37 hours ((EPISUITE, 2001). EPISUITE (2001) also contains a measured value of 8.57 E^{-12} cm^3/molecule-sec, which gives a slightly faster half-life of 30 hours, using the same assumptions. This latter value was chosen by the model for Level III distribution modeling as discussed below.

2.2.3 Stability in Water

No Data Available.

2.2.4 Transport between Environmental Compartments

The vapor pressure of BA is 0.56 hPa at 20°C (0.42 mm Hg) and the water solubility is 77 g/L at 20°C. Using a molecular mass of 74.12 g/mol, a Henry's Law constant was calculated to be 5.32 x 10^{-7} atm-m^3/mole. For chemicals with a Henry's Law constant >1.0 x 10^{-3} atm/m^3/mole, volatilization from water is expected to be rapid. BA, therefore, would only be expected to volatize at a moderate rate.

The potential for BA to volatilize from model rivers and lakes was calculated by EPISUITE (v. 3.10) using preferred physical properties and default model assumptions. Volatilization half-lives from a model river and lake were 40 days and 43 days, respectively. Thus, volatilization from surface-water is not a very important removal process for BA.

The preferred log Kow value is 0.88 (Howard, 1990). This octanol/water partition coefficient suggests that BA would not be expected to move readily from water to soil, sediment, or biota. Similarly, BA in these media would tend to move to water or groundwater if available. Using EPISUITE (v. 3.10) and PCKOCWIN (v. 1.66), the soil or sediment Koc for BA waqs calculated to be 2.44 L/kg, based on the structural features of BA. These soil/sediment partitioning values indicate that BA moves fairly rapidly through soil to groundwater, with little sorption to soil expected.

Fugacity modeling (Level III) was conducted using EPISUITE (v. 3.10), which can be obtained from the U.S. EPA (2001). Results from the model were obtained using the preferred properties from the dossier, half-lives calculated by EPISUITE and the assumption that all releases were to air. All other parameters used were the model default values. Specifically, molecular weight was 74.12 g/mol, melting point was –89.9°C, boiling point was 117.6°C, vapor pressure was 0.42 mm Hg (0.56 hPa) at 25°C, log K_{ow} was 0.88, water solubility was 77,000 mg/L, and Henry's Law constant was 5.32 E-7 atm-m3/mol. The results support the above conclusions regarding the movement of

BA in the environment with 40% distributing to air, 15.7% to water, and 44% to the soil and less than 0.1% to the sediment.

2.2.5 Biodegradation

Several studies have been conducted to assess the biodegradation of BA in water and treated sewage. A test was conducted using American Public health Association (APHA) Standard Methods. The 20 day BOD (Biochemical Oxygen Demand) test was conducted using unacclimated settled domestic wastewater as the microbial seed (3 mL/BOD bottle). The results showed a BOD_5 of 68% ThOD (percent of theoretical oxygen demand), a BOD_{10} of 87% ThOD, a BOD_{15} of 92% ThOD, and a BOD_{20} of 92% ThOD. n-Butanol is considered readily biodegradable. This study is supported by several other studies that measured BOD using a variety of sources of microbial seed, including artificial seawater, and other sewage seeds.

Aerobic biodegradation in unadapted sludge was found to be 36% of ThOD after 24 hours (Gerhold and Malaney, 1966). Aerobic biodegradation in adapted sludge was measured to be 44 % of ThOD after 23 hours (McKinney and Jeris, 1955). Aerobic biodegradation in synthetic seawater was measured, resulting in the biochemical oxygen demand (BOD_5) at 45% of ThOD (Price *et al.,* 197*4).* Aerobic biodegradation in fresh water based on BOD_5 was reported to be 68% of ThOD (Price *et al.,* 197*4)* and 33% of ThOD (Dore *et al*., 1974). Aerobic biodegradation in fresh water-unadapted seed measured the BOD_{20} at 92% of ThOD (Union Carbide Corporation, 1992b). Aerobic biodegradation in adapted sludge was measured, resulting in a concentration affecting 10 percent of the population (EC_{10}) of 990 mg/L for a 30-minute test duration (BASF, 1991a). Loss of BA in soil due to biodegradation is expected to occur (Howard, 1990) but studies verifying and quantifying the phenomenon have not been identified. These soil/sediment partitioning values indicate that BA moves fairly readily through soil to groundwater (i.e., leach), with little sorption to soil expected.

2.3 Human Exposure

Human exposure to butyl alcohol may occur in the workplace during manufacture and industrial/commercial use, during consumer use of products containing BAand from presence of butyl alcohol in the environment. Inhalation and dermal absorption are the expected routes of exposure in the workplace and from the use of consumer products containingBA.

2.3.1 Occupational Exposure

Workplace exposure during manufacture or use of BA as an industrial intermediate is limited based on these processes being enclosed, and through engineering controls. For the same reasons, low exposure potential is associated with processes in which BA is used to produce formulated products (lacquers, varnishes, coatings). The American Conference of Governmental Industrial Hygienists (ACGIH) established in 2003 a Threshold Limit Value (TLV) of 20 ppm (60.6 mg/m^3) for BA**.** Other exposure guidelines that have been established include the following:

ACGIH TLV-TWA: 20 ppm.

OSHA PEL: 50 ppm (skin) ceiling (vacated)

OSHA PEL: 100 ppm TWA-8 (skin)

NIOSH REL: 50 ppm (skin) ceiling.

NIOSH IDLH: 1400 ppm.

DFG MAK: 100 ppm.

DFG MAK STEL: 200 ppm, 30 minutes, 4 times per shift.

AUSTRALIA: 50 ppm peak limitation (skin).

NETHERLANDS: 15 ppm, 15-minute STEL.

SWEDEN: 15 ppm, 15-minute STEL = 30 ppm (skin).

UNITED KINGDOM: 50 ppm (skin).

Most applications of formulated products containing BA also occur in the workplace. These include application of varnishes, lacquers, dyes and other commercial grade coatings that contain various concentrations of butyl alcohol, as well as solvent use in the manufacture of various products in the food, pharmaceutical, and agricultural industries. Since more open processing may occur in the application of varnishes, lacquers and other coatings, exposure potential is greater. Exposures are minimized in these cases by the use of spray booths, industrial exhaust systems, and the wearing of protective clothing. Since butyl alcohol is flammable at a concentration range of 1.4-11.2%, precautions are taken to limit open vapor concentrations in the workplace.

Percent use of open or closed systems for butyl alcohol manufacture or processing has been estimated as follows for the United States (CMA, 1999):

Industrial Closed System	81%
Industrial Open System	4%
Export	15%

2.3.2 Consumer Exposure

BA solvent use is predominately industrial, limited largely to commercial/industrial grade coatings and varnishes. Also, BA is not as widely used as a solvent as compared to butyl acetate (BAc) and other esters or alcohols, which have superior overall solvent performance. Use of butyl alcohol as a solvent in some consumer products has been reported. BA has been identified in 1096 products and 170 consumer products (mainly as a raw material or solvent). Consumer exposure may occur via ingestion, inhalation, or contact with the skin depending on the use. BA occurs naturally as a product of fermentation of carbohydrates in alcoholic beverages (Bonte, 1978, 1979; Schreier *et al.*, 1979; Woidich *et al.*, 1978; Bikfalvi and Pasztor, 1977; Postel and Adam, 1978) and has been detected in the volatiles of various foods such as cheese, heat-treated milk, muskmelon, and cooked rice (Jaddou *et al.*, 1978; Yabumoto *et al.*, 1978; Dumont and Adda, 1978; Yajima *et al.*, 1978). Deep-frying corn and cottonseed oil can produce BA (Chang *et al.*, 1978).

2.3.3 Indirect Exposure via the Environment

Environmental exposure to BA may result from inhalation of ambient air from industrial emissions or from waste sites. Environmental exposure is also possible via ingestion of surface, drinking or well water that may contain small concentrations of BA. Concentrations of BA ranging from 0.07 to 26 ppb, with a mean of 5 ppb, were detected when the air in mobile homes was tested for the presence of organic chemicals (Connor *et al.,* 1985).

3 HUMAN HEALTH HAZARDS

The results of selected studies with BAc have been used to supplement BA data for certain, specific health effects endpoints. This use of BAc data as a surrogate for BA data (or vice versa) has now become known, in general, as the "metabolic series approach." This relatively new approach to hazard evaluation (Barton et al., 2000) is intended to facilitate the maximal use of toxicity data.

BAc is the ester of BA and acetic acid. Due to this structural similarity, butyl acetate and butanol can be considered "surrogates" to some extent. However, they are really more than just surrogates. They are part of a metabolic series that includes BAc and its primary metabolites, BA, butyraldehyde, and butyric acid. BAc is the parent, or immediate precursor, of BA. In an *in vivo* toxicokinetics study in rats using radiolabeled BAc administered intravenously, hydrolysis of BAc in blood and brain was 99 percent complete within 2.7 minutes (Deisinger and English, 1997). Because BAc is so rapidly metabolized (hydrolyzed) to form BA, organisms exposed to BAc can experience appreciable tissue concentrations of BA. In this way, information from toxicity studies for BAc inherently provides information on the toxicity of BA (and vice versa). This is a credible approach primarily due to rapid metabolism, however, not because of analogous structures.

The use of BAc results to supplement BA data 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 any endpoints dependent upon the physical-chemical properties of the material. Thus, it would be inappropriate to use surrogate BAc data for skin irritation, eye irritation, skin sensitization, certain *in vitro* mutagenicity studies, dermal studies of any type, aquatic studies, or any other environmental studies. These type of surrogate data are inappropriate because studies have not yet been conducted to confirm the rapid hydrolysis of BAc to BA under specialized exposure conditions such as skin contact, eye contact, *in vitro*, dermally, in fish, or in other non-mammalian species. These endpoints addressed with the use of data on BAc include Repeated Dose Toxicity, Reproductive Toxicity, Neurotoxicity, and Toxicokinetics and Metabolism.

3.1 Effects on Human Health

The toxicology of BA has been thoroughly reviewed in the BA SIDS Dossier (ACC, 2001a). Only those data that are considered most relevant to the assessment of potential human health hazards are summarized here. In addition, the rapid *in vivo* hydrolysis of BAc to BA makes certain BAc studies directly applicable to the hazard assessment of BA. The *in vivo* BAc hydrolysis study (Deisinger and English, 1997) is summarized below under Toxicokinetics and Metabolism. Surrogate data from BAc studies relevant to the hazard assessment of BA are summarized and/or referenced under their appropriate endpoint headings.

3.1.1 Toxicokinetics, Metabolism and Distribution

BA is readily absorbed through the skin, intestinal tract, and lungs (Sander, 1933; Theorell and Bonnichsen, 1951; Winer, 1958; Merritt and Tomkins, 1959; Wartburg *et al*., 1964) and is eliminated after metabolism primarily by alcohol and aldehyde dehydrogenases. Two hours after rats (strain not specified) were given an oral dose of 2,000 mg/kg body weight, the maximum blood-alcohol concentration was 500 mg/l (Gaillard and Derache, 1965). After four hours, the concentration dropped to 150 mg/l, and only 0.03% of the administered dose was excreted in the urine after eight hours. In another study, CD rats excreted 83.3% of the dose (450 mg/kg body mass) as carbon dioxide and 4.4% in the urine after 24 hours (DiVincenzo and Hamilton, 1979). Beagle dogs dermally exposed through an absorption cell on the thorax absorbed the compound at a

rate of 8.8 mg/min per cm 2 over a 60-minute period (DiVincenzo and Hamilton, 1979). In an inhalation study, beagle dogs exposed to 50 ppm BA over a 6-hour period absorbed approximately 55% of the inhaled vapor (DiVincenzo and Hamilton, 1979).

In order to confirm the rapid hydrolysis of BAc to BA, an *in vivo* toxicokinetics study was conducted in rats with intravenously administered BAc (Deisinger and English, 1997). Radiolabeled BAc was administered via tail vein to 32 male rats at a mean dose of 30.2 mg/kg body weight. This was the highest dose attainable limited by the solubility of test material in saline. Clinical signs observed immediately following the IV administration demonstrated that this dose level was higher than would be expected following inhalation or oral administration of the material. Therefore, this hydrolysis experiment can be used to explain the exposure concentrations that were used in the repeated dose, reproductive and developmental toxicity studies. Liquid scintillation analysis of whole blood and brain tissue for total radioactivity following this dose revealed rapid systemic distribution of the dose and rapid elimination from both whole blood and brain tissue. Results of high performance liquid chromatography indicated that BAc was very rapidly eliminated from the blood (elimination t1/2 = 0.41 minute), and was detected in brain tissue only at low concentrations (mean maximum of 3.8 mg equivalents at 1.9 minutes) in the first 2.5 minutes following dosing. BA was detected in blood and brain tissue at higher levels than BAc, but the BA was also rapidly eliminated and was not detectable 20 minutes after dosing. At the dose level used (20 mg/kg), the hydrolysis of BAc in blood and brain was estimated to be 99 percent complete within 2.7 minutes. Thus, dosing with BAc may be considered a surrogate for dosing with BA in examining systemic effects.

A physiologically-based pharmacokinetic (PBPK) model for the n-butyl series has been developed, validated, and published (Teeguarden, et al., accepted for publication, Toxicological Sciences, 2005). The human equivalent concentrations (HEC) for n-butanol inhalation exposures (in ppm) from rat n-butyl acetate inhalation exposures can be derived from the equation "HEC (a n-butanol exposure in ppm) = $(1x10^{-11} \times ppm^3_{butyl\ acetate} + 2x10^{-8} \times ppm^2_{butyl\ acetate} + 0.0022\ ppm_{butyl\ acetate})/0.0066$" Rat n-butyl acetate inhalation exposures of 500 or 3000 ppm (relevant to the repeat-dose and neurotoxicity studies) would yield HEC n-butanol inhalation exposures of 169 and 1066 ppm, respectively.

3.1.2 Acute Toxicity

The acute toxicity data for BA are summarized in Table 3-2. The most robust studies for all three routes of administration (oral, dermal, inhalation) are considered to be those conducted by Union Carbide Corporation (1951, 1966). These data suggest that BA is only slightly acutely toxic to experimental animals via the oral, dermal, and inhalation routes of exposure.

Table 3-2. Acute Toxicity of n-Butanol in Experimental Animals

Species	Sex	Route	Type	Value	References
Rat	F	Oral*	LD_{50}	4360 mg/kg	Union Carbide Corp., 1951
Rat	F	Oral*	LD_{50}	2290 mg/kg	Union Carbide Corp., 1966
Rat	M/F	Oral*	LD_{50}	2510 mg/kg	Jenner, 1964
Rat	M	Oral	LD_{50}	2020 mg/kg	Purchase, 1969
Rat	F	Oral	LD_{50}	790 mg/kg	Purchase, 1969
Mouse	NS	Oral	LD_{50}	2680 mg/kg	Rumyanstev *et al*., 1979
Rabbit	NS	Oral	LD_{50}	3500 mg/kg	Munch and Schwarze, 1925
Rabbit	NS	Oral	ND_{50}	800 mg/kg	Munch and Schwarze, 1925
Hamster	NS	Oral	LD_{50}	1200 mg/kg	Dubina and Maksimov, 1976
Dog	NS	Oral	LD_{50}	1782 mg/kg	Von Oettingen, 1943
Rabbit	M	Dermal*	LD_{50}	3402 mg/kg	Union Carbide Corp., 1951
Rabbit	NS	Dermal	LD_{50}	5300 mg/kg	Patty, 1978
Rabbit	NS	Dermal	LD_{100}	7500 mg/kg	Patty, 1978
Rat	M	Inhalation*	LC_0	8000 ppm (4h)	Union Carbide Corp., 1951
Rat	M	Inhalation	EC_{50}	6530 ppm (4h)	Korsak *et al*., 1993
Mouse	NS	Inhalation	ED_{50}	3010 ppm (4h)	Korsak *et al.,* 1993
Mouse	NS	Inhalation	TC0	650 ppm (7h)	Patty, 1978
Mouse	NS	Inhalation	TCLo	6600 ppm (2h)	Patty, 1978

* = Key Study, NS = Not Specified, LD = Lethal Dose, ND = Narcotic Dose, RD = Respiratory Dose, LC = Lethal Concentration, EC = Effective Concentration, TC = Toxic Concentration

Oral LD_{50} values for BA in experiments in rats range from 790 to 4,360 mg/kg (Union Carbide Corporation, 1951, 1966; Jenner, 1964; Purchase, 1969). The difference in values between the three key studies (Union Carbide Corporation, 1951, 1966, Jenner 1964) is most likely due to strain differences. Sherman rats were used in the earlier study (1951), whereas Wistar (1966) and Osborne-Mendel (1964) rats were used in the more recent studies. Oral LD_{50} values reported for experiments in other species include 2,680 mg/kg for mice (Rumyanstev *et a*l., 1979), 3,500 mg/kg for rabbits (Munch, 1972; Munch and Schwarze, 1925), 1,200 mg/kg for Golden hamsters (Dubina and Maksimov, 1976), and 1,782 mg/kg for dogs (Von Oettingen, 1943). The oral dose causing narcosis in 50% of rabbits was determined to be 800 mg/kg (Munch and Schwarze, 1925).

A dermal LD_{100} value of 7,500 mg/kg (Patty, 1982) and dermal LD_{50} values of 3,402 mg/kg (Union Carbide Corporation, 1951) and 5,300 mg/kg (Patty, 1982) were observed for rabbits.

An inhalation LC_0 value of 8,000 ppm (4-hour exposure) was observed for rats (Union Carbide Corporation, 1951). Similarly, in 4-hour exposures, an inhalation EC_{50} value of 6,530 ppm was observed for disturbance of rotarod performance by male Wistar rats and an inhalation ED_{50} value (concentration for 50% reduction in respiratory rate) of 3,010 ppm was observed for mice (Korsak *et al.,* 1993). Available information suggests that the acute toxicity (central nervous system or CNS effects) of BA is moderate in several animal species (Patty, 1982). A 7-hour inhalation exposure of mice to 650 ppm BA produced no evidence of toxicity. Signs of CNS depression were, however, observed in a 2-hour exposure to 6,600 ppm (Patty, 1982).

The acute toxicity data for BAc presented in the BA SIDS Dossier and SIAR (ACC, 2001c; ACC, 2001d) provide supporting evidence for the above BA toxicity values. By the oral route of administration, BAc appeared to be somewhat less toxic than BA. This is not unexpected, however, since the materials were dosed by weight rather than concentration, and the gram molecular weight of BAc is 116.16 compared to only 74.12 for BA. Thus, the oral doses were not equimolar. Acute inhalation studies, however, produced LC_0 values of 8000 ppm for both BA and BAc.

3.1.3 Irritation

Data from studies using experimental animals (Union Carbide Corporation, 1951; USDHEW, 1978) indicate that BA was nonirritating to moderately irritating to skin, whereas it was severely irritating to eyes.

In an experiment with rabbits, BA did not produce any skin irritation (Union Carbide Corporation, 1951). USDHEW (1978) observed moderate skin irritation in a 24-hour patch test where 405 or 500 mg BA was applied to the skin of rabbits.

In studies in which 1.62 or 20 mg BA was instilled into rabbit eyes, severe eye irritation occurred after 72 and 24 hours, respectively (USDHEW, 1978). In another study, 0.005 ml BA instilled in rabbit eyes resulted in severe corneal irritation (Patty, 1982).

de Ceaurriz *et al.* (1981) studied the effects of BA on the respiratory rate in mice and predicted that 40 mg/m 3 (13 ppm) in air would have a minimal or no effect on humans, 390.9 mg/m 3 (127 ppm) would be uncomfortable, and 3,909 mg/m 3 (1,268 ppm) would be intolerable.

3.1.4 Sensitisation

No relevant animal studies were found for this endpoint.

3.1.5 Repeated Dose Toxicity

CNS effects (ataxia and hypoactivity) were observed only during the final six weeks of a study in which CD rats (30/sex/dose group) were exposed to BA via gavage for 13 weeks (Toxicity Research Laboratories, 1986). The NOAEL in this study was 125 mg/kg/day and the LOAEL was 500 mg/kg/day. The appearance of post dosing ataxia and hypoactivity only after the interim sacrifice suggests that, with the reduced number of animals, technicians were able to do more thorough observations in a shorter time frame. It is likely that the post dosing effects simply went unnoticed during the first half of the study. No treatment related signs were observed in the 30 or 125 mg/kg/day treatment groups.

In a dermal study, 42 to 55 ml/kg applied to the skin of rabbits each day for 1 to 4 consecutive days resulted in 100% mortality; however, 30 applications of 20 ml/kg over a period of six weeks did not produce any fatalities (Patty, 1982).

Rats exposed to 4000 ppm BA (6 h/day x 5 days, N=10/group) had no impairment of hearing when tested using reflex modification audiometry (Crofton *et a*l., 1994).

Unfortunately, the above repeated dose studies with BA could not be considered very robust. However, as described above, the rapid *in vivo* hydrolysis of BAc to BA makes certain BAc studies directly applicable to provide surrogate data for BA exposures. In this particular case, several repeated dose inhalation toxicity studies were conducted using BAc, the metabolic precursor of BA, which provide excellent surrogate data for BA.

Two definitive BAc studies were conducted that are considered to be the robust studies for this endpoint. Decreased body weight and feed consumption were observed in Sprague-Dawley rats exposed to 1,500 and 3,000 ppm BAc for 13 weeks. However, no systemic, organ-specific toxicity was observed. Minimal, transient narcosis and sedation effects were also observed in rats exposed to 1,500 and 3,000 ppm BAc during exposure only, but a cumulative effect on activity during the 13-week exposure was not observed (Bernard and David, 1996; David *et a*l., 1996). There was no evidence of subchronic neurotoxicity based on functional observational battery (FOB) endpoints, quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. A NOAEL of 500 ppm was reported for systemic effects in rats, and a NOAEL of 3,000 ppm was reported for postexposure neurotoxicity in rats (Bernard *et a*l., 1996; David *et al.,*1998). The equivalent values for BA, corrected for molecular weight, would be 223 ppm and 1338 ppm, respectively.

3.1.6 Mutagenicity

In vitro Studies

BA was not mutagenic in bacteria (Salmonella typhimurium) (McCann et al., 1975; Kier et al., 1986). No mutagenic effects were observed in experiments on cultured Chinese hamster lung (V79) cells at concentrations up to 50 microliters/milliliter (Lasne et al., 1984) or Chinese hamster ovary (CHO) cells at concentrations up to 0.1% (Obe and Ristow, 1997).

In vivo Studies

The most robust test for genetic toxicity was the in vivo mouse micronucleus test conducted by the BASF Corporation (Engelhardt and Hoffman, 1998). BA was administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight (limit dose). The mice were sacrificed at 24 and 48 hours postdosing and evaluated for clastogenicity and spindle poison effects. Positive and negative controls all produced appropriate responses. BA 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).

3.1.7 Carcinogenicity

No reliable data are available. However, based upon the battery of negative mutagenicity and clastogenicity findings, BA presents a very small potential for carcinogenicity.

3.1.8 Toxicity for Reproduction

Effects on Fertility

The most robust study available for reproductive effects was conducted by Nelson *et a*l. (1989a).

No detectable effect on pregnancy rate was found for Sprague-Dawley rats for females (15/group) exposed throughout gestation or males (18) exposed for six weeks prior to mating unexposed females for inhalation exposure levels of 3,000 or 6,000 ppm BA (Nelson *et al*., 1989a).

No testicular toxicity was observed in male Sprague-Dawley rats given 533 mg/kg/day in corn oil (via intubation) for six days even though an equimolar dose of its parent compound (2,000 mg/kg/day of dibutyl phthalate) did decrease testes weights, produce testicular atrophy, and alter zinc metabolism (Cater *et al*., 1977).

The reproductive toxicity data for BAc presented in BAc SIDS Dossier and SIAR (ACC, 2001c; ACC, 2001d) provide supporting evidence for the above conclusions regarding BA. No changes in

reproductive performance were observed in female rats exposed to 1500 ppm of BAc for three weeks prior to mating and during gestation. The males were unexposed, however (Hackett *et a*l., 1982).

There was no evidence of testicular toxicity in male rats exposed via inhalation to 0, 500, 1500, or 3000 ppm of BA (6 hrs/day) for at least 65 exposures over 14 weeks. Therefore, the NOAEL for male reproductive toxicity following repeated inhalation exposure was 3000 ppm (CMA Oxo-Process Panel, 1999).

Developmental Toxicity

The most robust studies available for developmental effects were conducted by Nelson *et a*l. (1989a, 1989b).

Only a few behavioral or neurochemical alterations in offspring and no maternal toxicity were detected in a study of Sprague-Dawley rats exposed to 3,000 or 6,000 ppm BA via inhalation throughout gestation (females) or for six weeks prior to mating (males). The offspring effects were discounted by the authors themselves due to the small number of differences and the lack of a pattern (dose/response) effect (Nelson *et al.,* 1989a). In another study, reduction in fetal weights at 6000 and 8000 ppm and a slight increase in skeletal malformations at 8,000 ppm were observed in offspring of Sprague-Dawley rats exposed to BA on gestation days 1 through 19. The high dose (8,000 ppm) was also toxic to the dams (reduced weight gain and food consumption; two deaths). No such effect was observed following similar exposures at 3500 ppm BA (Nelson *et al.,* 1989b).

The reproductive/developmental toxicity data for BAc presented in BAc SIDS Dossier and SIAR (ACC, 2001c; ACC, 2001d) provide supporting evidence for the above conclusions regarding BA. A NOAEL for developmental effects of 1500 ppm was reported for rats and rabbits exposed to BAc during gestation (Hackett *et a*l., 1982).

3.2 Initial Assessment for Human Health

n-Butyl alcohol (BA) was only slightly toxic to experimental animals following acute oral, dermal, or inhalation exposure. The acute oral LD_{50} values for female rats ranged from 790 to 4360 mg/kg. Different strains of rat were used in each of four studies, which may account for the variability. Oral LD_{50} values for mice, rabbits, hamsters, dogs, and male rats all fell within the same range. The rat inhalation LC_0 of 8000 ppm (24000 mg/m^3) indicates very low inhalation toxicity (no lethality at 8000 ppm). The rabbit dermal LD_{50} was 3402 mg/kg, indicating that BA can penetrate the skin, but not very readily. Animal experiments and human experience indicate that BA is, at most, moderately irritating to the skin, but it is a severe eye irritant. These effects are most likely due to BA's localized defatting and drying characteristics. Although no animal data are available, human studies and experience show that BA is not likely to be a skin sensitizer. A recent *in vivo* toxicokinetics study confirmed the rapid metabolism of n-butyl acetate (BAc) to BA. Hydrolysis of BAc in blood and brain was estimated to be 99 percent complete within 2.7 minutes (elimination $t_{½}$ = 0.41 minute). Thus, organisms exposed to BAc can experience appreciable tissue concentrations of BA. In this way, the results of toxicity studies with BAc can be used as supplemental, surrogate data to provide information on the toxicity of BA. A thirteen-week, subchronic exposure to BAc, the metabolic precursor of BA, produced transient hypoactivity (during exposure only) at 1500 and 3000 ppm (7185 and 14370 mg/m^3) along with decreased body weight and food consumption, but no post exposure neurotoxicity even at 3000 ppm. A concurrent subchronic neurotoxicity study under the same exposure conditions showed no evidence of cumulative neurotoxicity based upon functional observational battery endpoints, quantitative motor activity, neuropathology and scheduled-controlled operant behavior endpoints. A no observable effect level (NOAEL) of 500 ppm (2395 mg/m^3) was reported for systemic effects in rats, and a NOAEL of 3000 ppm (14370

mg/m^3) was reported for post exposure neurotoxicity in rats. Several studies indicate that BA is not a reproductive toxicant. Female rats exposed to 6000 ppm (18000 mg/m^3) BA throughout gestation and male rats exposed to 6000 ppm (18000 mg/m^3) BA for six weeks prior to mating showed no effects on fertility or pregnancy rate. Male rats given BA at 533 mg/kg/day for 5 days had no testicular toxicity. BA produced only mild fetotoxicity and developmental alterations at or near the maternally toxic (even lethal) dose of 8000 ppm (24000 mg/m^3) throughout gestation. An entire battery of negative *in vitro* tests and a negative *in vivo* micronucleus test indicate that BA is not genotoxic. The median odor threshold for BA (0.17 ppm) is well below the lowest nasal irritation threshold in humans (289 ppm), allowing warning of possible chemical exposure prior to nasal irritation occurring. Human studies are complicated by the odor characteristics of the material, as the odor threshold is well below the levels at which irritation is observed.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Information on the aquatic toxicity of BA is available for several species of fish, aquatic invertebrates, amphibians, plants and algae, and microorganisms (bacteria and protozoa). Minimal toxicity was observed in fish, aquatic invertebrates, amphibians, algae, and microorganisms. However, algae appeared to be the most sensitive to BA. The available data for BA indicate that acute toxicity to aquatic life may occur at concentrations greater than 100 mg/L. Results for fish, aquatic invertebrates, amphibians, plants and algae, and microorganisms are summarized below and in Appendix B.

Fish

Eight studies were identified that evaluated the toxicity of BA to fish survival. Fathead minnows *(Pimephales promela*s) were test subjects in four studies (Brooke *et al*., 1984; Mattson *et al*., 1976; Union Carbide Corporation, 1992c; Wong et al., 1998). The LC_{50}s for *Pimephales promelas* exposed to BA for 96 hours in static tests ranged from 1,376 mg/L (Wong et al., 1998) to 1,940 mg/L (Mattson et al., 1976). A study by Gillette *et al.* (1952) reported a LC_0 of 1,000 mg/L and a LC_{100} of 1,400 mg/L for creek chub *(Semotitus atromaculatu*s) exposed to BA in a static system for 24 hours. Bridie *et al.* (1979) reported a 24-hour LC_{50} of 1,900 mg/L for goldfish *(Carassius auratu*s) in a static exposure. Juhnke and Lüedeman (1978) reported LC_{50}s of 1,200-1,770 mg/L for golden orfe *(Leuciscus idus melanotu*s) in a 48-hr static test. Reported LC_{50}s for the saltwater bleak (*Alburnus alburnus*) exposed to BA in 96-hour static tests ranged from 2,250 mg/L (Linden et al., 1979; Bengtsson et al., 1984). A study by Tsuji et al. (1986) reported a 48-hr LC_{50} range of 500 to >1,000 mg/L in static

The preferred fathead minnow study conducted as static exposures reported a 96-hr LC_{50} of 1,376 mg/L based on measured concentrations that averaged 82% of nominal concentrations (Wong et al., 1998) and was conducted under Good Laboratory Practices (GLP). The Bridie et al. study (1979) with goldfish also determined the concentration of BA in the static test solutions. Results from other static tests with LC_{50} values of 1,400 to 1,910,mg/L for fathead minnows, 1,200 to 1,770 mg/L for golden orfe *(Leuciscus idu*s), and 2,300 mg/L for the marine *Alburnus alburnus* were based upon nominal concentrations (Union Carbide Corporation, 1992; Mattson et al., 1976; Juhnke and Ludemann, 1978; Linden et al., 1979; Bengtsson et al., 1984). The results obtained using static test systems with nominal or measured concentrations were similar to those obtained from flow-through tests with measured concentrations.

To further support the key studies, the ecotoxicity estimation program ECOSAR (v.0.99f) was employed to estimate similar values (Cash and Nabholz, 2000). ECOSAR estimates were calculated

using the following model inputs: CAS Reg. No. 71-36-3 (to obtain the structure-based SMILES notation), molecular weight of 74.12 g/mol, log Kow of 0.88, melting point of -89.8 deg C, and an aqueous solubility of 77,000 mg/L. ECOSAR calculated a 96-h LC_{50} for fish of 621 mg/L, which was a factor of about two lower than the measured 96-LC_{50} of 1376 mg/L from the key fish study.

Invertebrates

Five studies were identified which evaluated the toxicity of BA to three species of invertebrates. Four studies evaluated *Daphnia magn*a. Bringmann and Kuhn (1977,1982) reported a 24-hr EC_{50}s of 1,855 mg/L for *Daphnia magna* (the observed effect was immobilization). Kuehn *et al.* (1989) exposed *Daphnia magna* to BA for 24 hours and 48 hours. The reported 24-hour EC_0, EC_{50}, and EC_{100} for immobilization were 1,677 mg/L, 2,337 mg/L, and 5,700 mg/L, respectively. The reported 48-hour EC_0, EC_{50}, and EC_{100} for immobilization were 1,260 mg/L, 1,983 mg/L, and 2,455 mg/L, respectively. A recent static study by Wong et al. (1998) reported a 48-hr EC_{50} of 1,328 mg/L for *D. magna* based on measured concentrations and conducted using GLP. Two studies evaluated brine shrimp *(Artemia salin*a). Price *et al.* (1974) reported a 24-hr LC_{50} of 2,950 mg/L for immobilization of *Artemia salina* exposed in a static system. The remaining study evaluated the harpacticoid copepod (Nitocra spinipes). Bengtsson et al. (1984) reported a 96-hr LC50 of 2,100 mg/L.

The toxicity of BA to the water flea *(Daphnia magn*a) based on immobilization of the daphnid, ranged from 24-hr EC_{50} values of 1,885 to 2,337 mg/L to 48-h EC_{50} values of 1,328 to 1,983 mg/L. Static tests using the saltwater brine shrimp, *Artemia salin*a, resulted in 24 hr EC50s of 2,600 to 2,950 mg/L. Static studies with the harpacticoid copepod, *Nitocra spinipes,* resulted in 96-hr EC_{50} values of 1,900 to 2,300 mg/L.

To further support the key studies, the ecotoxicity estimation program ECOSAR (v.0.99f) was employed to estimate similar values (Cash and Nabholz, 2000). ECOSAR estimates were calculated using the following model inputs: CAS Reg. No. 71-36-3 (to obtain the structure-based SMILES notation), molecular weight of 74.12 g/mol, log Kow of 0.88, melting point of -89.8 deg C, and an aqueous solubility of 77,000 mg/L. ECOSAR calculated a 48-h LC_{50} for Daphnia of 615 mg/L, about a factor of about two lower than the measured 48-LC_{50} of 1328 mg/L from the key daphnid study.

Amphibia

Information on effects of BA on amphibians is limited to two studies. Münch (1972) reported a threshold concentration for narcosis of 2,820 mg/L for frog tadpoles *(Rana* sp.). A 48-hr LC_{50} of 1,200 mg/L for *Xenopus laevis* from a static test was reported by DeZwart and Slooff (1987).

Plants and Algae

No data have been reported on the effects of BA on freshwater or marine vascular plants. However, toxicity studies for four different species of algae were identified. BASF (1991b) reported an EC_{50} of > 500 mg/L for green algae *(Scenedesmus subspicatu*s) exposed to BA for 96 hours (the observed effect was not reported). Jones (1971) reported an EC_{50} of 8,500 mg/L for *Chlorella pyrenoidosa* based on effects on chlorophyll content (exposure duration was not reported). Jones (1971) also reported an IC_{10} (fluorescence inhibition) of 889 mg/L and an IC_{10} (growth inhibition) of 222 mg/L for *Scenedesmus subspicatu*s.

A 96-hr EC_{50} of 225 mg/L, a 96-hr NOEC of 129 mg/L, and a 96-hr LOEC of 241 mg/L for growth inhibition of *Selenastrum capricornutum* were reported by Wong et al. (1998), which was conducted under GLP conditions. Bringmann and Kuehn (1978) reported 8-day toxicity thresholds (TT) of 100 mg/L for bluegreen algae *(Microcystis aeruginos*a) and 875 mg/L for green algae

*(Scenedesmus quadricaud*a) based upon a turbidmetric measurement of the concentration of algal suspensions. The toxicity threshold was the concentration inhibiting the onset of cell multiplication.

Toxicity of BA to blue-green algae and green algae has been reported. Chronic endpoints include the 8-day toxicity thresholds, equivalent to LOEC of 100 mg/L for *M. aeruginosa* and 875 mg/L for *S. subspicatus* and 96-hr LOEC and NOEC values of 241 and 129 mg/L for *Selenastrum capricornutu*m. Acute toxicity values (96-hr EC_{50}) ranged from 225 mg/L to less reliable values of >500 and 8,500 mg/L because observed effects and exposure duration were not reported in the respective studies.

To further support the key studies, the estimation program ECOSAR (v.0.99f) was employed to estimate similar values (Cash and Nabholz, 2000). ECOSAR estimates were calculated using the following model inputs: CAS Reg. No. 71-36-3 (to obtain the structure-based SMILES notation), molecular weight of 74.12 g/mol, log Kow of 0.88, melting point of -89.8 deg C, and an aqueous solubility of 77,000 mg/L. ECOSAR calculated a 96-h EC_{50} for algae of 361 mg/L, which was close to the measured 96-hr EC_{50} of 225 mg/L from the key algae study.

Bacteria – There were five toxicity tests identified that evaluated bacteria. *Pseudomonas putida* was the subject of two tests. Huels (unpublished data) reported a 16-hour TT (no effect concentration) of 2,250 mg/L and Bringmann and Kuehn (1978) reported a 16-hour TT of 650 mg/L for *P.putid*a. The endpoint evaluated by Bringmann and Kuehn (1978) was total biomass. Toxicity tests whose results take into account cellular division or the number of young produced are not considered acute tests, even if the duration was 96 hours or less. Yasuda-Yasaki et al. (1976) exposed *Bacillus subtilis* to BA and reported an EC_{50} (the effect was spore germination) of 1,258 mg/L (the duration of the test was unreported). Chou *et a*l. (1978) also exposed *B. subtilis* to BA and reported that no inhibition of degradation by methane culture on acetate substrate occurred at a concentration of 7,400 mg/L. Blum and Speece (1991) conducted a 5-minute Microtox assay with the bacteria *Photobacterium phosphoreum* and reported effects at 2,041 mg/L.

Protozoa

Information on effects of BA on protozoans is limited to two studies, which evaluated four species of protozoa. Bringmann and Kuhn (1980a,), Bringmann et al. (1980) and Bringmann (1978) exposed three species of protozoa *(Uronema parducz*i, *Chilomonas paramecium*, and *Entosiphon sulcatu*m) to BA for 20 hours, 48 hours, and 72 hours, respectively. The authors reported toxicity thresholds of 8 mg/L for *Uronema parducz*i, 28 mg/L for *Chilomonas paramecium*, and 55 mg/L for *Entosiphon sulcatum* for total biomass production. The reported toxicity thresholds are considered to be chronic, because of the endpoint evaluated in these studies (total biomass). Schultz et al. (1990) reported an IC_{50} (growth) of 2,466 mg/L for the protozoan, *Tetrahymena pyriformi*s, in a 48-hr static test.

Two tests with the bacteria, *Pseudomonas putid*a, were conducted for 16-hr and gave toxicity thresholds of 650 to 2,250 mg/L. Toxicity endpoints for other bacteria ranged from 1,258 to 7,400 mg/L. Tests with three protozoan species *(Uronema parduczi, Chilomonas paramecium, and Entosiphon sulcatu*m) gave toxicity threshold values of 8, 28, and 55 mg/L respectively. BA is of generally low concern to microorganisms, although somewhat more toxic to protozoa than bacteria.

No chronic data for fish or invertebrates are available for BA. A 21-day chronic assay with isobutyl alcohol using *Daphnia magna* was conducted and measured effects on mortality and reproduction (Kuhn et al., 1989). The NOEC for reproduction for isobutyl alcohol was 20 mg/L.

Chronic toxicity of BA can also be estimated by ECOSAR v. 0.99f (Cash and Nabholz, 2000). A SAR for neutral organics was used and chronic values for fish (30-day ChV) and invertebrates (16-

day EC50) were estimated to be 72 and 21 mg/L, respectively. The estimated invertebrate value of 21 mg/L for BA compares well with the measured chronic daphnid value of 20 mg/L for isobutanol.

4.2 Terrestrial Effects

Information on effects of BA on terrestrial organisms (birds, mammals, plants, invertebrates, etc.) is limited to four studies. Three studies were identified which evaluated the toxicity of BA to plants, and one study was identified which evaluated the toxicity of BA to birds.

Plants

Three toxicity studies for three different species of domesticated plants were identified. Two of the three studies evaluate the effect of BA on seed germination. Reynolds (1977) observed a 50% reduction in lettuce *(Lactuca sativ*a) seed germination following exposure to BA at a concentration of 390 mg/L. In a similar study, Smith and Siegal (1975) report seed germination inhibition in cucumber *(Cucumis sativu*s) exposed to BA at a concentration of 2500 mg/L. In another study, BA was determined to have beneficial effects on oat seedlings *(Avena sativ*a). Satler and Thimann (1980) exposed oat seedlings to BA, however, exposure duration and exposure concentration(s) were not reported. Satler and Thimann (1980) reported that exposure of oat seedlings to BA reduced senescence (aging) in leaves, and prevented hydrolytic breakdown of proteins into simpler soluble substances (proteolysis) in the dark.

Birds

Information on effects of BA on birds is limited to a single study. Schafer *et al.* (1983) dosed wild-trapped European starlings by gavage (forced feeding) with a BA solution. The estimated LD_{50} was less than 2,500 mg/kg-day.

4.3 Other Environmental Effects

The bioaccumulation potential of BA is low. A reliable predictor of bioaccumulation potential of very water soluble compounds is the bioconcentration factor (BCF). A BCF of 3 L/kg was estimated with EPISUITE (v. 3.10) and BCFWOM (v. 2.14) using a log K_{ow} of 0.88. This low BCF suggests that BA would not be expected to accumulate in biological tissue or biomagnify in food chains.

4.4 Initial Assessment for the Environment

BA's vapor pressure is 0.56 kPa at 20^0C, water solubility is 77 g/L at 20^0C and a Log K_{ow} is 0.88. Based on level III fugacity modeling, BA will partition 83.5% in air, 5.9% in soil, 10.6% in water, <0.1% in suspended solids, and <0.1% in biota and in sediment. BA degrades in air by reaction with hydroxyl radicals, having a half-life in air of 1.2 to 2.3 days. The volatilization half-life for BA in water is estimated to be 2.4 hours for streams, 3.9 hours for rivers and 126 days for lakes. BA exhibits low toxicity to fish, amphibians and aquatic invertebrates, plants, algae, bacteria and protozoans. However, some algal species are sensitive to BA. Acute toxicity to aquatic life may occur at concentrations greater than 500 mg/l. BA is classified as "readily biodegradable" under aerobic conditions. The octanol:water partitioning coefficient (log K_{ow}) for BA ranges from 0.88 to 0.97, and the calculated bioconcentration factor (BCF) is 3. These data indicate that BA has a low potential to bioaccumulate. BA is expected to migrate readily through soil to groundwater and not to sorb to soil particles.

5 RECOMMENDATIONS

The data collected for SIDS elements were considered adequate for hazard identification. BA is currently recommended for low priority for further work.

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ANNEX

Endpoint	Required SIDS Element	Key Study Available	Comments	Data Quality *	References
Toxicokinetics	No	butyl acetate	Metabolism	1	Deisinger and English, 1997
Acute Toxicity	Yes	Butanol	Rat Oral, Dermal, Inhalation	2	Union Carbide Corp., 1951, 1966
Repeat Dose Toxicity	Yes	butyl acetate	Subchronic	1	David *et al*., 1996
		butyl acetate	Neurotoxicity	1	David *et al*., 1998
Reproductive Toxicity	Yes	Butanol	Inhalation Exposure	2	Nelson *et al*., 1989a
Developmental Toxicity	Yes	Butanol	Inhalation Exposure	2	Nelson *et al*., 1989b
In Vitro Genotoxicity	Yes	Butanol	Ames Test	2	Kier *et al*., 1986; McCann *et al*., 1975
In Vivo Genotoxicity	Yes	Butanol	Micronucleus Test	1	Engelhardt and Hoffman, 1998
Irritation	No	Butanol	Rabbit	2	Union Carbide Corp, 1951
Human Experience	No	Butanol	Odor vs. Irritation	2	Wysocki and Dalton, 1996

* Klimisch, H.J., Andreae, E. and Tillmann, U. 1997. A systematic approach for evaluating the quality of experimental and ecotoxicological data. Reg. Tox. And Pharm. 25: 1-5.

n-butyl alcohol - Environmental Effects

	LC_{50} or EC_{50} (mg/L)	Fresh / Marine	Test	Comments
Fish				
Fathead minnow *Pimephales promelas*	1,730	F	96 hr static; mortality	Measured concentrations
Fathead minnow *Pimephales promelas*	1,910	F	96 hr static; mortality	Lake Superior water or reconstituted laboratory water
Fathead minnow *Pimephales promelas*	1,400	F	96 hr static; mortality	
Fathead minnow *Pimephales promelas*	1,386	F	96 hr static; mortality	Measured concentrations, GLP
Goldfish *Carassius auratus*	1,900	F	24 hr static; mortality	
Golden orfe *Leuciscus idus melanotus*	1,200 to 1,770	F	48 hr static; mortality	
Creek chub *Semotitus atromaculatus*	LC0=1,000 LC100=1,400	F	24 hr static; mortality	
Bleak *Alburnus alburnus*	LC50=2,250 to 2,400	Brackish	96 hr static; mortality	
Invertebrates				
Water flea *Daphnia magna*	24 hr. EC_{50}= 2,337 48 hr EC50=1,983	F	24 hr; immobilization	Measured concentrations
Water flea *Daphnia magna*	EC_{50} = 1,328	F	48 hr; immobilization	Measured concentrations
Water flea *Daphnia magna*	EC50=1,880	F	24 hr; immobiliation	
Brine shrimp *Artemia salina*	3,000	M	24 hr static	24.5 ∀C; immobilization
Haracticoid copepod *Nitroca spinipes*	2,100	M	96 hr static	
Haracticoid copepod *Nitroca spinipes*	96-hr LC50s=1,900 to 2,300	M	96 hr static	
Algae				
Bluegreen algae *Microcystis aeruginosa*	TT = 100	F	8 day; inhibition of onset of cell multiplication	
Green algae *Scenedesmus subspicatus*	EC_{10}>500 EC_{50}>500 EC_{90}>500	F	96 hr, DIN Test Method 38412 Part 9	
Green algae *Scenedesmus quadricauda*	TT = 875	F	7 or 8 day; inhibition of onset of cell multiplication	

Green algae *Selenastrum capricornutum*	EC_{50} = 225	F	96 hr, growth inhibition	Day 0 measured concentrations, GLP
Microorganisms				
Bacteria *Bacillus subtilis*	LC50=1,258	F	Spore germination	
Bacteria *Pseudomonas putida*	TT = 650	F	16 hr toxicity threshold	
Bacteria *Bacillus subtilis*	NOEC=7,400	F	No inhibition of degradation by methane culture on acetate substrate.	
Protozoa *Uronema parduczi*	EC_3 = 8	F	20 hr toxicity threshold for growth rate	
Protozoa *Chilomonas paramecium*	EC_3 = 28	F	48 hr toxicity threshold for growth rate	
Protozoa *Entosiphon sulcatum*	EC_3 = 55	F	72 hr toxicity threshold for growth rate	

ROBUST SUMMARIES
and
SIDS DOSSIER for:
1-BUTANOL

.....

CAS No. 71-36-3

Sponsor Country: U.S.A.

DATE: September 2001, revised July 2004

Analog Justification
The Metabolic Series Approach

The results of selected studies with butyl acetate have been used in this submission to supplement butanol data for certain, specific health effects endpoints. This use of butyl acetate data as a surrogate for butanol data (or vice versa) has now become known, in general, as the "metabolic series approach." This relatively new approach to hazard evaluation (Barton et al., 2000) is intended to facilitate the maximal use of toxicity data.

Butyl acetate is the ester of butanol and acetic acid. Due to this structural similarity, butyl acetate and butanol can be considered "analogs" to some extent. However, they are really more than just analogs. They are part of a metabolic series that includes butyl acetate and its primary metabolites, butanol, butyraldehyde, and butyric acid. Butyl acetate is the parent, or immediate precursor, of butanol. In an in vivo toxicokinetics study in rats using radiolabeled butyl acetate administered intravenously, hydrolysis of butyl acetate in blood and brain was 99 percent complete within 2.7 minutes (Deisinger and English, 1997). Because butyl acetate is so rapidly metabolized (hydrolyzed) to form butanol, organisms exposed to butyl acetate can experience appreciable tissue concentrations of butanol. In this way, information from toxicity studies for butyl acetate inherently provides information on the toxicity of butanol (and vice versa). This is a credible approach primarily due to rapid metabolism, however, not because of analogous structures. For this reason, we have decided to use the term "metabolic series approach."

The use of butyl acetate results to supplement butanol data 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 any endpoints dependent upon the physical-chemical properties of the material. Thus, it would be inappropriate to use surrogate butyl acetate data for skin irritation, eye irritation, skin sensitization, certain in vitro mutagenicity studies, dermal studies of any type, aquatic studies, or any other environmental studies. These type of surrogate data are inappropriate because studies have not yet been conducted to confirm the rapid hydrolysis of butyl acetate to butanol under specialized exposure conditions such as skin contact, eye contact, in vitro, dermally, in fish, or in other non-mammalian species. Because the use of surrogate data is limited to only a few, specific endpoints, we chose to submit the butanol and butyl acetate SIAR's separately.

For the same reason, the dossiers for the two chemicals were prepared and submitted separately also. The butanol dossier does, however, contain selected summaries of butyl acetate studies that were used to support specific butanol endpoints in the SIAR. These endpoints include Repeated Dose Toxicity, Reproductive Toxicity, Neurotoxicity, and Toxicokinetics and Metabolism. Under each endpoint in which the butyl acetate data is used in the SIAR, it is presented in a separate paragraph under the subheading "Metabolic Series Approach." We believe that this novel approach provides for the maximum use and most effective presentation of the available data.

1.0 GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS-Number 71-36-3

B. Name (IUPAC Name)

C. Name (OECD Name) 1-Butanol

D. CAS Descriptor

E. EINECS-Number

F. Molecular Formula $C_4H_{10}OH$

G. Structural Formula CH_3-CH_2-CH_2-CH_2OH

H. Substance Group

I. Substance Remark Conversion factor: 1 ppm = 3.03 mg/m^3 at 25°C

J. Molecular Weight 74.12

1.02 OECD INFORMATION

A. Name of Sponsor Country: United States of America

B. Lead Organization:

Name of Lead Organization: American Chemistry Council
Contact person: Doug Anderson
Address:
American Chemistry Council
1300 Wilson Blvd.
Arlington Virginia 22209
Telephone: (703)-741-5616
Fax: (703)-741-6091

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance element [ ]; inorganic [ ]; natural substance [ ];
organic [X]; organometalic [ ]; petroleum product [ ]

B. Physical State (at 20° C and 1.013 hPa)
gaseous [ ]; liquid [X]; solid [ ]

C. Purity (indicate the percentage by weight/weight)
99.9%

IMPURITIES Isobutanol 0.1% max. by wt.
Other alcohols and aldehyde impurities 0.2% max. by wt.

ADDITIVES None.

1.4 SYNONYMS n-butanol
1-butanol, butan-1-ol

1-butyl alcohol
n-butyl alcohol
butyl alcohol
butyl hydroxide
butyric alcohol
1-hydroxy butane
hydroxybutane
methylolpropane
NBA
normal primary butyl alcohol
BA
propylcarbinol
propyl methanol

1.5 QUANTITY 1991 = 1,361 MMlbs U.S.A. (619,000 metric tonnes)
1992 = 1,266 MMlbs U.S.A. (575,000 metric tonnes)

Reference: CMA, 1999.

1.6 USE PATTERN

Butyl alcohol is used predominately as an industrial intermediate. For example, it is used to make butyl acetate and other butyl esters; butyl ethers, such as ethylene glycol monobutyl ether, di- and triethylene glycol monobutyl ether, and the corresponding butyl ether acetates. It is used to manufacture dibutyl phthalate, pharmaceuticals, polymers, pyroxylin plastics, butyl xanthate and other butyl compounds. Butyl alcohol is used as a diluent/reactant in the manufacture of urea/formaldehyde and melamine/formaldehyde resins. When used as an industrial intermediate, butyl alcohol is consumed by chemical conversion to the desired product.

Butyl alcohol is used to a lesser extent as a solvent and in formulations to make, dyes, lacquers (including cellulose lacquers), resins and varnishes. It is a component in some nail polish formulations. It is used to make rubber cement, safety glass, rayon, waterproofed cloth, artificial leather, raincoats, motion picture and photographic film. It is used as a softener in the fabrication of cellulose nitrate plastics (Tabershaw *et. al.*, 1944; Cogan and Grant, 1945; Sterner *et al.*, 1949; Mellan, 1950; Doolittle, 1954). It is also used in the manufacture of pharmaceuticals, in microscopy (preparing paraffin imbedding materials), in veterinary medicine (as a bactericide), as a dehydrating agent, in perfumes, fruit essences, and as a flavoring agent in foods and beverages (Genium, 1993; Hall and Oser, 1965).

According to the CEH Marketing Research Report for Oxo Chemicals- SRI, consumption of butyl alcohol in the United States is as follows:

Uses	1997	2002
Acrylate/methacrylate Esters	595(a)	771(a)
Glycol Ethers	362	402
Butyl Acetate	220	245
Direct Solvent	125	128
Plasticizers	43	46
Other uses	69	74

Millions of pounds annually.

In the United States, butyl alcohol is approved by the Federal Food and Drug Administration (FDA) as an indirect food additive for use only as a component of adhesives (21 CFR 175.105). It is a food additive permitted by the FDA for direct addition to food for human consumption (21 CFR 172.515)

Percent use of open or closed systems for butyl alcohol manufacture or processing has been estimated as follows for the United States (CMA, 1999):

Industrial Closed System	81%
Industrial Open System	4%
Export	15%
Total	100%

The Swedish Product Register (2001) identifies butyl alcohol in 1096 products and 170 consumer products (mainly as a raw material or solvent).

1.7 SOURCES OF EXPOSURE

1-Butanol is produced via hydroformylation reaction of propylene and syngas in the presence of a catalyst to form a mixture of n-butyraldehyde and isobutyral-dehyde. The mixed butyraldehyde stream is hydrogenated in the presence of a catalyst to form the corresponding alcohol products, 1-butanol and isobutanol. This alcohol mixture is refined to form two high purity product streams, 1-butanol and isobutanol. The entire process is continuous and takes place in closed vessels which are arranged in series and are connected with process lines. The process waste streams are combined and collected and sold to a third party for extraction and resale of the valuable components. The potential for human exposure in the industrial environment is extremely low due to the entirely closed manufacturing process.
Reference: Union Carbide Corporation, Internal Data.

Release Data from the U.S. EPA Toxics Release Inventory
Release data for the U.S. from the most recent year available, 2001, was retrieved on May 21, 2004. The results are shown below. Combined releases directly to the environment, to air, water and soil (marked by asterisk), totaled 16,905,396 pounds (7,684,271 kg). Of this amount, releases to air were 16,893,093 pounds (7,678,679 kg) or 99.75% of the total direct emissions to the environment were to air. These numbers do not include emissions to air from consumer uses of products containing n-butanol as a solvent. Thus, for the purposes of distribution modeling, 100% of emissions were assumed to go to air.

*Total emissions to air:	16,893,093 pounds (7,678,679 kg)
*Surface water discharges:	40,175 pounds (18,261 kg)
Underground injection	834,584 pounds (379,356 kg)
*Releases to land:	2,128 pounds (967 kg)
Total off-site releases (e.g., to STPs):	1,258,379 pounds (571,900 kg)

ADDITIONAL INFORMATION

1.8.1 LABELLING AND CLASSIFICATION

The following classifications have been established:
EPA Carcinogen Designation.
EPA-D (not classifable as to human carcinogenicity).
MAK EMBRYO/FETUS RISK OF DAMAGE CLASSIFICATION
Group D (classification not yet possible).
NFPA HAZARD IDENTIFICATION

H = 2 F = 3 R = 0

Type:	Directive 67/548/EEC	
Category of danger:		
R-phrases:	(10)	Flammable
	(22)	Harmful if swallowed
	(37)	Irritating to the respiratory system
	(38)	Irritating to the skin
	(41)	Risk of serious damage to the eyes
	(67)	Vapours may cause drowsiness and dizziness
Remarks:	(Xn)	Harmful
	(Xi)	Irritant

1.8.2 OCCUPATIONAL EXPOSURE LIMIT

The following exposure guidelines have been established:
ACGIH TLV: 20 ppm TWA .
OSHA PEL: 50 ppm (skin) ceiling (vacated).
OSHA PEL: 100 ppm TWA-8 (skin).
NIOSH REL: 50 ppm (skin) ceiling.
NIOSH IDLH: 1400 ppm.
DFG MAK: 100 ppm.
DFG MAK STEL: 200 ppm, 30 minutes, 4 times per shift.
AUSTRALIA: 50 ppm peak limitation (skin).
NETHERLANDS: 15 ppm, 15-minute STEL.
SWEDEN: 15 ppm, 15-minute STEL = 30 ppm (skin).
UNITED KINGDOM: 50 ppm (skin

1.8.3 OPTIONS FOR DISPOSAL

1.) Incinerate in a furnace.
2.) At very low concentrations in water, this material is biodegradable in a biological wastewater treatment plant.

2.0 PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

Value:	-89.9 ^{o} C
Method:	Method not listed.
GLP:	YES [ ] NO [X]
Reliability:	(2) Valid with restrictions, full experimental details are not available.
Reference:	Union Carbide Corporation, Solvents & Coatings Materials Division. Material Safety Data Sheet: C0296F, Dated 10/18/95

2.2 BOILING POINT

Value:	117.6 ^{o} C at 101.325 kP_a
Method:	Method not listed.
GLP:	YES [ ] NO [X]
Reliability:	(2) Valid with restrictions, full experimental details are not available.
Reference:	Union Carbide Corporation, Solvents & Coatings Materials Division Material Safety Data Sheet: C0296F, Dated 10/18/95

2.3 DENSITY

Value:	0.8097
Comments:	Calculated at 20/4°C
Reliability:	(2) Valid with restrictions, full experimental details are not available.
Reference:	Othmer, Kirk. 3rd Edition 21:378. Beilstein a. E III, 2; b. E IV 1/3.
Value:	0.8098 g/cm 3 @ 20º C
Reliability:	(2) Valid with restrictions, full experimental details are not available.
Reference:	(Weast and Astle, 1985)

2.4 VAPOUR PRESSURE

(A.) Preferred Value

Value:	0.56 hPa at 20°C
Method:	Method not listed.
GLP:	no
Comments:	As cited in Chemical Manufacturers Association. Summary of Responses to the OECD Request for Available Data on HVP Chemicals. February 8, 1999.)
Reliability:	(2) valid with restrictions, full experimental data not available.
Reference:	Union Carbide Corporation. 1992a. Material Safety Data Sheet. Dated March 20, 1992. C0269D. Solvents and Coatings Materials Division, Union Carbide Corporation.

(B.)	Value:	0.658 hPa (0.49 mm Hg) at 20°C
	Method:	Calculated
	GLP:	no
	Reliability:	(2) valid with restrictions, full experimental data not available
	Reference:	Munday, E.B. Mullins, J.C. and Edie, D.D. 1980. Vapor pressure data for toluene, 1-pentanol, 1-butanol, water and 1-propanol. K. Chem Eng Data 25: 191-4
(C.)	Value:	0.82 KPA at 25°C
	Method:	method not listed
	GLP:	no
	Reliability:	(2) valid with restrictions, full experimental data not available
	Reference:	Bernstein a.EIII, 2; b. E IV 1/3.
(D.)	Value:	8.70 Hpa (6.47 mm Hg) at 20°C
	Method:	calculated
	GLP:	no
	Reliability:	(2) valid with restrictions, full experimental data not available
	Reference:	Boublik, T. V Fried, and E. Hala. 1984. The vapor pressure of pure substances: selected values of the temperature dependence of the vapor pressures of some pure substances in the normal and low temperature regions. Vol. 17. Elsevier Science Publishers, Amsterdam, Netherlands.
(E.)	Value:	9.36 hPa (7.024 mm Hg) at 20°C
	Method:	Calculated
	GLP:	no
	Reliability:	(2) valid with restrictions, full experimental data not available
	Reference:	Howard, P.H. 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume II. Lewis Publishers, Chelsea MI.

2.5 PARTITION COEFFICIENT n-Octanol/Water

Preferred Value	
Value:	log K_{ow} =0.88 at 20°C
Method:	Calculated [ ] Measured [X]
GLP:	YES [ ] NO [X]
Analytical Method:	Internal Union Carbide
Reliability:	(2) valid with restrictions, calculated
Reference:	Hansch, C. and A. J. Leo. 1985. Medchem Project. Pomona Colllege, Issue 26, Claremont, CA.

2.6 WATER SOLUBILITY

Preferred Value	
Value:	77,000 mg/l at 20° C
Method:	Not Stated
GLP:	YES [ ] NO [X]
Analytical Method:	

Reliability: (2) valid with restrictions, full experimental details not available
Reference: Howard, P.H. 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume II. Lewis Publishers, Chelsea, MI

2.7 FLASH POINT (Liquids):

a)
Preferred result
Value: 37° C
Remark: 98° F
Reliability: (2) valid with restrictions, full experimental data not available
Reference: NFPA. 1994. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 11th edition. NFPA. Quincy, MA.

b)
Value: 29°C closed cup [X] open cup [ ]
35°C closed cup [X] open cup [ ]
GLP: YES [ ]
NO [X]
Reliability: (2) valid with restrictions, full experimental data not available.
Reference: Montgomery, John H. Groundwater Chemicals (Desk Reference). 2nd Edition, 1996.
Othmer, Kirk. 3rd Edition 21:378.

2.8 AUTO FLAMMABILITY (Solid/Gases)

Value: 365°C
Reference: Othmer, Kirk. 3rd Edition. 21:378

2.9 FLAMMABILITY (Solid/Gases):

Preferred Value
Comments: Flammable range is 1.4-11.2% volume in air (14,000 – 112,000 ppm)
Flashpoint is 98 degrees F.
Reliability: (2) valid with restrictions, full experimental data not available
Reference: National Fire Protection Association (NFPA). 1986. Fire Protection Guide on Hazardous Materials 9 th ed. NFPA, Boston, MA.

2.10 EXPLOSIVE PROPERTIES No Data Available.

2.11 OXIDIZING PROPERTIES No Data Available.

2.12 ADDITIONAL REMARKS No Data Available.

2.13 ADDITIONAL DATA

3.0 ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(A.) Preferred Value

Type:	Other, see remarks
Light Source:	
Light spect.:	
Rel. intensity:	based on intensity of sunlight
Degradation:	30 hour half-life
Method:	
GLP:	
Test substance:	butanol
Remark:	Atmospheric photo-oxidation potential was estimated using a measured or estimated second order half-life with units of cm^3/molecules-cm reported by Kwok and Atkinson (1994). Vapor phase butanol is expected to degrade in the atmosphere by reaction with photochemically produced hydroxyl (OH) radicals. The 2^{nd} order rate constant was reported to be 8.57 e-12 cm^3 (molecule/sec) at 25°C. Based on 1.5E6 OH molecules/cm^3 and assuming 12 hours of sunlight per day, the estimated half-life was 1.25 days or 30 hours.
Reliability:	(2) valid with restrictions, full experimental data not available
Reference:	Kwok and Atkinson (1994) as reported in AOPWIN version 1.90. Atmospheric Oxidation. EPIWIN (Estimation Program Interface for Windows) version 3.10. U.S. Environmental Protection Agency (2001).

(B.)

Type:	Other, see remarks
Light Source:	
Light Spect.	
Rel. Intensity:	Based on intensity of sunlight
Degradation:	37 hour half-life
Method:	
GLP:	
Test Substance:	butanol
Remark:	Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN that calculates a second order half-life with units of cm^3/molecules-cm. Vapor phase butanol is expected to degrade in the atmosphere by reaction with photochemically produced hydroxyl (OH) radicals. Chemical-specific input parameters for EPIWIN modeling were: molecular weight 74.12 g/mol, vapor pressure 0.42 mm Hg, log K_{ow} 0.88, melting point –89.9°C, boiling point 117.6°C and aqueous solubility 77,000 mg/L. The second order rate constant was calculated as 6.89 E-12 cm^3/(molecule-sec) at 25°C. Based on 1.56E6 OH molecules/cm^3 and assuming 12 hours of sunlight per day, the estimated half-life was 1.552 days or 37 hours.
Reliability:	(2) valid with restrictions, calculated value

Reference: Meylan, W.M. and P.H. Howard. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere. 26: 2293-2299.
Meylan, W. and PH Howard. 2000a. User's Guide for AOPWIN, Version 1.90. EPIWIN (Estimation Program Interface for Windows) version 3.10. U.S. Environmental Protection Agency, 2000.

3.1.2 STABILITY IN WATER No Data Available.

3.1.3 STABILITY IN SOIL No Data Available.

3.2 MONITORING DATA (ENVIRONMENT)

Test substance: 1-Butanol
Indicate whether the data are measurements or background concentrations or measurements at contaminated sites:

air:	(ug/m ^{3})	in	as of 19
surface water:	(ug/l)	in	as of 19
ground water:	(ug/l)	in	as of 19
soil/sediment:	(ug/g)	in	as of 19
biota * :	(ug/g)	in	as of 19
food:	(ug/g)	in	as of 19

* (specify species)

Reference:

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.1.1 SEWAGE TREATMENT

Remark: Based on the biodegradability of n-butanol as measured in a 20 day BOD assay using unacclimated sewage seed of 68% ThOD in 5 days, 87% BOD in 10 days, and 92% after 15 days, n-butanol is expected to be easily biodegraded in municipal sewage treatment plants outfitted with at least secondary treatment (i.e., biological treatment).
Based on the aqueous solubility of 77,000 mg/L, negligible accumulation onto sewage sludge particles is expected.
Reference: Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. *J Water Pollution Control Federation* 46: 63-77.

3.3.1.2 DISTRIBUTION BETWEEN COMPARTMENTS

(A.) Type: Volatilization from surface waters
Test substance: 1-butanol

	Method:	Calculated using EPISUITE v3.10 (U.S. EPA, 2001)
	Result:	Half-life from model river: 39.51 days Half-life from model lake: 434.1 days
	Remark:	Based on Henry's law constant of 5.3 E-7 atm-m^3/mol, vapor pressure of 0.42 mm Hg, water solubility of 77,000 mg/L, and a molecular weight of 74.12 g/mole, and model defaults (for model river: river 1 m deep, water flow at 1 m/sec, wind speed of 5 m/sec; for model lake: 1 m deep, water flow 0.05 m/sec, wind speed 0.5 m/sec).
	GLP:	Not applicable
	Reliability:	(2) valid with restrictions, calculated values
	Reference:	EPISUITE v. 3.10, U.S. Environmental Protection Agency, April 2001.
(B.)	Type:	Soil or sediment partition coefficient (Koc)
	Test substance:	1-butanol (CAS no. 71-36-3)
	Method:	Calculated using EPISUITE v. 3.10 and PCKOCWIN v. 1.66 using structural features of the molecule
	Result:	2.44 L/kg
	GLP:	not applicable
	Reliability:	(2) valid with restrictions, calculated values
	Reference:	EPISUITE v. 3.10, U.S. Environmental Protection Agency, April 2001.
(C.)	Type:	Henry's Law Constant
	Test Substance:	1-butanol (CAS No. 71-36-3)
	Method:	Calculated using water solubility 77,000 mg/L, vapor pressure 0.56 hPa or 0.42 mm Hg, and molecular weight 74.12 g/mol.
	Result:	5.32 E-7 atm-m^3/mol
	GLP:	Not applicable
	Reliability:	(2) valid with restrictions, calculated values
	Reference:	Lyman, W.J., et al. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill, NY.
(D.)	Type:	Henry's Law Constant
	Test Substance:	1-butanol
	Method:	not specified
	Result:	5.57 E-6 atm m^3/mol
	References:	Howard, P.H. 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Volume II. Lewis Publishers, Chelsea, MI.

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Type:	Level III Fugacity-based distribution modeling
Test substance:	1-butanol (CAS No. 71-36-3)
Method	Level III fugacity based model, EPISUITE v. 3.10
GLP:	Not applicable
Remark:	Default values were assumed for environmental compartment descriptions, dimensions, and properties, advective and dispersive properties. Chemical-specific parameters were: molecular weight (74.12 g/mol), vapor pressure (0.56 hPa or 0.42 mm Hg), log Kow

(0.88), melting point –89.9°C, aqueous solubility 77,000 mg/L, boiling point of 117.6 °C, and a Henry's Law constant of 5.3 E-7 atm-m^3/mol. Half-lives calculated by the model based on the properties of the test substance were: water and soil half-lives 208 hr, and sediment half-life 832 hr. half-life in air was 30 hours and was based on a second-order rate constant for atmospheric hydroxy radical-mediated photo-oxidation of 8.57 E-12 cm^3/molecule-sec that was cited in EPISUITE (Kwok E, Atkinson R, 1994). No other information on the measured value was available, but was used by the model based on a 12 hour day and assuming 1.5 E+6 HO molecules/cm^3. Physical properties were the preferred values from the SIDS dossier.

Emissions were assumed to be only to air. Due to its uses as a solvent and manufacture with closed systems, essentially all releases will be through its uses. Releases to soil and water will be negligible, compared to air releases.

Distribution: Air (40.2%), Water (15.7%), Soil (44.1%), Sediment (>0.1%)
Source: EPISUITE v. 3.10, U.S. Environmental Protection Agency, April 2001.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABIITY IN ACTUAL USE

3.5 BIODEGRADATION

(A.) Preferred study

Type:	Aerobic biodegradation
Test Substance:	1-butanol (CAS No. 71-36-3)
Method:	APHA Standard Methods BOD (Standard Methods for the Examination of Water and Wastewater. 1971. 13th Ed. American Public Health Association, New York, NY) 20 day BOD (Biochemical Oxygen Demand) test Settled domestic wastewater (3 mL per bottle), unacclimated Three test chemical concentrations (3, 7, and 10 mg/L)
Results:	BOD5 = 6% ThOD (percent of theoretical oxygen demand) BOD10 = 87% ThOD BOD15 = 92% ThOD BOD20 = 92% ThOD
GLP:	No
Remark:	Readily biodegradable
Remark:	ThOD = 2.59 g/g
Remark:	(2) valid with restrictions, not all typical study information was provided. Reference: Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. *J Water Pollution Control Federation* 46: 63-77.

(B.)

Type:	aerobic
Inoculum:	saltwater w/raw sewage added (non-adapted)
Concentration:	3, 7, and 10 mg/L
Contact Time:	20 days
Degradation:	82% after 20 days
Results:	5 day = 45%, 10 day = 68%, 15 day = 71%, 20 days = 82%
Method:	BOD (Standard Methods for the Examination of Water and Wastewater. 1971. 13th Edi. American Public Health Association, New York, NY)
Year:	1971

	GLP:	no data available
	Test substance:	n-butanol
	Remark:	Synthetic seawater screening study.
	Reliability:	(2) valid with restrictions, not all typical study information was provided.
	Reference:	American Public Health Association. 1971. Standard Methods for the Examination of Water and Wastewater. 1971. 13th Edi., New York, NY) Price, K.S., G.T. Waggy, and R.A. Conway. 1974. Brine Shrimp Bioassay and Seawater BOD of Petrochemicals. J. Water Pollut. Contr. Fed. 46: 63-77.
(C.)	Test substance:	1-Butanol
	Test type:	aerobic [X] anaerobic [ ]
	Test medium:	unadapted municipal sludge
	Test method:	Not Stated.
	GLP:	YES [ ] NO [X]
	Test results:	36% of ThOD removed in 24 hrs.
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	Gerhold, R.M., Malaney, G.W. (1966) Structural determinants in the oxidation of aliphatic compounds by activated sludge. *J. Water Pollut. Control Fe*d., 38(4):562-579.
(D.)	Test substance:	1-Butanol
	Test type:	aerobic [X] anaerobic [ ]
	Test medium:	adapted municipal sludge
	Test method:	Not Stated.
	GLP:	YES [ ] NO [X]
	Test results:	44% of ThOD removed in 23 hrs.
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	McKinney, R.E., Jeris, J.S. (1955) Metabolism of low molecular weight alcohols by activated sludge. *Sewage Ind. Waste*s, 27(6):728-735.
(E.)	Test substance:	1-Butanol
	Test type:	aerobic [X] anaerobic [ ]
	Test medium:	fresh water
	Test method:	AFNOR Test
	GLP:	YES [ ] NO [X]
	Test results:	BOD_5 33% of ThOD.
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	Dore, M., Brunet, N., Legube, B. (1974) Participation de differérents composés organiques à la valeur des critè
(F.)	Test results:	BOD_{10} 87% of ThOD.
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	Union Carbide Corporation. 1992b. Ecological Effects Data on Carbide Products and Process Chemicals. South Charleston, WV. 25303. (6.12.92).

(G.) Test substance: 1-Butanol
Test type: aerobic [X]
anaerobic [ ]
Test medium: fresh water-unadapted seed
Test method: Modified APHA Test
GLP: YES [ ]
NO [X]
Test results: BOD_{20} 92% of ThOD.
Reliability: (2) valid with restrictions, not all study information available
Reference: Union Carbide Corporation. 1992b. Ecological Effects Data on Carbide Products and Process Chemicals. South Charleston, WV. 25303. (6.12.92).

(H.) Test substance: 1-Butanol
Test type: aerobic [X]
anaerobic [ ]
Test medium: adapted municipal sludge
Test method: ISO 8192
GLP: YES [ ]
NO [X]
Test results: EC_{10} 990 mg/l 30 min. test duration
Reliability: (2) valid with restrictions, not all study information available
Reference: BASF Corp. Internal Toxicology Report dated 9/10/91

3.6 BOD_5, COD OR RATIO BOD_5/COD

(A.) Test substance: 1-Butanol
Test type: aerobic [X]
anaerobic [ ]
Test medium: filtered, sewage effluent, unadapted seed
Test method: Standard dilution method (APHA Test Standard Method #219), 1971
GLP: YES [ ]
NO [X]
Test results: BOD_5 66% of ThOD (2.59 g/g).
Reliability: (2) valid with restrictions, full experimental details not presented
Reference: Bridie AL, Wolff CJM, Winter M. 1979. BOD and COD of some petrochemicals. Water Research 13: 627-630.

3.7 BIOACCUMULATION

(A.) Type: Bioconcentration Factor (BCF)
Test substance: 1-butanol (CAS No. 71-36-3)
Method: Calculated using EPISUITE v.3.10 and BCFWIN v.2.14 with a log K_{ow} of 0.88.
Result: 3.162 L/kg
GLP: Not applicable
Reliability: (2) valid with restrictions, calculated value
Reference: EPISUITE v.3.10, U.S. Environmental Protection Agency, April (2001).

3.8 ADDITIONAL REMARKS

4.0 ENVIRONMENTAL TOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(A.) Preferred value

Test Substance:	n-Butyl Alcohol
Method:	OECD 203, USEPA TSCA 40 CFR 797.1400
Year (guideline):	1992, 1994
Type (test type):	Static Fish Acute Toxicity Test
GLP:	Yes
Year (study performed):	1998
Species:	Fathead minnow *(Pimephales promelas)*
Analytical Monitoring:	Yes
Exposure Period:	96 Hours
Statistical Method:	(FT – ME)* Moving Average Method
Note:	Test solutions were prepared by diluting a 50-mg/mL stock solution of n-butyl alcohol (99.9% purity) with moderately hard, filtered [0.2 mm] well water to nominal concentrations of 389, 648, 1080, 1800, and 3000 mg/L. Stock solution was also prepared with well water. Test vessels were 19-L glass aquaria containing approximately 15 L (12-cm depth) of test solution. Two replicate test vessels were maintained for each treatment and control (dilution water) group. Vessels were covered and maintained in an environmental chamber for the test duration at 22 ±2 °C with a 16-hour light: 8-hour dark photoperiod (381 lux). Water samples for analytical verification were collected from each replicate of the control and treatments at test initiation and termination. Dissolved oxygen exceeded 60% saturation and pH ranged from 7.8 to 8.6. Temperature ranged from 22.2 to 22.8 °C. Dilution water total organic carbon was <1 mg C/L. Total hardness, alkalinity, acidity, and specific conductance of dilution water were 132 mg/L as CaCO3, 178 mg/L as CaCO3, 20 mg/L as CaCO3, and 310 mmhos/cm, respectively. Fish were obtained from in-house cultures. Twenty minnows (10 per replicate) were exposed to each test concentration and control (dilution water). Average length of 10 control fish at test termination was 25 mm (range: 21 to 28 mm). Average weight (blotted dry) was 0.34 g (0.16 to 0.50 g). Loading was 0.23 g fish/L in test vessels.
Results:	(FT - RS) 96-hour LC50 was 1376 mg/L (95% CL: 1216 and 1587 mg/L) based on mean measured concentrations
Reliability:	(1) Valid without restrictions
Reference:	Wong, D.C.L, P.B. Dorn, and J.P. Salanitro. 1998. Aquatic Toxicity of Four Oxy-Solvents. Equilon Enterprises, LLC Technical Information Record WTC-3520.

(B.)

Test substance:	1-Butanol
Test species:	Creek Chub *(Semotitus atromaculatus)*
Test method:	

	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	YES [ ] NO [X]
	Test results:	24Hr. LC_{50} 1000-1400 mg/l
	Comments:	
	Reliability:	(4) not valid, non-standard study duration
	Reference:	Gillette L.A., Miller D.L. and Redman H.E. Appraisal of a chemical waste problem by fish toxicity tests. *Sewage Ind. Wastes* 24(11):1397-1401, 1952.
(C.)	Test substance:	1-Butanol
	Test species:	Golden Orfe *(Leuciscus idus melanotu*s)
	Test method:	
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	No YES [ ] NO [X]
	Test results:	48 Hr. LC_{50} 1200 - 1770 mg/l
	Reliability:	(4) not valid, non-standard study duration
	Reference:	Juhnke I. and Lüedemann D. (1978) Results of the testing of 200 chemical compounds for acute toxicity in fish by the orfe test. *Z. Wasser- Abwasser-Forsch*., 11(5):161-164.
(D.)	Test substance:	1-Butanol
	Test species:	Goldfish *(Carassius auratu*s)
	Test method:	
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	No YES [ ] NO [X]
	Test results:	24 Hr. LC_{50} 1900mg/l
	Reliability:	(4) not valid, non-standard study duration
	Reference:	Bridie A.L., Wolff C.J.M. and Winter M. The acute toxicity of some petrochemicals to goldfish. *Water Res*., 13:623-626,1979.
(E.)	Test substance:	1-Butanol
	Test species:	Fathead Minnow *(Pimepheles promela*s)
	Test method:	Static test in Lake Superior Water or reconstituted laboratory water
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	Test results:	96 Hr. LC_{50} 1910 mg/l (Lake Superior water) 96 HR LC_{50} 1940 mg/L (reconstituted laboratory water)
	Reliability:	(2) valid with restrictions, not all study information available

	Reference:	Mattson V.R., Arthur J.W. and Walbridge C.T. Acute toxicity of selected organic compounds to fathead minnows. Duluth (MN.) EPA Environ. Res. Lab., EPA-600/3-76-097, 1976.
(F.)	Test substance:	1-Butanol
	Test species:	Fathead Minnow *(Pimepheles promelas)*
	Test method:	
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	YES [ ] NO [X]
	Test results:	96 Hr. LC_{50} 1400 mg/l
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	Union Carbide Corporation. 1992b. Ecological Effects Data on Carbide Products and Process Chemicals. South Charleston, WV. 25303. (6.12.92).
(G.)	Test substance:	1-Butanol
	Test species:	Fathead Minnow *(Pimepheles promelas)*
	Test method:	
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	YES [ ] NO [X]
	Test results:	96 Hr. LC_{50} 1730 mg/l
	Reliability:	(2) valid with restrictions, not all study information available
	Reference:	Brooke, L.T., D.J. Call, D.L Geiger, and C.E. Northcott. 1984. Acute Toxicities of Organic Chemicals to Fathead Minnows *(Pimephales promelas)*, Vol. I. Center for Lake Superior Environmental Studies, University of Wisconsin, Superior, WI.
(H.)	Test substance:	1-Butanol
	Test species:	Bleak *(Alburnus alburnus)*
	Test method:	
	Type of test:	static [X] semi-static [ ] flow-through [ ] Other (e.g., field test) [ ]
	GLP:	YES [ ] NO [X]
	Methods:	Six concentrations (not specified) plus a control were prepared using 10 fish in each of two replicates. Concentrations were not measured and pH was not controlled. Wild caught bleaks of about 8 cm were used and fed until 48-h before testing. Testing occurred in 70-liter aquaria with 60-liter natural brackish water pumped into the laboratory from a nearby bay on the Baltic Sea. Test water had a salinity of 7 ppth, alkalinity of 1.5 meqv/L and a pH of 7.8. DO was maintained at 5 mg/L or higher and the temperature was controlled at 10∀C. Lighting was 12 hr each light/dark. Mortality was recorded daily. Effect concentrations

were calculated using the graphical method described by Litchfield and Wilcoxon.
Test results: 96 Hr. LC_{50} 1730 mg/l
Reliability: (2) valid with restrictions, not all study information available
References: Bengtsson B. E., Renberg L., Tarkpea M. Molecular Structure and Aquatic Toxicity: an Example with C 1 -C 13 Aliphatic Alcohols. *Chemosphere* 13(5/6):613-622. 1984.

Linden E, Bengtsson B-E, Svanberg O, Sundstrom G. 1979. The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the Bleak (*Alburnus alburnus*) and the harpacticoid *Nitocra spinipes*. Chemosphere 11/12: 843-851.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. DAPHNIA

(A.) Preferred method
Test Substance: n-Butyl Alcohol
Method: OECD 202, USEPA TSCA 40 CFR 797.1300
Year (guideline): 1984, 1994
Type (test type): Static Daphnid Acute Toxicity Test
GLP: Yes
Year (study performed): 1998
Species: Water flea *(Daphnia magn*a)
Analytical Monitoring: Yes
Exposure Period: 48 Hours
Statistical Method: (FT – ME)* Binomial probability with non-linear interpolation
Test Conditions: (FT – TC)
Note: Test solutions were prepared by diluting a 50-mg/mL stock solution of n-butyl alcohol (99.9% purity) with moderately hard, filtered [0.2 mm] well water to nominal concentrations of 156, 259, 432, 720, 1200, and 2000 mg/L. Stock solution was also prepared with well water. Test vessels were 250-mL beakers containing approximately 200 mL (7.8-cm depth) of test solution. Two replicate test vessels were maintained for each treatment and control (dilution water) group. Vessels were covered to prevent evaporation and placed in a water bath at 20±1°C with a 16-hour light: 8-hour dark photoperiod (391 lux).

Water samples for analytical verification were collected from each replicate of the control and treatments at test initiation and termination.

Dissolved oxygen exceeded 60% saturation and pH ranged from 8.2 to 8.5. Temperature ranged from 19.4 to 19.7 °C. Dilution water total organic carbon was <1 mg C/L. Total hardness, alkalinity, and specific conductance of dilution water were 128 mg/L as CaCO3, 180 mg/L as CaCO3, and 300 mmhos/cm, respectively.

		Daphnids were obtained from in-house cultures. Adult organisms were held for at least 16 days prior to collection of neonates for testing. Twenty daphnids (10 per replicate) <24 hours old were exposed to each test concentration and control (dilution water).
	Results: (FT - RS)	48-hour EC50 was 1328 mg/L (95% CL: 1123 and 1925 mg/L) based on mean measured concentrations. Some organisms appeared lethargic in the 675 mg/L test solution after 48 hours and in the 1123 mg/L treatment after 21, 24, and 48 hours. All surviving organisms exposed to 1925 mg/L appeared lethargic at the 21 and 24-hour observations.
	Reliability:	(1) valid without restriction
	Reference:	Wong, D.C.L, P.B. Dorn, and J.P. Salanitro. 1998. Aquatic Toxicity of Four Oxy-Solvents. Equilon Enterprises, LLC Technical Information Record WTC-3520.
(B.)	Test substance:	1-Butanol
	Test species:	Water flea *(Daphnia magn*a)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	48 Hr. EC_{50} 2337 mg/L 48 Hr. EC_{50} 1983 mg/L
	Reliability:	(2) valid with restrictions, full experimental data not presented
	Reference:	Kuehn, R., M. Pattard, K.D. Pernak, and A. Winter. (1989). Results of the Harmful Effects of Water Pollutants to *Daphnia Magna* in the 21 Day Reproduction Test. *Water Res* 23(4):495-499.
(C.)	Test substance:	1-Butanol
	Test species:	Water flea *(Daphnia magn*a)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	24 Hr. EC_{50} 1880 mg/l
	Reliability:	(4) not valid, non-standard study durationReference: Bringmann G., Kuehn R. (1982). Findings concerning the harmful effect of water pollutants on *Daphnia magna* in an advanced standardized test procedure. *Z. Wasser Abwasser Forsc*h.,15(1):1-6.
(D.)	Value:	615 mg/L
	Remark:	An acute daphnid 48-h LC_{50} was calculated using ECOSAR, from the U.S. EPA. The preferred physical properties were used. The SAR for esters was employed. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR. Chemical-specific input parameters were: molecular weight (74.12 g/mol), vapor pressure (0.56 hPa or 0.42 mm Hg), log K_{ow} (0.88), melting point -89.9° C, aqueous solubility 77,000 mg/L,

boiling point of 117.6° C, and a Henry's Law constant of 5.3 E-7 atm-m^3/mol.

Reliability: (2) valid with restriction, calculated value

Reference: EPA's ECOSAR model (v. 0.99f). EPISUITE v.3.10, U.S. Environmental Protection Agency, April (2001).

B. OTHER

(A.) Test substance: 1-Butanol

Test species: *Nitocra spinipes* (Harpacticoid copepod)

Test method:

Type of test: static [X]
semi-static [ ]
flow-through [ ]
other (e.g., field test) [ ]

GLP: YES [ ]
NO [X]

Methods: Six concentrations (not specified) plus a control were prepared using 10 copepods in each of two replicates. Concentrations were not measured and pH was not controlled. Testing occurred in 15 mL test tubes with 10 mL filtered natural brackish water pumped into the laboratory from a nearby bay on the Baltic Sea. Test water had a salinity of 7 ppth, alkalinity of 1.5 meqv/L and a pH of 7.8. DO was maintained at 5 mg/L or higher and the temperature was controlled at 10∀C. Lighting was 12 hr each light/dark. Mortality was recorded at 96 hours using a microscope. Effect concentrations were calculated using the graphical method described by Litchfield and Wilcoxon.

Test results: 96-hr. LC_{50} = 1900 to 2300 mg/l

Reliability: (2) valid with restrictions, full experimental details not presented

References: Bengtsson B. E., Renberg L., Tarkpea M. Molecular Structure and Aquatic Toxicity: an Example with C 1 -C 13 Aliphatic Alcohols. *Chemosphere* 13(5/6):613-622. 1984.

Linden E, Bengtsson B-E, Svanberg O, Sundstrom G. 1979. The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the Bleak (*Alburnus alburnus*) and the harpacticoid *Nitocra spinipes*. Chemosphere 11/12: 843-851.

(B.) Test substance: 1-Butanol

Test species: *Artemia salina* (Brine Shrimp)

Test method: Not Stated

Type of test: static [X]
semi-static [ ]
flow-through [ ]
other (e.g., field test) [ ]

GLP: YES [ ]
NO [X]

Test results: 24-hr. LC_{50} = 2950 mg/l

Reliability: (2) valid with restrictions, full experimental data not available

Reference: Price, K.S., Waggy, G.T., Conway, R.A. (1974) Brine Shrimp Bioassay and Seawater BOD of Petrochemicals. *J. Water Pollut. Control Fe*d.,46(1):63-77.

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

(A.) Preferred Value

Test Substance: n-Butyl Alcohol
Method: OECD 201, USEPA TSCA 40 CFR 797.1050
Year (guideline): 1984, 1994
Type (test type): Static Algal Toxicity Test
GLP: Yes
Year (study performed): 1998
Species: Freshwater green alga *(Selenastrum capricornutu*m)
Analytical Monitoring: Yes
Exposure Period: 96 Hours
Statistical Method: (FT -ME)*Linear interpolation for EC values, Dunnett's test for NOAEC
Test Conditions: (FT – TC)Test solutions were prepared by diluting a 50-mg/mL stock solution of n-butyl alcohol (99.9% purity) with laboratory-prepared algal nutrient medium to nominal concentrations of 125, 250, 500, 1000, and 2000 mg/L. Stock solution was also prepared with nutrient medium. Test vessels were sterile, 250-mL Erlenmeyer flasks plugged with foam stoppers and contained 100 mL of test or control (nutrient medium) solution. Vessels were continuously shaken mechanically at 100 rpm. Three replicate vessels were maintained for each treatment and control group. Initial cell density was 1.0 x 10 4 cells/mL (nominal). Samples were collected from each replicate test vessel at each 24-hour interval and held at 4°C until cell density measurement. Cell counts were obtained using an electronic particle counter (Coulter Electronics, Inc.). Cell densities were used to calculate growth inhibition values and effects concentrations (EC10, EC50, and EC90) relative to the control. Algal growth inhibition was differentiated as algicidal or algistatic effects at test termination by subculturing test solutions with maximally inhibited growth to fresh nutrient medium for a 9-day recovery period.

Water samples for analytical verification were collected at test initiation from the preparation vessels of each treatment and the control. Samples collected at test termination were a composite of the replicates for each treatment and the control and were filtered to remove the algae prior to analysis.

Temperature ranged from 23.2 to 25.3 °C. Light was continuous at 4240 to 4568 lux. Measurements of pH 7.4 at test initiation and ranged from 6.8 to 7.7 at 96 hours.

Original algal cultures were obtained from UTEX – The Culture Collection of Algae at the University of Texas at Austin and were maintained in culture medium for at least two weeks prior to testing.

Based on Day 0 measured n-butyl alcohol concentrations:
96-hour EC_{10} = 134 mg/L (95% CL: 124 - 167 mg/L)
96-hour EC_{50} = 225 mg/L (95% CL: 204 - 246 mg/L)
96-hour EC_{90} = 717 mg/L (95% CL: 586 - 809 mg/L)

96-hour growth rate inhibition:

Day 0 Measured Concentration (mg/L)	96-hour % Inhibition	96-hour Cell Density
Control	--	4,206,362
129	7.7	3,883,813
241	57	1,808,913*
491	83	732,225*
1010	100	15,521*
1980	100	15,754*

*

Indicates significant difference from control using Dunnett's test ($p \leq 0.05$)

Changes in cell density indicated that exponential growth occurred in the control replicates. The coefficient of variation for the control replicates was 8.5%.

Algal cells in 1980 mg/L (2000 mg/L nominal) resumed normal growth after 9 days. Effects on algal growth were considered algistatic.

Measured concentrations of test solutions at test initiation ranged from 97 to 103% of nominal values. Measured concentrations after 96 hours ranged from <LOQ to 73% of nominal.

n-Butyl Alcohol concentrations in test chambers were determined using a Hewlett-Packard Model 5890 Gas Chromatograph with flame ionization detector.

Reliability: (1) Reliable without restriction. OECD endpoints were not determined.

Reference: Wong, D.C.L, P.B. Dorn, and J.P. Salanitro. 1998. Aquatic Toxicity of Four Oxy-Solvents. Equilon Enterprises, LLC Technical Information Record WTC-3520.

(B.) Test substance: 1-Butanol
Test species: *Scenedesmus subspicatus (Green* Algae)
Test method: DIN Test Method 38412 Part 9
GLP: YES [ ]
NO [X]
Test results: 96 Hr. EC_{10} >500 mg/l
96 Hr. EC_{50} >500 mg/l
96 Hr. EC_{90} >500 mg/l

Reliability: (2) valid with restrictions, full experimental data not presented
Reference: BASF Corp. Internal Report dated 9/19/91

(C.)	Test substance:	1-Butanol
	Test species:	*Scenedesmus quadricauda* (Green Algae)
	Test method:	Cell Multiplication Inhibition Test
	GLP:	YES [ ] NO [X]
	Test results:	875 mg/l
	Reliability:	(4) not valid, non-standard study duration
	Remark:	Maximum concentration at which no effect was observed within the period of the test. 8-day NOAEL (Total Biomass)
	Reference:	Bringmann G., Kühn R. Comparison of the Toxicity Thresholds of Water Pollutants to Bacteria, Algae and Protozoa in the Cell Multiplication Inhibition Test. *Water Research* 14:231-241. 1980.
(D.)	Test substance:	1-Butanol
	Test species:	*Microcystis aeruginosa* (Blue-Green Algae)
	Test method:	Cell Multiplication Inhibition Test
	GLP:	YES [ ] NO [X]
	Test results:	100 mg/l*
	Remark:	Maximum concentration at which no effect was observed within the period of the test. 8-day NOAEL (Total Biomass)
	Reliability:	(4) not valid, unknown study duration
	Reference:	Bringmann G., Kühn R. *Gwf-Wasser/Abwasser* 117(9), 1976. as cited in: Verschueren K. Handbook of Environmental Data on Organic Chemicals 2nd Ed. 1983. Van Nostrand Reinhold Co. Inc. NY.NY p. 301 Reference No.329.
(E.)	Test substance:	1-Butanol
	Test species:	*Chlorella pyrenoidosa* (Green Algae)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	EC_{50} = 8500 mg/l (chlorophyll content).
	Remark:	Maximum concentration at which no effect was observed within the period of the test.
	Reliability:	(4) not valid, unknown study duration
	Reference:	Jones H. R., Environmental Control in the Organic and Petrochemical Industries. Noyes Data Corp. 1971.
(F.)	Value:	361 mg/L
	Remark:	An acute 96-h EC50 for green algae was calculated using ECOSAR, from the USEPA. The preferred physical properties were used. The SAR for esters was employed. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR. Chemical-specific input parameters were: molecular weight (74.12 g/mol), vapor pressure (0.56 hPa or 0.42 mm Hg), log K_{ow} (0.88), melting point -89.9° C, aqueous solubility 77,000 mg/L, boiling point of 117.6° C, and a Henry's Law constant of 5.3 E-7 atm-m^3/mol.
	Reliability:	(2) valid with restriction, calculated value

Reference: EPA's ECOSAR model (v. 0.99f). EPISUITE v.3.10, U.S. Environmental Protection Agency, April (2001).

4.4 TOXICITY TO MICROORGANISMS

(A.) Test substance: 1-Butanol
Test species: *Pseudomonas putida*
Test method:
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: 16 hour TT = 650 mg/l Total Biomass
Reliability: (2) valid with restrictions, full study details not availableReference: Bringmann G., Kühn R. Comparative Findings Concerning the Harmful Effects of Water Pollutants on Bacteria *Pseudomonas Putida* and Blue-Green Algae *Microcystis Aeruginosa. GWF-Z. Wasser Abwasser* , 117(9):410-413. 1976.

(B.) Test substance: 1-Butanol
Test species: *Bacillus subtilis*
Test method:
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: EC_{50} = 1258 mg/l Spore germination
Reliability: (2) valid with restrictions, full study details not available
Reference: Yasuda-Yasaki Y., Namike-Kanie S. and Hachisaku Y. Inhibition of Germination of *Bacillus Subtilis* Spores by Alcohols. *Spores* 7:13-16. 1976.

(C.) Test substance: 1-Butanol
Test species: *Bacillus subtilis*
Test method:
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: * 7400 mg/l
Comments: * No inhibition of degradation by methane culture on acetate substrate.
Reliability: (2) valid with restrictions, full study details not available
Reference: Chou W.L., Speece R.E., Siddiqie R.H. and McKeon K. The Effect of Petrochemical Structure on Methane Fermentation Toxicity. *Prog. Water Technol.* 10(5/6):545-558. 1978.

(D) Test substance: 1-Butanol
Test species: Flagellates *Entosiphon sulcatum*
Test method: 72 hours, total biomass production
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: TT5 = 55 mg/L
Reliability: (2) valid with restrictions, full study results not available
Reference: Bringmann, G. 1978. Determination of the biological effect of water pollutants on protozos. Part II. Bacteriovorous flagellates

(model organism: *Entosiphon sulcatum* Stein). *Z. Wasser Abwasser Forsc*h., 11: 210-215.

(E) Test substance: 1-Butanol
Test species: Ciliate protozoa, *Uronema parduczi*
Test method: 20 hours, 25∀C, cell growth inhibition
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: TT5 = 8.0 mg/L
Reliability: (2) valid with restrictions, full study results not available
Reference: Bringmann, G. and R. Kuehn. 1980. Determination of the biological effect of water pollutants on protozoa. Part II. Bacteriovorous ciliates. *Z. Wasser Abwasser Forsc*h.,13: 25-31.

(F) Test substance: 1-Butanol
Test species: Saprozoic flagellates, *Chilomonas paramaecium*
Test method: 48 hours, 20∀C, cell growth inhibition
Type of test: Other (e.g., field observation) [X]
GLP: YES [ ]
NO [X]
Test results: TT5 = 28 mg/L
Reliability: (2) valid with restrictions, full study results not available
Reference: Bringmann, G. and R. Kuehn. 1980. Determination of the biological effect of water pollutants on protozoa. Part III. Saprozoic flagellates. *Z. Wasser Abwasser Forsc*h.,13: 170-173.

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

No Data Available.

4.5.1 CHRONIC TOXICITY TO FISH

(A.) Value: 72 mg/L
Remark: A chronic fish 30-d LC_{50} was calculated using ECOSAR, from the USEPA. The preferred physical properties were used. The SAR for esters was employed. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR. Chemical-specific input parameters were: molecular weight (74.12 g/mol), vapor pressure (0.56 hPa or 0.42 mm Hg), log K_{ow} (0.88), melting point -89.9° C, aqueous solubility 77,000 mg/L, boiling point of 117.6° C, and a Henry's Law constant of 5.3 E-7 atm-m^3/mol.
Reliability: (2) valid with restriction, calculated value
Reference: EPA's ECOSAR model (v. 0.99f). EPISUITE v.3.10, U.S. Environmental Protection Agency, April (2001).

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Value: 21 mg/L
Remark: A chronic daphnid 16-d LC_{50} was calculated using ECOSAR, from the USEPA. The preferred physical properties were used. The SAR for esters was employed. The structure was determined from the CAS RN as stored in the accompanying

database of SMILES notations within ECOSAR. Chemical-specific input parameters were: molecular weight (74.12 g/mol), vapor pressure (0.56 hPa or 0.42 mm Hg), log K_{ow} (0.88), melting point -89.9° C, aqueous solubility 77,000 mg/L, boiling point of 117.6° C, and a Henry's Law constant of 5.3 E-7 atm-m^3/mol.

Reliability: (2) valid with restriction, calculated value
Reference: EPA's ECOSAR model (v. 0.99f). EPISUITE v.3.10, U.S. Environmental Protection Agency, April (2001).

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

No Data Available.

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

(A.) Test substance: 1-Butanol
Test species: *Lactuca sativa* (Lettuce)
Test method:
GLP: YES [ ]
NO [X]
Test results: EC_{50} = 390 mg/l seed germination
Reliability: (2) valid with restrictions, full study details not available
Reference: Reynolds, T. 1977. Comparative Effects of Aliphatic Compounds on Inhibition of Lettuce Fruit Germination. *Ann. Bot.* 41(173):637-648. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

(B.) Test substance: 1-Butanol
Test species: *Cucumis sativus* (Cucumber)
Test method:
GLP: YES [ ]
NO [X]
Test results: EC_{50} = 2500 mg/l seed germination
Reliability: (2) valid with restrictions, full study details not available
Reference: Smith, C.W. and Siegel, S.M. 1975. Differential Permiation of *Artemia* Cysts and Cucumber Seeds in Alcohols. *J. Histochem. Cytoche*m.., 23(1): 80-83. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

(C.) Test substance: 1-Butanol
Test species: *Avena sativa* (Oat Seedling)
Test method:
GLP: YES [ ]
NO [X]
Test results: Beneficial effects - reduced senescence in leaves and prevented proteolysis.
Reliability: (2) valid with restrictions, full study details not availableReference: Satler, S.D., and Thimann, K.V. 1980.

The Influence of Aliphatic Alcohols on Leaf Senecences. *Plant Physio*l., 66: 395-399. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

4.6.3 TOXICITY TO OTHER NON-MAMMALIAN TERESTRIAL SPECIES (INCLUDING BIRDS)

(A.)	Test substance:	1-Butanol
	Test species:	Wild Bird (species not stated)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	Oral LD_{50} = 2500 mg/kg
	Reliability:	(2) valid with restrictions, full study details not available
	Reference:	RTECS, 1990 as cited in: Information Profile. TSCA Inter-agency Testing Committee. U.S. EPA/OPPT (TS-792) 401 M Street, SW, Washington, DC. 20460 dated 21 Sept. 1993.

(B.)	Test substance:	1-Butanol
	Test species:	*Sturnus vulgaris* (European Starling)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	Oral LD_{50} = <2500 mg/kg-day
	Comments:	No toxic effects noted.
	Reliability:	(2) valid with restrictions, full study details not available
	Reference:	Schafer, E.W. Jr., W.A. Bowles, Jr., and J. Hurlbut. 1983. The Acute Oral Toxicity, Repellancy, and Hazard Potential of 998 Chemicals to One or More Species of Wild and Domestic Birds. *Arch. Environ. Contam. Toxicol.* 12:355-382.

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

4.8 BIOTRANSFORMATION AND KINETICS No Data Available.

4.9 ADDITIONAL REMARKS

5.0 MAMMALIAN TOXICITY

5.1 TOXICODYNAMICS, TOXICOKINETICS

(A.)	Test Substance:	n-Butyl Acetate
	Species:	rat
	Strain:	Sprague-Dawley
	Sex:	male
	Route of Admin:	intravenous
	Exposure Period:	Bolus injection into indwelling catheter
	Freq. of Treatment:	Single
	Duration of Test:	Intravenous blood sampling occurred from immediately post dosing until approximately 6 hours after bolus injection
	Exposure Concentration:	0.28 mmol/Kg
	Control Group:	yes, concurrent vehicle
	Method:	Preliminary studies were conducted to select dose levels, dose formulations, and sampling times for the definitive studies. N-Butyl acetate in saline with 1% Tween 20 was administered individually to five animals via an indwelling femoral vein catheter. Serial blood samples were collected from an indwelling jugular vein catheter and immediately deproteinized to halt enzymatic activity. Concentrations of n-butyl acetate as well as down stream metabolites (n-butanol, n-butyraldehyde, n-butyric acid) were assayed by an internal standard GC-MS selected ion monitoring method.
	Year:	2001
	GLP:	yes
	Result:	Following intravenous administration of n-butyl acetate, target blood collection times were 0, 0.5, 1.0, 1.5, 2.5, 5, 10, and 30 minutes post dosing. Analysis of these blood samples demonstrated a very rapid hydrolysis of n-butyl acetate to form n-butanol. Peak n-butyl acetate levels were found at 0.5 minutes, the earliest time point tested. N-Butyl acetate levels were at or below the limit of quantitation by ten minutes. Peak levels of n-butanol was found at the one minute sampling time and n-butanol was already present in the 0.5 minute sample. n-Butyric acid was also found in the initial 0.5 minute sample and peak levels were noted at the 1 minute time point. This study demonstrate a very rapid hydrolysis of n-butyl acetate, with a half-life measured in seconds. It also demonstrates the rapid appearance and disappearance of the down stream metabolites, n-butanol and n-butyric acid. This study also includes data from direct intravenous injections of n-butanol, n-butyraldehyde, and n-butyric acid. The data from this study was used to support the development of a physiologically-based pharmacokinetic (PBPK) model for the butyl series of compounds. The use of this model in quantitative risk assessment for the butyl series of compounds has been demonstrated in the publication; Barton, et al., (2000) Family Approach for Estimating Reference Concentrations/Doses for Series of Related Organic Chemicals. Toxicol. Sci. 54, 251-261.
	Reference:	Deisinger, P.J. and English, J.C. Pharmacokinetics of n-Butyl Acetate and Its Metabolites in Rats After Intravenous Administration. Toxicological Health Sciences Laboratory,

Health and Environment Laboratory, Eastman Kodak Company, Rochester, NY. Report TX-2000-277, for the Oxo-Process Panel, CHEMSTAR, American Chemistry Council, Arlington, VA, Ref. OXO-49.0-Kodak-Butyl Acetate, as presented in Deisinger, et al., Family Approach PBPK Modelling of n-Butyl Acetate and Its Metabolites in Male Rats, Abstract #699, The Toxicologist, Vol. 60, No. 1, March 2001.

(B.) Test substance: n-Butyl Acetate, n-Butanol, n-Butyraldehyde, n-Butyric Acid
Test species/strain:
Test Method: n-Butyl alcohol (BA) is considered to belong to a category of similar butyl compounds that are part of a metabolic series. A "family" approach has been developed for n-butyl acetate (BAA) and its primary metabolites, which include BA, butyraldehyde, and butyric acid. This approach is based upon a consideration of issues related to four factors: (1) exposure, (2) tissue dosimetry, (3) mode of action, and (4) response. Because BAA is rapidly metabolized to form BA, organisms exposed to BAA can experience appreciable tissue concentrations of BA. In this way, information from toxicity studies for BAA inherently provides information on the toxicity of BA. For this reason, BAA toxicity information is used to supplement some of the information for BA presented in this document.
Test Results:
GLP: YES [ ]
NO [X]
Comments: It should be noted that the "family" approach is only appropriate for endpoints directly related to the systemic blood levels of the "family" members (i.e. the parent compound and its metabolites). It is not relevant for all routes of exposure, site-of-contact effects, or any endpoints dependent upon the physical-chemical properties of the material.
Reference: Barton HA, Deisinger PJ, English JC, Gearhart JN, Faber WD, Tyler TR, Banton MI, Teeguarden J, Andersen ME. 2000. Family approach for estimating reference concentrations/doses for series of related organic chemicals. Toxicol. Sci. 54(1), 251-261.

(C.) Test substance: 1-Butanol
A number of animal studies have demonstrated that 1-butanol is readily absorbed through the lungs, skin and intestinal tract and is primarily eliminated after metabolism by alcohol and aldehyde dehydrogenases.
No further information available.
Reference: Gaillard, D. and R. Derache: Trav. Soc. Pharmacol. Montpellier 25: 51-62, 1965. As cited in: *The International Programme on Chemical Safety. Environ-mental Health Criteria 65. Butanols-Four Isomers: 1-Butanol, 2-Butanol, tert-Butanol , Isobutano*l. World Health Organization. Geneva,1987. p.21. (ISBN 92 4 154265 9).

(D.) Test substance: 1-Butanol
Test species/strain: Charles River CD rat and beagle dog
Test method: 1-{1-^{14}C)Butanol was mixed with corn oil and administered by gavage to male rats at doses of 4.5, 45 or 450 mg/kg of body

weight. Dogs were exposed to 50 ppm 1-Butanol vapor for 6 hrs. Using a absorption cell taped to the thorax, dogs were exposed to 1-{1-^{14}C)Butanol for 60 min.

GLP: YES [ ]
NO [X]

Test results: Rats dosed at 450 mg/kg excreted 83% of the dose as $^{14}CO_2$ at 24 hrs. 4.4% of the dose was excreted in the urine. 1% was eliminated in the feces and 12% remained in the carcass. Rats dosed at 4.5 or 45 mg/kg exhibited a similar pattern of excretion. 1-{1-^{14}C) Butanol was absorbed through the skin of dogs at a rate of 8.8 µg min^{-1} cm^{-2}. Dogs exposed to 1-Butanol vapor absorbed about 55% of the inhaled vapor. However, the elimination of 1-Butanol in the postexposure breath was relatively low compared to the quantity absorbed during the exposure.
No further information available.

Reference: DiVincenzo GD., Hamilton ML. Fate of N-Butanol in rats after oral administration and its uptake by dogs after inhalation or skin application. *Toxicology and Applied Pharmacology.* 48:317-325 1979.

(E.) Test substance: 1-Butanol
Test species/strain: rat
Test method: oral
GLP: YES [ ]
NO [X]

Test results: After an oral dose of 2000 mg/kg bw, the maximum blood-alcohol concentration was 500 mg/l after 2 hrs. the concentration dropped to 150 mg/l after 4 hrs., and only 0.03% of the dose was excreted in the urine after 8 hrs.
No further information available.

Reference: Gaillard D. and Derache R.: Trav. Soc. Pharmacol. Montpellier 25:51-62, 1965. As cited in: *The International Programme on Chemical Safety. Environmental Health Criteria 65. Butanols-Four Isomers: 1-Butanol, 2-Butanol,tert-Butanol , Isobutanol.* World Health Organization. Geneva,1987. p.21. (ISBN 92 4 154265 9).

(F.) Test substance: 1-Butanol
Test species/strain: Human
Test method: inhalation
GLP: YES [ ]
NO [X]

Test results: Twelve human volunteers were exposed for 2 hrs. to 1-butanol at 300 or 600 mg/m3 in inspired air during rest and during exercise (50, 100 or 150 w) on a bicycle ergometer. At the highest dose level, the difference between levels in inspired and expired air indicated an uptake of 47% 1-butanol at rest and 37, 40 and 41% at 50, 100 and 150 w, respectively. After 30 min. exposure to 300 or 600 mg/m3, the 1-butanol concentrations in the arterial blood were 0.3 and 0.5 mg/liter, respectively. The combination of an apparently high uptake and low concentrations in arterial blood is probably because 1-butanol is dissolved in the water of the dead space mucous membranes.

Reference: Astrand I. et al.: Scand. J. Work Environ. Health 3:165-175, 1987. As cited in: *The International Programme on Chemical Safety*. *Environmental Health Criteria 65. Butanols-Four Isomers: 1-Butanol, 2-Butanol, tert-Butanol Isobutano*l. World Health Organization. Geneva,1987. p.21. (ISBN 92 4 154265 9).

5.2 ACUTE TOXICITY

5.21 ACUTE ORAL TOXICITY

(A.)

Test substance:	1-Butanol, Union Carbide sample procured 12/20/48 from Fellowship 155.
Method:	Method/guideline followed: Internal Union Carbide method (gavage). Thompson's method of calculating median-effective dose.
Test type:	Acute oral by gavage
GLP:	YES [ ] NO [X]
Year performed:	12/48 – 1/49
Species/strain:	Rat, albino Sherman
Sex:	Female, 5-6 weeks old, 90-120 grams.
Number of animals/ sex/dose:	10 females/dose
Vehicle:	20% dispersion of n-butanol in 1% Tergitol 7.
Route of admin.:	orally in liquid.
Results	LD_{50} = 4.36 (3.98 to 4.78) g/kg Number of deaths at each dose level: 10/10 at 6.3 g/kg. 8/10 at 5.0 g/kg. 3/10 at 3.98 g/kg. 0/10 at 3.16 g/kg.
Comments:	After 6.3 g/kg dose, six rats died on day 0 and four rats died on day 1. After 5.0 g/kg dose, four rats died on day 0 and four rats died on day 1. After 3.98 g/kg dose, one rat died on day 0, one rat died on day 1, and one rat died on day 3. After 3.16 g/kg dose, all ten rats survived for the total observation period of 14 days. 11, 9, and 1 deaths occurred on days 0, 1, or 3, respectively. Narcosis and prostration preceded death. It could not be determined from the study report whether narcosis was observed at the lowest dose tested. T he higher doses produced hemorrhage of the stomach and intestinal irritation. Livers were congested and kidneys pale.
Data quality:	Reliability: Key study. Klimisch quality 2.
References:	Union Carbide Corp. Bushy Run Research Center, Project Report No.14-73. Export, PA. 1951.

(B.)

Test substance:	1-Butanol, Union Carbide undiluted sample.
Method:	Method/guideline followed: Internal Union Carbide method (intubation). The moving average method of calculating median-effective dose was used based upon a 14-day observation period.

	Test type:	Acute oral by gavage.
	GLP:	YES [ ] NO [X]
	Year performed:	Not specified.
	Species/strain:	Rat, Harlan Wistar.
	Sex:	Female, 60 days old, 180-260 grams.
	Number of animals/ sex/dose:	Not specified.
	Vehicle:	None
	Route of admin.:	Orally as neat (undiluted) liquid.
	Results:	LD_{50} = 2.83 ml/kg = 2.290 g/kg = 2290 mg/kg Number of deaths at each dose level: Not specified.
	Comments:	Dosage levels differed by a factor of 2 in a geometric series.
	Data quality:	Reliability: Key study. Klimisch quality 2.
	References:	Union Carbide Corp. Bushy Run Research Center, Project Report No. 29-126. Export, PA. 1966.
(C.)	Test substance:	Identity: 1-Butanol.
	Method:	Method/guideline followed: FDA method. LD_{50}'s were computed by the method of Litchfield & Wilcoxon.
	Test type:	Acute oral toxicity by gavage.
	GLP:	YES [ ] NO [X]
	Year performed:	Not specified.
	Species/strain:	Rat, adult Osborne-Mendel.
	Sex:	Male and female, evenly divided.
	Number of animals/ sex/dose:	5/sex/dose.
	Vehicle: None.	
	Route of admin.:	Orally by gavage as a neat (undiluted) liquid. Animals were fasted approximately 18 hours prior to administration.
	Results:	LD_{50} = 2.51 (2.22 to 2.84) g/kg
	Comments:	Observation period was 14 days postdosing. Symptoms included depression and coma. Mortality occurred between 4 and 18 hours postdosing.
	Data quality:	Reliability: Klimisch quality 2.
	References:	Jenner, P.M., Hagan, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. 1964. Food flavourings and compounds of related structure. 1. Acute oral toxicity. Fd. Cosmet. Toxicol. 2: 327-343.
(D.)	Test substance:	1-Butanol
	Test species/strain:	Rat, male and female (unspecified strain)
	Test method:	single dose, stomach tube
	GLP:	YES [ ] NO [X]
	Test results:	LD_{50} = 2.02 g/kg, male *LD_{50} = 0.79 g/kg, female
	Comments:	* The 95% confidence intervals overlapped, indicating that the LD_{50}'s were not significantly different for male or female.
	Reference:	Purchase I.H.F. Studies in Kaffir Corn Malting and Brewing. XXII. The Acute Toxicity of Some Fusel Oils Found in Bantu Beer. *So. Afr. Med. Jo*r. 43(25):795-798. 1969.
(E.)	Test substance:	1-Butanol

	Test species/strain:	Mouse (unspecified strain)
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	LD_{50} = 2.68 g/kg
	Comments:	
	Reference:	Rumyanstev A.P., Lobanova I.YA., Tiunova L.V. and Chernikova V.V. Toxicology of Butyl Alcohol. *Khim. Prom.-st. Ser. Toksikol. Sanit. Khim. Plastmas*s. 2:24-26. 1979.
(F.)	Test substance:	1-Butanol
	Test species/strain:	Rabbit (unspecified strain)
	Test method:	single dose, stomach tube
	GLP:	YES [ ] NO [X]
	Test results:	LD_{50} = 3.5 g/kg 24-Hr. *ND_{50} = 0.8 g/kg
	Comments:	* ND_{50} is the quantity that caused narcosis in half the rabbits.
	References:	Munch J.C. Aliphatic Alcohols and Alkyl Esters: Narcotic and Lethal Potencies to Tadpoles and to Rabbits. *Ind. Med. Surg.* 41(4):31-33. 1972. Munch J.C. and Schwarze E.W. Narcotic and Toxic Potency of Aliphatic Alcohols upon Rabbits. *Jor. Lab. Clin. Med.* 10:985-996. 1925.
(G.)	Test substance:	1-Butanol
	Test species/strain:	Golden hamster
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	* LD_{50} = 1.2 g/kg
	Comments:	* 95% confidence limits 0.6-2.3 g/kg
	Reference:	Dubina O.N. and Maksimov G.G. Testing the use of Golden Hamsters in Toxicological Research. *Gig. Tr. Ohkhr. Zdorov'ya Rab. Neft. Neftekhim. Prom-sti.* 9:100-103. 1976.
(H.)	Test substance:	1-Butanol
	Test species/strain:	Dog
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	LD_{50} = 2.2 ml/kg = 1.782 g/kg = 1782 mg/kg
	Comments:	LD_{50} = The minimum fatal dose.
	Reference:	Von Oettingen W.F. The aliphatic alcohols, their toxicity and potential dangers in relation to their chemical constitution and their fate in metabolism. U.S. Public Health Service., *Public Health Bulletin., No. 281.* U.S.Government Printing Office., Washington D.C. 1943.

5.2.2 ACUTE INHALATION TOXICITY

(A.)	Test substance:	1-Butanol, Union Carbide sample procured 12/20/48 from Fellowship 155.
	Method:	Method/guideline followed: Internal Union Carbide method for inhalation exposure.

	Test type:	Acute inhalation.
	GLP:	YES [ ] NO [X]
	Year performed:	Not specified.
	Species/strain:	Rat, albino Sherman
	Sex: Female.	
	Number of animals/ sex/dose:	6 females/dose x one dose (saturation – calculated saturated vapour concentration approximately 7200 ppm @ 20 degrees C).
	Vehicle:	Air.
	Route of admin.:	8 hour exposure to substantially saturated vapor produced by aeration of n-butanol at room temperature.
	Results:	All animals survived and gained weight normally during the 14-day observation period.
	Comments:	At the end of the exposure, the only symptoms of distress were poor coordination or prostration.
	Data quality:	Reliability: Key study. Klimisch quality 2.
	References:	Union Carbide Corp. Bushy Run Research Center, Project Report No.14-73. Export, PA. 1951.
(B.)	Test substance:	1-Butanol, Union Carbide sample number A1939.
	Method:	Method/guideline followed: Internal Union Carbide method for inhalation exposure.
	Test type:	Acute inhalation.
	GLP:	YES [ ] NO [X]
	Year performed:	Not specified.
	Species/strain:	Rat, albino Sherman
	Sex: Male.	
	Number of animals/ sex/dose:	6 males/dose x one dose (8000 ppm).
	Vehicle:	Air.
	Route of admin.:	4 hour exposure to 8000 ppm n-butanol.
	Results:	LC_{50} > 8000 ppm. All animals survived and gained weight normally during the 14-day observation period.
	Comments:	At the end of the exposure, no symptoms of distress were noted. The rats were normal.
	Data quality:	Reliability: Key study. Klimisch quality 2.
	References:	Union Carbide Corp. Bushy Run Research Center, Project Report No.14-73. Export, PA. 1951.
(C.)	Test substance:	1-Butanol
	Test species/strain:	Mouse
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	650 ppm, 7-hours, no evidence of toxicity 6600 ppm, 2-hours, signs of CNS depression.
	Comments:	
	Reference:	Patty, F.A. 1982. Industrial Hygiene and Toxicology, 3rd ed., New York, Chichester, Brisbane, Toronto, Singapore, Wiley-

Interscience. IIC: 4571-4578. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

(D.)	Test substance:	1-Butanol
	Test species/strain:	Male Wistar rats mouse (strain not specified)
	Test method:	4hr. Dynamic inhalation to n-butyl alcohol or 4hr. Dynamic inhalation to a 50Vol-% mixture of 1-butanol and m-xylene.
	GLP:	YES [ ] NO [X]
	Test results:	EC_{50} = 6530 ppm, rat ED_{50} = 3010 ppm, mouse
	Comments:	EC_{50} = The medial effective concentration which caused rotarod performance disturbances. ED_{50} = The concentration which caused a 50% reduction in respiratory rate.
	Reference:	Korsak, Z, Swiercz, R. and Jedrychowski R. Effects of Acute Combined Exposure to n-Butyl Alcohol and m-Xylene. *Polish Jor. of Occup. Med. and Environmental Health.* 6(1):35-41, 1993.
(E.)	Test substance:	1-Butanol
	Test species/strain:	Scs:CF-1 male mice.
	Test method:	ASTM E981-84, 1984
	GLP:	YES [ ] NO [X]
	Test results:	RD_{50} = 233 ppm RD_{50} = 11,696 ppm
	Data Quality:	Klimisch rating of 4 due to lack of original source documents
	Reference:	Registry of Toxic Effects of Chemical Substances. p. 1301 1985-86.

5.2.3 ACUTE DERMAL TOXICITY

(A.)	Test substance:	1-Butanol, Union Carbide sample procured 12/20/48 from Fellowship 155.
	Method:	Internal Union Carbide method for dermal toxicity. Thompson's method of calculating the LD_{50} was used.
	Test type:	Acute dermal toxicity (skin penetration).
	GLP:	YES [ ] NO [X]
	Year performed:	1951
	Species/strain:	Rabbit, albino New Zealand, 3-5 months old, 2.5 kg average weight.
	Sex:	Male
	Number of animals/ sex/dose:	4 males/dose x four doses (10.0, 5.0, 2.52, or 1.26 ml/kg).
	Vehicle:	None
	Route of admin.:	Undiluted n-butanol was applied for 24 hours to the clipped trunks of the rabbits.
	Results:	Dermal LD50 = 4.2 (3.0 to 6.0) ml/kg. = 3.402 g/kg = 3402 mg/kg

Mortality at 10.0 ml/kg = 4/4
Mortality at 5.0 ml/kg = 3/4
Mortality at 2.52 ml/kg = 0/4
Mortality at 1.26 ml/kg = 0/4

Comments: Observation period was 14 days. All mortality occurred on day 0.
Data quality: Reliability: Key study. Klimisch quality 2.
References: Union Carbide Corp. Bushy Run Research Center, Project Report No.14-73. Export, PA. 1951.

(B.) Test substance: 1-Butanol
Test species/strain: Rabbit
Test method: Not Stated
GLP: YES [ ]
NO [X]
Test results: LD_{50} = 5.3 g/kg
Comments:
Reference: Patty, F.A. 1982. Industrial Hygiene and Toxicology, 3rd ed., New York, Chichester, Brisbane, Toronto, Singapore, Wiley-Interscience. IIC: 4571-4578. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

(C.) Test substance: 1-Butanol
Test species/strain: Rabbit
Test method: Not Stated
GLP: YES [ ]
NO [X]
Test results: LD_{100} = 7.5 g/kg
Comments:
Reference: Patty, F.A. 1982. Industrial Hygiene and Toxicology, 3rd ed., New York, Chichester, Brisbane, Toronto, Singapore, Wiley-Interscience. IIC: 4571-4578. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

5.2.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

5.3 CORROSIVENESS/IRRITATION

(A.) Test substance: n-butanol
Test species/strain: human
Test method: Draize-Shelanski repeat insult patch test using a nail color preparation containing 3% n-butanol
GLP: YES [ ]
NO [X]
Test results: Negative
Number of humans with
skin reaction at challenge: No subjects reacted to the n-butanol
Number of humans with
skin reaction at control site

at challenge:	not provided
Comments:	A total of six studies were conducted with preparations (nail color and nail enamel) containing 3% n-butanol. None of these studies were considered positive for sensitization due to n-butanol. The very low concentration of n-butanol used in this study does not provide adequate information regarding the skin sensitization potential of n-butanol in other consumer or industrial applications where higher concentrations or even neat material may be used. Therefore, this study was assigned a reliability rating of 4.
Reference:	The original study reports were provided to the Cosmetics, Toiletries, and Fragrances Association (CTFA) and summary reports provided by the CTFA were provided to the authors (unknown) who prepared the Cosmetic Ingredient Review (CIR) Assessment that was published in the Journal of the American College of Toxicology, Vol. 6(3), pages 403-424.

5.3.1 SKIN IRRITATION/CORROSION

(A.)

Test substance:	Identity: 1-Butanol, Union Carbide sample procured 12/20/48 from Fellowship 155.
Method:	Internal Union Carbide method for skin irritation.
Test type:	Rabbit belly vesicant test (uncovered).
GLP:	YES [ ] NO [X]
Year performed:	Not specified.
Species/strain:	Rabbit
Sex:	Not specified.
Number of animals/ sex/dose:	Not specified.
Vehicle:	None
Route of admin.:	Undiluted n-butanol was applied to the belly of rabbits and left uncovered.
Results:	No irritation was observed. Graded 1 on a scale of 1 to 10.
Comments:	No further details available.
Data quality:	Reliability: Key study. Klimisch quality 2.
References:	Union Carbide Corp. Bushy Run Research Center, Project Report No.14-73. Export, PA. 1951.

(B.)

Test substance:	1-butanol
Test species/strain:	Rabbit
Test method:	Not Stated
GLP:	YES [ ] NO [X]
Test results:	405 mg/24-Hr. Moderate skin irritation observed.
Comments:	
Reference:	US DHEW. 1978. *Registry of toxic effects of chemical*s, Washington DC, US Department of Health, Education and Welfare. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO. Registry of Toxic Effects of Chemical Substances. p.1301, 1985-86.

(C.)

Test substance:	1-butanol

	Test species/strain:	Rabbit
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	500 mg/24-Hr. Moderate skin irritation observed.
	Comments:	
	Reference:	US DHEW. 1978. *Registry of toxic effects of chemical*s, Washington DC, US Department of Health, Education and Welfare. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO. Registry of Toxic Effects of Chemical Substances. p.1301, 1985-86.
(D.)	Test substance:	1-butanol
	Test species/strain:	Human
	Test method:	Occupational observation
	GLP:	YES [ ] NO [X]
	Test results:	Dermatitis of the fingers and hands has been described after exposure to 1-butanol. Other observations noted included fissured eczema around fingernails and along the sides of fingers.
	Comments:	
	Reference:	Tabershaw I.R., Fahy J.P. and Skinner J.B. Industrial exposure to butanol. *Ind. Hyg. Toxicol.* 26:328-331. 1944.
(E.)	Test substance:	1-Butanol
	Test species/strain:	Human
	Test method:	Chamber Test method
	GLP:	YES [ ] NO [ ]
	Test results:	105 patients were tested for 1-butanol induced non immunological contact urticaria. 20 µl of undiluted 1-butanol was applied to the upper back with an occlusive patch for 20 minutes. No redness was observed in any subject. 4 patients were positive for edema.
	Comments:	
	Reference:	Lahti A. Nonimmunologic contact urticaria. *Acta. Dermato-Venereol.* Suppl.,60(91): 1-49. 1980.

5.3.2 EYE IRRITATION/CORROSION

(A.)	Test substance:	1-butanol
	Test species/strain:	Rabbit
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	When 1.62 or 20 mg BA was instilled into rabbit eyes, severe eye irritation occurred after 72 and 24 hours, respectively.
	Comments:	
	Reference:	US DHEW. 1978. *Registry of toxic effects of chemical*s, Washington DC, US Department of Health, Education and Welfare. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-*

Butanol 2-Butanol tert-Butanol Isobutanol. WHO. Registry of Toxic Effects of Chemical Substances. p.1301, 1985-86.

(B.)	Test substance:	1-butanol
	Test species/strain:	Rabbit
	Test method:	Not Stated
	GLP:	YES [ ] NO [X]
	Test results:	When 0.005 ml BA was instilled into rabbit eyes, severe corneal irritation resulted.
	Comments:	
	Reference:	Patty, F.A. 1982. *Industrial hygiene and toxicology*, 3 rd ed., New York, Chichester, Brisbane, Toronto, Singapore, Wiley-Interscience. IIC: 4571-4578. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.
(C.)	Test substance:	1-butanol
	Test species/strain:	Humans
	Test Method:	Sixteen subjects were exposed (i.e. eye only) to n-butanol at concentrations up to 300 mg/m 3 (990 ppm) for up to an hour, three times daily on 5 different days. Ratings of ocular irritation intensity were obtained continuously during all 3 runs.
	Test Results:	During run 2, the authors observed a slight increase in perceived eye irritation intensity for all exposure concentrations. However, the threshold for irritation (conjunctival hyperemia) was never clearly exceeded.
	GLP:	YES [ ] NO [X]
	Comments:	
	Reference:	Hempel-Jorgensen, A., Hudnell, H.K., Kjaergaard, S.K., and Molhave, L. 1999. Time Course of Sensory Eye Irritation in Humans Exposed to n-Butanol and 1-Octene. *Arch. Environ. Health* 54(2), 86-94.

5.3.3 RESPIRATORY IRRITATION

Test substance:	1-butanol, “high-purity”
Test species/strain:	male OF1 mice (25 ∂ 2g) from IFFA CREDO Laboratories (France).
Test method:	RD_{50} method developed by Yves Alarie.
GLP:	YES [ ] NO [X]
Test results:	RD_{50} = 1268 ppm, predicted to be intolerable in humans. 0.1 RD_{50} = 127 ppm, predicted to be uncomfortable in humans. 0.01 RD_{50} = 13 ppm, predicted have no effect in humans.
Comments:	Six mice per concentration x 4 concentrations (not specified) were exposed via nose-only inhalation for 5 minutes and the RD_{50} was determined. The RD_{50} is the concentration of an irritant that causes a 50% decrease in breathing rate.
Reference:	de Ceaurriz, J.C., Micillino, J.C., Bonnet, P., and Guenier, J.P. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicology Letters, 9: 137-143.

5.4 SKIN SENSITISATION

Test substance:	
Test species/strain:	
Test method:	
GLP:	YES [ ] NO [ ]
Test results:	
Number of animals with skin reaction at challenge:	
Number of animals with skin reaction in control group at challenge	
Comments:	No data submitted.
Reference:	

5.5 REPEATED DOSE TOXICITY

(A.)	Species:	rat
	Strain:	Sprague-Dawley (SD)
	Sex:	male and female
	Route of Admin.:	inhalation
	Exposure Period:	13 weeks
	Freq. of Treatment:	6 h/day, 5 days/week 65 exposure days (13 weeks)
	Post Exposure Observation Period:	N/A
	Doses:	0, 500, 1500, and 3000 ppm
	Control Group:	yes
	NOAEL:	500 ppm
	LOAEL:	1500 ppm
	Method:	Conducted according to the US EPA Toxic Substances Control Act Health Effects Testing Guidelines:40 CFR 798.2450, Inhalation Toxicology (with the exception that the tissues from the central and peripheral nervous systems were not examined histologically. A histological examination of the central and peripheral nervous systems from the companion neurotoxicity study was conducted. Male and female Sprague-Dawley (SD) rats were exposed to concentrations of 0, 500, 1500, or 3000 ppm of n-butyl acetate for at least 65 exposures over 14 weeks. The animals were exposed in 4200 L glass and stainless steel chambers for 6 hours per day. Metering the liquid test substance through heated glass distillation columns packed with glass beads generated vapors of the test substance. The time-weighted average analytical concentrations were within 10% of the target concentrations. The target analytical concentration for the 500-ppm group was increased to 550 ppm after consultation with the Sponsor because determination of chamber atmosphere homogeneity showed that the variation in actual exposure concentration at various locations in the chamber was on average 13% lower than the reference point. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to one hour after exposure. Body weights and feed consumption data were measured weekly throughout the study. Blood was collected

from 5 animals per group after 30 days of exposure (these animals were then discarded), and from 10 animals per group at termination. Clinical chemistry and hematology parameters were determined on all blood samples collected. Ophthalmic exams were conducted on all animals prior to study start. During the last week of exposure, animals from the control and high-concentration groups were re-examined. Since no changes were detected in the eyes of the high-concentration animals, the animals from the low- and mid-concentration groups were not re-examined. The animals killed after 93-94 days on study were necropsied, examined for gross lesions and tissues saved for histopathological examination. Terminal body weights and selected organ weights were collected from the animals killed on study days 93-94.

Year: 1996
GLP: yes
Test substance: n-butyl acetate (>99.9% pure)
Remark: No spontaneous mortality occurred during the study. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to one hour after exposure.
Results: No spontaneous mortality occurred during the study. Animals exposed to 3000 ppm had reduced activity levels during exposure that were of generally minor severity. Signs of sialorrhea and red discoloration on the chin hair were also observed. Animals exposed to 1500 ppm exhibited reduced activity during exposure of generally minimal severity. Control and 500 ppm animals appeared normal during exposure. After exposure, animals in all groups had porphyrin nasal discharges and dried porphyrin stains around the nose. These clinical signs were occasionally seen during the morning examination before exposure. Mean body weights for the 3000 ppm groups were significantly lower than the control group throughout the study. Overall weight gains for the 3000 ppm group were 62 and 78% of weight gains for the control group (males and females, respectively). Mean feed consumption for the 3000 ppm groups was significantly lower than for the control group throughout the study. Mean weekly feed consumption values for the 3000 ppm groups were 14-25% lower than the control group for male rats and were 6-16% lower than the control group for female rats. Mean body weights for the 1500 ppm groups were significantly lower than the control group at certain times during the study. Overall weight gains were 90 and 107% of the control group (males and females, respectively). Mean feed consumption values for the 1500 ppm groups were significantly lower than for the control group throughout the study. Mean weekly feed consumption values for the 1500 ppm groups were 4-17% lower than the control group for male rats and were 10-15% lower than the control group for female rats. Mean body weights for the 500 ppm groups were comparable to the control group throughout the study. However, mean feed consumption values for the 500 ppm groups were significantly lower than for the control group on several days throughout the study. Mean weekly feed consumption values for the 500 ppm groups were 3-12% lower than the control group for male rats and were from

2% higher to 7% lower than the control group for female rats. No biologically significant differences in hematologic parameters were seen after 30 days or 90 days of exposure. No biologically significant differences in serum chemistries were observed among groups. No treatment-related ophthalmologic changes were observed. Mean terminal body weights were significantly lower for the 1500 and 3000 ppm male and female groups compared with the control group. Organ weight changes independent of the body weight changes (noted above) were slight and limited to lower spleen weights in the male 3000 ppm group, higher testes weights in the male 1500 and 3000 ppm groups, higher lung weights for the 3000 ppm male group, and higher adrenal gland weights for the 1500 ppm female and 3000 ppm male and female groups. Signs of necrosis of the olfactory epithelium in some 1500 and 3000-ppm rats represent a localized, site-of-contact effect due to n-butyl ac tate. No other lesions were observed microscopically that were considered to be compound-related. There was no effect on either epididymidal or testicular sperm counts.

Comments: The rapid *in vivo* hydrolysis of n-butyl acetate to 1-butanol makes this study directly applicable to 1-butanol exposures. The NOAEL for systemic effects and the NOAEL for neurotoxicity can be calculated for 1-butanol after corrections for molecular weight. These values would be 223 ppm and 1,300 ppm, respectively.

Reference: David, R.M., T. R. Tyler, R.E. Ouellette, W. D. Faber, and M. I. Banton. Evaluation of Subchronic Toxicity of n-Butyl Acetate Vapor. Accepted for publication, Food Chemical Toxicology, 39: 877-886.

(B.)

Species:	rat
Strain:	Sprague-Dawley (SD)
Sex:	male and female
Route of Admin.:	inhalation
Exposure Period:	13 weeks
Freq. of Treatment:	6 h/day, 5 days/week 65 exposure days (13 weeks)
Post Exposure Observation Period:	2 weeks
Doses:	0, 500, 1500, and 3000 ppm
Control Group:	yes
NOAEL:	3000 ppm
LOAEL:	N/A

Method: The study consisted of two sets of animals, male and female *ad libitum*-fed Sprague-Dawley (SD) rats designated for functional observational battery, motor activity, and neuropathology endpoints (FOB/MA/NP) and male (SD) rats restricted to 12-14 g of feed per day and which were designated for schedule-controlled operant behavior (SCOB). Both sets of animals were exposed to concentrations of 0, 500, 1500, or 3000 ppm of n-butyl acetate for at least 65 exposures over 14 weeks. The animals were exposed in 4200 L glass and stainless steel chambers for 6 hours per day. Metering the liquid test substance through heated glass distillation columns packed with glass beads generated vapors of the test substance. The time-weighted average analytical concentrations were within 10% of

the target concentrations. The target analytical concentration for the 500-ppm group was increased to 550 ppm after consultation with the Sponsor because determination of chamber atmosphere homogeneity showed that the variation in actual exposure concentration at various locations in the chamber was on average 13% lower than the reference point. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to one hour after exposure. Body weights were collected weekly. Feed consumption data was not collected on the *ad libitu*m-fed animals. At the end of the 14-week exposure period, five male and five female animals from the FOB/MA/NP groups were randomly selected and perfused systemically for neuropathologic examination. Brain, spinal cord swellings (with dorsal and ventral routes), dorsal root ganglia, sciatic nerve, and tibial nerves were examined microscopically.

Year: 1996
GLP: yes
Test substance: n-butyl acetate (>99.9% pure)
Remark: The SCOB testing paradigm involved both fixed-interval (FI) and fixed-ratio (FR) schedules.
Results: NOAEL Neurotoxicity = 3000 ppm
Animals exposed to 1500 or 3000 ppm had minimal to minor reduced activity levels. There was no evidence of a cumulative effect of exposure on the severity of reduced activity. There was no evidence of a cumulative effect of exposure on the severity of reduced activity. Control and 500 ppm animals appeared normal during exposure. There were no other apparent differences in the clinical condition of FOB/MA/NP and SCOB animals. Body weights and/or body weight gains were reduced in the 1500 and 3000-ppm male and female animals. No differences in body weight or rate of weight gain were noted in the 500-ppm exposure group animals when compared to control groups. There was no evidence of neurotoxicity based on FOB, motor activity, neuropathology, and SCOB endpoints. Therefore, the no-observable effect level (NOAEL) for subchronic neurotoxicity for this study is 3000 ppm based on the lack of cumulative neurotoxicity following repeated exposure.
Comments: The rapid *in vivo* hydrolysis of n-butyl acetate to 1-butanol makes this study directly applicable to 1-butanol exposure*s*.
References: David, R.M., Tyler, T.R., Ouellette, R.E., Faber, W.D., Banton, M.I., Garman, R.H., Gill, M.W., and O'Donoghue, J.L. Evaluation Of Subchronic Neurotoxicity Of N-Butyl Acetate Vapor. NeuroToxicology 19: 809-822, 1998.

Bernard, L.G., David, R.M., and Hosenfeld. 1996 A Thirteen-Week Subchronic Inhalation Neurotoxicity Study in the Rat. HAEL NO. 94-0305 and 94-0306, KAN 900710, CAS 000123-86-4. Final Report. Toxicological Sciences Laboratory, Health and Environmental Laboratories Eastman Kodak Company Rochester, New York.

(C.) Test substance: 1-Butanol

	Test species/strain:	male and female CD rats
	Test method:	SOP for Toxicity Research Laboratories. Four groups of male and female rats (30/sex/group) were dosed daily by gavage with 0, 30, 125 or 500 mg/kg/day of 1-butanol for 13 weeks. Dosing solutions of butanol in deionized water were used and 10 mL/kg was the constant dosing volume. Body weights and feed consumption were recorded weekly. Clinical signs were recorded daily. Blood and urine were collected for clinical pathology at pre-dose (10 sentinel animals), and at the 13-week necropsies. Organ weights and results of gross pathology exams were recorded at the 13-week necropsies. Histopathological examinations of tissues from the control and 1000 mg/kg groups were conducted.
	GLP:	YES [X] NO [ ]
	Test results:	Four groups of male and female rats (30/sex/group) were dosed daily by gavage with 0, 30, 125 or 500 mg/kg/day of 1-butanol for 13 weeks. There were no dose-related differences observed between treatment or control rats on body or organ weight changes, food consumption or mortality. In addition, there were no dose-related differences observed in gross or histopathological examination of the eye. Ataxia and hypo-activity were observed in both sexes of the high dose group (500/mg/kg/day) during the final six weeks of the dosing period. The appearance of post dosing ataxia and hypoactivity only after the interim sacrifice suggests that, with the reduced number of animals, technicians were able to do more thorough observations in a shorter time frame. It is likely that the post dosing effects simply went unnoticed during the first half of the study. No treatment related signs were observed in the 30 or 125 mg/kg/day treatment groups. Dose or concentration at which no toxic effects were observed: NOAEL: 125 mg/kg/day LOAEL: 500 mg/kg/day
	Reference:	Rat Oral Subchronic Toxicity Study of Normal Butanol Toxicity Research Laboratories, Ltd. Muskegon, MI. TRL Study #032-006 dated 1986.
(D.)	Test substance:	1-Butanol
	Test species/strain:	Adult Male Long-Evans Rats
	Test Method:	Exposed to 4000 ppm (6 hours/day for 5 days, N = 10/group). Tested for auditory function 5 to 8 weeks post exposure using reflex modification audiometry (RMA).
	Test Results:	No change in hearing following exposure to n-butanol under these conditions.
	GLP:	YES [ ] NO [X]
	Comments:	These data contradict the results of a poorly-conducted human study (reported elsewhere in this document).
	Reference:	Crofton, K.M., Lassiter, T.L., and Rebert, C.S. 1994. Solvent-induced ototoxicity in rats: an atypical selective mid-frequency hearing deficit. *Hearing Research* 80 (1), 25-30.

(E.) Test substance: 1-butanol
Test species/strain: Rabbit
Test method: Not Stated
GLP**:** YES [ ]
NO [X]
Test results: Dermal application of 42 to 55 ml/kg/day for 1 to 4 consecutive days to rabbits resulted in 100 percent mortality. Repeated applications to rabbits of 20 ml/kg/day for 30 days over a period of 6 weeks produced no fatalities.

20 ml/kg = 16.20 g/kg = 16200 mg/kg
42 ml/kg = 34.02 g/kg = 34020 mg/kg
55ml/kg = 44.55 g/kg = 44550 mg/kg

Comments:
Reference: Patty, F.A. 1982. *Industrial hygiene and toxicology*, 3rd ed., New York, Chichester, Brisbane, Toronto, Singapore, Wiley-Interscience. IIC: 4571-4578. As cited in World Health Organization (WHO). 1987. *Environmental Health Criteria 65: Butanols – Four Isomers: 1-Butanol 2-Butanol tert-Butanol Isobutanol.* WHO.

5.6 GENETIC TOXICITY IN VITRO

A. Bacterial In Vitro Test

(A.) Test substance: 1-Butanol, from Mallinkrodt
Test species/strain: *Salmonella typhimurium:* Strains, TA98, TA100, TA1535, TA1537
Test method: Standard *Salmonella* plate incorporation test, with and without PCB-induced rat liver S9 metabolic activation.
GLP: YES [ ]
NO [X]
Test results: Minimum concentration of test substance at which toxicity to bacteria was observed:
with metabolic activation: >10 µg/plate
without metabolic activation:>10 µg/plate
Concentration of test compound resulting in precipitation:
Number of revertants: < 0.0005 revertants/nmole,
< 70 revertants/10^4 σg/plate

Genotoxic effects:	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No evidence of mutagenic activity in reverse point mutation assay in Salmonella with or without a metabolic activation system from arochlor treated rat liver homogenate.
The mice were sacrificed 24 and 48 hours postdosing and evaluated for clastogenicity and spindle poison effects. Positive and negative controls all produced appropriate responses. BA 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).

References: The *Salmonella* typhimurium/mammalian microsomal assay, a report of the U.S. EPA Gene-Tox Program, Kier, L.E., et al. M*utation Research* 168(2):69-240. 1986.

McCann J., Choi E., Yamasaki E. and Ames B.N. (1975) Detection of carcinogens as mutagens in the Salmonella/ microsome test: Assay of 300 chemicals. *Proc. Nat. Acad. Sci.* 72:5135-5139.

B. Non-Bacterial In Vitro Test

(A.) Test substance: 1-Butanol, from Prolabo (Paris, France)
Type of cell used: Chinese Hamster Lung Fibroblast Cell Line (V79)

Test method: Micronucleus:
Cells treated with test material for 1-hour, treated with BrdUrd (bromodeoxyuridine) for 7 hours and incubated for 48 hours (2nd cell cycle). 7000 interphase cells scored per treatment. No activation used. Solvent control = acetone.

GLP: YES [ ]
NO [X]

Test results: Lowest Concentration producing cell toxicity:
with metabolic activation: no activation used
without metabolic activation: 50 µl/ml

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[ ]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No evidence of mutagenic activity in micronucleus assay using CHL V79 Cell Line at concentrations up to 50 µl/ml.
Number of micronuclei/1000 cells (mean ∂ S.E.) = 2.75 ∂ 0.48

Reference: Lasne, C., Gu, Z.W., Venegas, W. And I. Chouroulinkov (1984) "The *in vitro* micronucelus assay for detection of cytogenetic effects induced by mutagen-carcinogens: Comparison with the *in vitro* sister-Chromatid exchange assay. *Mutat. Res.* 130: 273-282.

(B.) Test substance: 1-Butanol
Type of cell used: Chinese hamster ovary cells (CHO)
Test method:
In vitro Sister
Chromatid Exchange: Cells were treated in culture once a day for 7 days with 1-butanol to a final concentration of 0.1%. One day after the last treatment, the cells were treated with Brdu. 20 hours later the cells were teated with colcemid. Mitotic chromosomes were prepared 4 hours later. 100 mitoses were examined for SCEs.

GLP: YES [ ]
NO [X]

Test results: Lowest Concentration producing cell toxicity:
with metabolic activation:
without metabolic activation: >0.1%
Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments:	No evidence of clastogenic activity in an *in vitro* SCE assay in CHO cells up to a concentration of 0.1%.
Reference:	Obe, G. And Ristow, H. (1977). "Acetaldehyde, but not Ethanol, Induces Sister Chromatid Exchanges in Chinese Hamster Cells *in vitro*." *Mutat. Res.* 56:211-213.

5.7 GENETIC TOXICITY IN VIVO

Test substance:	1-butanol
Test species/strain:	Mouse/NMRI (male and female)
Test method:	OECD No. 474 (Proposal for updating, ENV/EPOC (96)4) EPA/TSCA 789.5395 (August 1997) EEC Directive 92/69, B 12 (December 1992)
GLP:	YES [X] NO [ ]
Test results:	Oral gavage dose of 500, 1,000 or 2,000 mg/kg of n-butanol did not have any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis at either the 24 or 48 hour timepoints.
Lowest dose producing toxicity:	2000 mg/kg
Effect on Mitotic Index or P/N Ratio:	None
Genotoxic effects:	+ ? - [ ] [ ] [X]
Comments:	Both of the positive control chemicals, i.e. cyclophosphamide for clastogenicity and vincristine for spindle poison effects, led to the expected increase in the rate of polychromatic erythrocytes containing small or large micronuclei.
Reference:	Engelhardt, D., and Hoffmann, H.D. Cytogenetic Study In Vivo with n-butanol in the Mouse Micronucleus Test - Single Oral Administration. (1998) Project No. 26M0346/974126, Department of Toxicology, BASF Aktiengesellschaft, D-67056 Ludwigshafen/Rhein, FRG.

5.8 CARCINOGENICITY

(A.)	Test substance:	1-Butanol
	Test species/strain:	
	Test method:	
	GLP:	YES [ ] NO [X]
	Test results:	
	Comments:	No Data Submitted
	Reference:	

5.9 TOXICITY TO REPRODUCTION

(A.)	Species:	rat
	Strain:	Sprague-Dawley
	Sex:	male and female
	Route of Admin.:	inhalation
	Exposure Period:	Day 1-20 of gestation
	Freq. of Treatment:	7 hours/day

	Duration of Test:	20 Days
	Exposure Concentrations:	0, 3000, or 6000 ppm of n-butanol. .
	Control Group:	Yes
	NOAEL Maternal Toxicity:	not reported
	NOAEL Developmental Neurotoxicity:	6000 ppm
	Method:	Groups of 18 male Sprague-Dawley rats were exposed to concentrations of 0, 3000, or 6000 ppm nBA for 7 hours/day for 6 weeks. These males were then mated to non-exposed female rats of the same strain. In a separate experiment, groups of 15 pregnant female rats were exposed to concentrations of 0, 3000, or 6000 ppm for 7 hours/day from gestation Day 1-20. These females were then allowed to deliver. The offspring from these two groups were then observed for signs of developmental neurotoxic effects. Offspring were examined from postnatal days 10-90 for the following measures: ascent on a wire mesh screen, rotorod, open-field and photoelectrically-monitored activity, running wheel, avoidance conditioning, operant conditioning, acetylcholine, dopamine, norepinephrine, serotonin, met-enkephalin, beta-endorphin, and Substance P. neurotransmitter levels were measured from the cerebrum, cerebellum, brainstem, and midbrain.
	Year :	1989
	GLP:	No
	Test substance:	n-Butanol purity > 99%
	Result:	No detectable effect on pregnancy rate was found after either maternal or paternal exposure. In the 6000 ppm group, 4 of the 78 (5%) behavioural measures, and 4 of the 64 (6%) neurochemical measures differed from those of controls. There was no discernible pattern of effects. The authors conclude, ”In view of this, it is highly unlikely that administration of nBA at the current Permissible Exposure Limit (PEL) of 100 ppm would produce structural or behavioural teratogenicity in rats using the test employed here.”
	Reference:	Nelson, B.K., Brightwell, W.S., Robertson, S.K., Kahn, A., Krieg, E.F., Jr. and Massari, V.J. Behavioral Teratology investigation of 1-Butanol in Rats. *Neurotoxicology and Teratology.* 11(3): 313-315, 1989a.
(B.)	Test Substance:	1-Butanol, Analar reagent grade, from British Drug Houses, Ltd. (Poole, Dorset, England)
	Test Species:	Rat (3-4 weeks old, 70-100 g)
	Strain:	Sprague-Dawley
	Sex:	Male
	Number of Animals:	6/group
	Route of Admin.:	Oral intubation, dissolved in corn oil
	Exposure Period:	6 days
	Frequency of Treatment:	Daily
	Post Exposure:	None
	Observation Period:	In-Life (6 days)
	Doses:	533 mg/kg/day
	Control Group:	Yes, vehicle control
	NOAEL:	533 mg/kg/day

	LOAEL:	>533 mg/kg/day
	Test Method:	Research
	Test Results:	Daily oral administration of dibutyl phthalate (DBP) at 2000 mg/kg/day for 4 days to young male rats was found to produce testicular injury, loss in testicular weight, and altered zinc metabolism. Monobutyl phthalate (MBP), the major metabolite of DBP, produced similar, but somewhat more potent, effects. Under similar treatment conditions, an equimolar dose of 1-Butanol (533 mg/kg/day) did not cause any effect on testes weight or histopathology.
	GLP:	YES [ ] NO [X]
	Comments:	Since1-Butanol did not cause any effect on testes weight or histopathology, it was not tested for zinc metabolism.
	Reference:	Cater et al., (1977). "Studies on Dibutyl Phthalate-Induced Testicular Atrophy in the Rat: Effect on Zinc Metabolism". *Tox. And Applied Pharm.*, 41:609-618.
(C.)	Test substance:	n-Butyl Acetate
	Test species/strain:	Rat, male Sprague Dawley
	Test method:	Male *ad libitu*m-fed rats were exposed via inhalation to 0, 500, 1500, or 3,000 ppm (6 hrs/day) for at least 65 exposures over 14 weeks. At necropsy, right testes (n=40) were prepared for histological examination and left testes and left epidymis (n=40) from the same animal were frozen and processed for determination of sperm concentrations.
	Test result:	Overall there was no evidence of male reproductive toxicity at any exposure concentration based on lack of significant differences between treatments and controls for testicular spermatid head counts and epididymidal spermatozoa counts as endpoints of toxicity. Therefore, a NOAEL for male reproductive toxicity following repeated exposure was 3000 ppm. Overall weight gains for 3000 ppm exposure groups were 64% and 59% of controls for males and females, respectively. Overall weight gains for 1500 ppm exposure groups were 82% and 74% of controls for males and females, respectively. No significant differences in weight gain at 500 ppm vs. control.
	GLP:	YES [X] NO [ ]
	Comments:	Therefore, the NOAEL for male reproductive toxicity following repeated inhalation exposure with 3,000 ppm, the highest exposure tested. The rapid *in vivo* hydrolysis of n-butyl acetate to 1-butanol makes this study directly applicable to 1-butanol exposure*s*.
	Reference:	CMA Oxo-Process Panel; 1300 Wilson Blvd., Arlington Virginia 22209.
(D.)	Test substance:	n-butanol
	Test species/strain:	Rat, Imp:DAK; internal breeding colony to the Nofer Institute of Occupational Medicine in Lodz, Poland
	Number of Animals:	11-17/group
	Route of Admin.:	Aqueous solutions for drinking water

Exposure Period:	8 weeks premating, 3 weeks mating, gestation Days 0-20
Frequency of Treatment:	Daily
Post Exposure:	None
Observation Period:	Premating (8 weeks), mating (up to 3 weeks), gestation (20 days)
Doses:	0.24, 0.8, or 4% n-butanol (0.3, 1.0, and 5.0 grams/kg/day)
Control Group:	Yes, vehicle control
NOAEL:	5.0 grams/kg/day
LOAEL:	>5.0 grams/kg/day
Test method:	Groups of 11-17 female rats were given aqueous solutions containing 0.24, 0.8, or 4% n-butanol for 8 weeks prior to mating, during which time estrous cyclicity was evaluated. After the 8 week exposure period (with no effects on estrous cyclicity), the females were mated with untreated males. The females had continued access to the solutions of n-butanol (above) in the water until Day 20 of gestation when they were killed and the fetuses were collected and examined for both skeletal and visceral malformations. Weight gains and feed consumption as well as general behavior were recorded during the 8 week premating period, 3 week mating period and gestation. The authors state that the aqueous solutions delivered 0.3, 1.0, and 5.0 grams/kg/day, although there is no information as to how this was determined. The 4% solution was described as delivering daily doses twice as high as the acute oral LD_{50} (2.1 grams/kg/day). The unit of statistical analysis was the individual fetus, not the litter.
Test result:	General appearance, feed consumption, body weights, rate of weight gain, estrous cycle length and number, absolute and relative organ weights (not specified), hemoglobin concentrations, hematocrit values, fetal body weights, intrauterine mortality, corpora lutea, total implants, and placental weights were unaffected.
GLP:	YES [] NO [X]
Comments:	While the developmental toxicity data from this paper is problematic due to poor reporting and study design, the reproductive data corroborate what was observed earlier by Nelson, et al., (1989a).
Reference:	Sitarek, K., Berlinska, B., and Baranski, B. Assessment of the Effect of n-Butanol Given to Female Rats in Drinking Water on Fertility and Prenatal Development of Their Offspring. Int. J. of Occupational Medicine and Environmental Health, 7(4):365-370, 1994.

5.9.1 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(A.)	Species:	rat
	Strain:	Sprague-Dawley
	Sex:	male and female
	Route of Admin.	inhalation
	Exposure Period:	Day 1-20 of gestation
	Freq. of Treatment:	7 hours/day
	Duration of Test:	20 Days
	Exposure	

	Concentrations:	0, 3000, or 6000 ppm of n-butanol
	Control Group:	Yes
	NOAEL Maternal Toxicity:	not reported
	NOAEL Developmental Neurotoxicity:	6000 ppm
	Method:	Groups of 18 male Sprague-Dawley rats were exposed to concentrations of 0, 3000, or 6000 ppm nBA for 7 hours/day for 6 weeks. These males were then mated to non-exposed female rats of the same strain. In a separate experiment, groups of 15 pregnant female rats were exposed to concentrations of 0, 3000, or 6000 ppm for 7 hours/day from gestation Day 1-20. These females were then allowed to deliver. The offspring from these two groups were then observed for signs of developmental neurotoxic effects. Offspring were examined from postnatal days 10-90 for the following measures: ascent on a wire mesh screen, rotorod, open-field and photoelectrically-monitored activity, running wheel, avoidance conditioning, operant conditioning, acetylcholine, dopamine, norepinephrine, serotonin, met-enkephalin, beta-endorphin, and Substance P. neurotransmitter levels were measured from the cerebrum, cerebellum, brainstem, and midbrain.
	Year:	1989
	GLP:	No
	Test substance:	n-Butanol purity > 99%
	Result:	No detectable effect on pregnancy rate was found after either maternal or paternal exposure. In the 6000 ppm group, 4 of the 78 (5%) behavioural measures, and 4 of the 64 (6%) neurochemical measures differed from those of controls. There was no discernible pattern of effects. The authors conclude, ”In view of this, it is highly unlikely that administration of nBA at the current Permissible Exposure Limit (PEL) of 100 ppm would produce structural or behavioural teratogenicity in rats using the test employed here.”
	Reference:	Nelson, B.K., Brightwell, W.S., Robertson, S.K., Kahn, A., Krieg, E.F., Jr. and Massari, V.J. Behavioral Teratology investigation of 1-Butanol in Rats. *Neurotoxicology and Teratology.* 11(3): 313-315, 1989a.
(B.)	Species:	rat
	Strain:	Sprague-Dawley
	Sex:	female
	Route of Administration:	inhalation
	Exposure Period:	Day 1-19 of gestation
	Freq. of Treatment:	7 hours/day
	Duration of Test:	20 Days
	Exposure Concentrations:	0, 3500, 6000 or 8000 ppm of n-butanol
	Control Group:	Yes
	NOAEL Maternal Toxicity:	3500 ppm
	NOAEL Teratogenicity:	3500 ppm
	Method:	Groups of approximately 15 pregnant Sprague-Dawley rats were exposed via inhalation to 0, 3500, 6000 or 8000 ppm of n-butanol for 7 hours/ day from gestation Day 1 - 19. On

		gestation day 20, the fetuses were collected and examined for both skeletal and visceral malformations.
	Year:	1989
	GLP:	no
	Test substance:	n-Butanol purity > 99%
	Result:	8000 ppm produced narcosis in approximately one-half of the dams. No behavioural effects were noted at 6000 ppm nBA. Two of eighteen dams at 8000 ppm died during the exposure period. Feed consumption was decreased in the 6000 and 8000 ppm nBA exposed dams, but the 3500 ppm dams were similar to controls. No effect was observed on mean corpora lutea/litter, mean resorptions/litter, mean number of live foetuses/litter or sex ratio. Foetal weights were slightly decreased at 6000 and 8000 ppm groups, but the 3500 ppm group was unaffected. External foetal malformations were not observed. There were no differences in malformation rates (skeletal or visceral) or in rates of commonly observed variations. However, there was a slight increase in the percent of fetuses with any skeletal variation or malformation in the 8000 ppm group but not in the lower two exposure groups. The authors concluded that although high concentrations (8000 ppm) of nBA produced developmental toxicity, it was not a strong developmental toxicant. The NOAEL for maternal animals was 3500 ppm and the NOAEL for offspring was 3500 ppm (based on slight decrease in foetal weight at 6000 ppm).
	Reference:	Nelson, BK., Brightwell, WS., Kahn, A., Burg, JR. and Goad, PT. Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fundamental and Applied Toxicology.* 12(3):469-479.,1989b.
(C.)	Test substance:	n-butanol
	Test species/strain:	Rat, Imp:DAK; internal breeding colony to the Nofer Institute of Occupational Medicine in Lodz, Poland
	Number of Animals:	11-17/group
	Route of Admin.:	Aqueous solutions for drinking water
	Exposure Period:	8 weeks premating, 3 weeks mating, gestation Days 0-20
	Frequency of Treatment:	Daily
	Post Exposure:	None
	Observation Period:	Premating (8 weeks), mating (up to 3 weeks), gestation (20 days)
	Doses:	0.24, 0.8, or 4% n-butanol (0.3, 1.0, and 5.0 grams/kg/day)
	Control Group:	Yes, vehicle control
	NOAEL:	Not reported (questionable)
	LOAEL:	0.3 grams/kg/day (highly questionable)
	Test method:	Groups of 11-17 female rats were given aqueous solutions containing 0.24, 0.8, or 4% n-butanol for 8 weeks prior to mating, during which time estrous cyclicity was evaluated. After the 8 week exposure period (with no effects on estrous cyclicity), the females were mated with untreated males. The females had continued access to the solutions of n-butanol (above) in the water until Day 20 of gestation when they were killed and the fetuses were collected and examined for both skeletal and visceral malformations. Weight gains and feed consumption as well as general behavior were recorded during the 8 week premating period, 3 week mating period and

gestation. The authors state that the aqueous solutions delivered 0.3, 1.0, and 5.0 grams/kg/day, although there is no information as to how this was determined. The 4% solution was described as delivering daily doses twice as high as the acute oral LD_{50} (2.1 grams/kg/day). The unit of statistical analysis was the individual fetus, not the litter.

Test result: General appearance, feed consumption, body weights, rate of weight gain, estrous cycle length and number, absolute and relative organ weights (not specified), hemoglobin concentrations, hematocrit values, fetal body weights, intrauterine mortality, corpora lutea, total implants, and placental weights were unaffected. At 4% n-butanol in the drinking water, the crown-rump length is decreased from a control mean of 4.0 cm to 3.8 cm. The authors report developmental anomalies in all three dose levels. Fetal skeletal effects were limited to extra 14^{th} rib (1 fetus in the low dose group and 2 fetuses in the high dose group), and wavy ribs (1 fetus in the low dose group). Central nervous system defects were limited to dilation of either the subarachnoid space or lateral and/or third ventricles of the brain, dilated renal pelvis, or external or internal hydrocephalus. Of the 65 control fetuses examined for skeletal effects, none had an extra 14^{th} rib or wavy ribs(s) or any other skeletal malformation or variation. Of the 61 control fetuses examined for visceral observations, 2 had dilatation of the lateral and/or third ventricles of the brain and none had dilatation of the subarachnoid space or internal or external hydrocephalus. Although the authors considered all three dose levels to have increased levels of defects when compared to controls, there was no increase in incidence from the low exposure concentration (0.24% n-butanol; 0.3 grams/kg/day) to the high exposure concentration (4% n-butanol; 5.0 grams/kg/day).

GLP: YES []
NO [X]

Comments: Developmental anomalies reported by the authors (dilatation of the brain ventricles/spaces or renal pelvis, internal hydrocephalus, wavy or extra ribs) as being due to n-butanol exposure are listed as variations or delayed development in commonly used historical databases. Of importance, the incidence of these developmental defects in the control population was zero percent (with the exception of 2/61 pups with brain dilatation). The incidence of "cerebral ventricle, enlargement" was 2% on a per fetus basis and 4.4% on a per litter basis in the 1995 MARTA/MTA reference database for Sprague-Dawley rats (this is a database of common malformations/variations in control animals in studies conducted in the USA). The incidence of "renal pelvis, dilated" was 0.95% on a per fetus basis and 5.2% on a per litter basis in the same reference database. However, the "malformations reported in this paper that are termed "variations" in other established databases have to be classified based upon the incidence within the specific rat strain. The incidence of variations within the rat strain used in this study is unknown since the authors used a rat strain common only to their laboratory in Poland. The laboratory feed was also unique to

		their laboratory in Poland. Since the strain of rat and type and quality of diet can have a profound effect on rates or variations and malformations and since there is no historical database for these animals, the term "variation" has to be assigned with reservation. However, since these variations are common to several rat strains commonly used in the United States, the term "variation" appears appropriate. In fact, the data from Nelson, et al., (1989a) also reports some of these variations following inhalation exposure. It should not be surprising that high oral doses of n-butanol that would be expected to alter normal maternal physiology would cause an increase in common variations in laboratory rodents.
	Reference:	Sitarek, K., Berlinska, B., and Baranski, B. Assessment of the Effect of n-Butanol Given to Female Rats in Drinking Water on Fertility and Prenatal Development of Their Offspring. Int. J. of Occupational Medicine and Environmental Health, 7(4):365-370, 1994.
(D.)	Preferred Value:	Score=1
	Species:	rat
	Strain:	Sprague-Dawley
	Sex:	female
	Route of Admin.:	inhalation
	Exposure Period:	Group 1-Control Group 2-Day 7-16 of gestation Group 3- Day 1-16 of gestation Group 4- 3 weeks prior to mating and from Day 1-16 of gestation
	Frequency of Treatment:	Premating, 7h/day, 5 day/week During gestation, 7h/day, 7 days/week
	Duration of Test:	Variable (see exposure period)
	Exposure Concentration:	1,500 ppm (7,230 mg/mg^3)
	Control Group:	yes, concurrent no treatment
	LOEL (Maternal Toxicity):	1,500 ppm
	NOEL (Teratogenicity):	1,500 ppm
	Method Other:	Four groups, each containing 37-43 female Sprague-Dawley rats were exposed to n-butyl acetate air concentrations of either 0 or 1,500 ppm for 7 hours/day. The rats were maintained in the exposure chambers throughout the study period, 3 weeks pre-gestation until gestation day 21. Group 1 was not exposed to test material throughout the study and served as the control. Group 2 was exposed to 1,500 ppm n-butyl acetate from day 7 to 16 of gestation. Group 3 received n-butyl acetate from Day 1 to 16 of gestation and Group 4 was exposed from 3 weeks pre-gestation through day 16 of gestation. All test material exposures were discontinued from gestation day 17 through study termination. Premating exposures were for 5 days/week while gestational exposures were continuous. On gestation Day 21 (sperm positive = Day 1), the fetuses were collected and examined for both skeletal and visceral malformations. Vapor atmospheres of n-butyl acetate were generated using a heated,

		stainless steel vaporizer with vapor concentrations controlled by a pump metering the amount of liquid available. The chambers were 2.3 m^3 in volume and exposure concentrations were within 3% of target.
	Year:	1982
	GLP:	yes
	Test Substance:	n-butyl acetate, purity 99%
	Result:	Feed consumption was decreased in each test group in the week following initiation on n-butyl acetate exposure. The decrease in feed consumption was accompanied by decreases in body weight in Groups 3 and 4. Relative kidney and lung weights were increased in animals exposed to n-butyl acetate, with the greatest increase occurring in the animals receiving the longest exposure. There were no changes in histopathology that could be related to n-butyl acetate exposure. Mating and reproductive performance and intrauterine mortality was unaffected. Fetal growth measures (fetal body weights and crown-rump growth) and placental weights were lower in Groups 2, 3, and 4. However, the duration of exposure and period of gestation during which exposure occurred did not affect fetal growth indices. Sex ratios were unaffected. There was no increase in the incidence of "Major Malformations" in any of the n-butyl acetate exposed groups. There was an increase in the incidence of the skeletal anomalies ("total rib dysmorphology") and in skeletal variation "reduced ossification of the pelvis" in Groups 2 and 3, but not in Group 4. The incidence of rib dysmorphology in the control population was zero. Group 4 had an increased incidence in "hydroureter" when compared to the control group (Group 1). Groups 2 and 3 were unaffected. The lack of a uniform response between Groups 2,3, and 4 for the effects noted above that should have occurred during the same exposure period (Gestation Day 7-16), led the authors to conclude, "We hesitate to define this as a teratogenic effect of n-butyl acetate, since a similar increase was not seen in the group of rats exposed during this period of gestation subsequent to a pregestational exposure."
	Reference:	Hackett, P.L., M.G. Brown, R.L. Buschbom, M.L. Clark, R.A. Miller, R.L. Music, S.E. Rowe, R.E. Schirmer, and M.R. Sikov. 1982. Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl Acetate. Prepared by the U.S. Department of Health and Human Services. Public Health Service. Center for Disease Control. National Institute for Occupational Safety and Health. Division of Biomedical and Behavioral Science. Experimental Toxicology Branch, Cincinnati, Ohio 45266. NTIS PB83-258038.
(E.)	Preferred Value:	Score = 1
	Species:	rabbit
	Strain:	New Zealand White
	Sex:	female
	Route of Admin.:	inhalation
	Exposure Period:	Group 1- Control Group 2- Day 7-19 of gestation Group 3- Day 1-19 of gestation
	Frequency of	

Treatment:	7 hours/day
Duration of Test:	variable
Doses:	1,500 ppm (7,230 mg/m3)
Control Group:	yes, concurrent no treatment
NOEL Maternal Toxicity:	1,500 ppm
NOEL Teratogenicity:	1,500 ppm
Method Other:	Three groups of 21-25 female New Zealand White rabbits were exposed to n-butyl acetate air concentrations of either 0 or 1,500 ppm. Rabbits in all groups were placed in exposure chambers for 7-hours per day from study day 1 to 19. The rabbits were housed outside of the exposure chambers between exposure (sham or test material) periods. Group 1 received sham exposures to filtered air throughout the study and served as controls. Group 2 was exposed to 1,500 ppm n-butyl acetate from Day 7 to 19 of gestation. Group 3 was exposed to test material from gestation Day 1 to 19. All test material exposures were discontinued from gestation Day 20 through study termination. On gestation Day 30 the fetuses were collected and examined for both skeletal and visceral malformations. Feed consumption and body weight data were recorded. Vapor atmospheres of n-butyl acetate were generated using a heated, stainless steel vaporizer with vapor concentrations controlled by a pump metering the amount of liquid available. The chambers were 2.3 m^3 in volume and exposure concentrations were within 3% of target.
Year:	1982
GLP:	yes
Test Substance:	n-butyl acetate, purity 99%
Result:	Feed consumption was decreased in Groups 2 and 3 in the week following initiation of n-butyl acetate exposure. However, feed consumption was always lowest in Group 1 (controls). The body weight in Groups 2 and 3 were consistently higher than Group 1. Organ weights and histopathology were unremarkable in the n-butyl acetate exposed animals. Mating and reproductive performance and intrauterine mortality was unaffected for n-butyl acetate exposure. Fetal growth measures (fetal body weights and crown-rump length), placental weights, and sex ratios were not affected by n-butyl acetate exposures. There was no increase in the incidence of “Major Malformations” in any of the n-butyl acetate exposure groups. In terms of “Minor Anomalities,” there was an increase in the incidence of “misaligned sternabra” and “retinal folds” in Group 3; Group 2 was not affected. Only a single increased incidence of “Morphologic Variations” was found, an increase in “clear gallbladder”; and that only in Group 3. The authors concluded that rabbit fetuses were unaffected by n-butyl acetate exposure based upon a lack of uniform response between the two exposure groups.
Reference:	Hackett, P.L., M.G. Brown, R.L. Buschbom, M.L Clark, R.A. Miller, R.L. Music, S.E. Rowe, R.E. Schirmer, and M.R. Sikov. 1982. Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl Acetate. Prepared by the U.S. Department of Health and Human Services. Public Health Service. Center for Disease

Control. National Institute for Occupational Safety and Health. Department of Biomedical and Behavioral Science. Experimental Toxicology Branch. Cincinnati, Ohio 45266. NTIS PB83-258038.

5.10 OTHER RELEVANT INFORMATION

A. SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.)

Species:	rat
Strain:	Sprague-Dawley (SD)
Sex:	male and female
Route of Admin:	inhalation
Exposure Period:	13 weeks
Freq. of Treatment:	6 h/day, 5 days/week 65 exposure days (13 weeks)
Post Exposure Observation Period:	2 weeks
Doses:	0, 500, 1500, and 3000 ppm
Control Group:	yes
NOAEL:	3000 ppm
LOAEL:	N/A
Method:	The study consisted of two sets of animals, male and female *ad libitu*m-fed Sprague-Dawley (SD) rats designated for functional observational battery, motor activity, and neuropathology endpoints (FOB/MA/NP) and male (SD) rats restricted to 12-14 g of feed per day and which were designated for schedule-controlled operant behavior (SCOB). Both sets of animals were exposed to concentrations of 0, 500, 1500, or 3000 ppm of n-butyl acetate for at least 65 exposures over 14 weeks. The animals were exposed in 4200 L glass and stainless steel chambers for 6 hours per day. Metering the liquid test substance through heated glass distillation columns packed with glass beads generated vapors of the test substance. The time-weighted average analytical concentrations were within 10% of the target concentrations. The target analytical concentration for the 500-ppm group was increased to 550 ppm after consultation with the Sponsor because determination of chamber atmosphere homogeneity showed that the variation in actual exposure concentration at various locations in the chamber was on average 13% lower than the reference point. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to one hour after exposure. Body weights were collected weekly. Feed consumption data was not collected on the *ad libitu*m-fed animals. At the end of the 14-week exposure period, five male and five female animals from the FOB/MA/NP groups were randomly selected and perfused systemically for neuropathologic examination. Brain, spinal cord swellings (with dorsal and ventral routes), dorsal root ganglia, sciatic nerve, and tibial nerves were examined microscopically.
Year:	1996
GLP:	Yes
Test substance:	n-butyl acetate (>99.9% pure)
Remark:	The SCOB testing paradigm involved both fixed-interval (FI) and fixed-ratio (FR) schedules.

Results: NOAEL Neurotoxicity = 3000 ppm
Animals exposed to 1500 or 3000 ppm had minimal to minor reduced activity levels. There was no evidence of a cumulative effect of exposure on the severity of reduced activity. There was no evidence of a cumulative effect of exposure on the severity of reduced activity. Control and 500 ppm animals appeared normal during exposure. There were no other apparent differences in the clinical condition of FOB/MA/NP and SCOB animals. Body weights and/or body weight gains were reduced in the 1500 and 3000-ppm male and female animals. No differences in body weight or rate of weight gain were noted in the 500-ppm exposure group animals when compared to control groups. There was no evidence of neurotoxicity based on FOB, motor activity, neuropathology, and SCOB endpoints. Therefore, the no-observable effect level (NOAEL) for subchronic neurotoxicity for this study is 3000 ppm based on the lack of cumulative neurotoxicity following repeated exposure.

Comments: The rapid *in vivo* hydrolysis of n-butyl acetate to 1-butanol makes this study directly applicable to 1-butanol exposure*s*.

References: David, R.M., Tyler, T.R., Ouellette, R., Faber, W.D., Banton, M.I., Garman, R.H., Gill, M.W., and O'Donoghue, J.L. Evaluation Of Subchronic Neurotoxicity Of N-Butyl Acetate Vapor. NeuroToxicology 19: 809-822, 1998.
A Thirteen-Week Subchronic Inhalation Neurotoxicity Study in the Rat. HAEL NO. 94-0305 and 94-0306, KAN 900710, CAS 000123-86-4. Final Report. Toxicological Sciences Laboratory, Health and Environmental Laboratories Eastman Kodak Company Rochester, New York.

B. TOXICODYNAMICS, TOXICOKINETICS

(a) Preferred value (score = 2)

Species: rat, human

Method: The metabolic series approach for risk assessment uses a dosimetry-based analysis to develop toxicity information for a group of metabolically linked compounds using pharmacokinetic (PK) data for each compound and toxicity data for the parent compound. The metabolic series approach for n-butyl acetate and its subsequent metabolites, n-butanol and n-butyric acid (the butyl series) was first demonstrated using a provisional PBPK model for the butyl series. The objective of this work was to complete development of the PBPK model for the butyl series using all available human and rat data. Rats were administered test compounds by i.v. bolus dose, i.v. infusion, or by inhalation in a recirculating closed chamber. Hepatic, vascular and extravascular metabolic constants for metabolism were estimated by fitting the model to the blood time course data from these experiments.

Year: 2005

GLP: No, model validation - yes

Test substances: n-butyl acetate, n-butanol, n-butyric acid

Result: The respiratory bioavailability of n-butyl acetate (100% of alveolar ventilation) and n-butanol (50% of alveolar ventilation) was estimated from closed chamber inhalation studies and measured ventilation rates.

The resulting butyl series PBPK model successfully reproduces the blood time course of these compounds following i.v. administration and inhalation exposure to n-butyl acetate and n-butanol in rats and arterial blood n-butanol kinetics following inhalation exposure to n-butanol in humans. These validated inhalation route models can be used to support species and dose-route extrapolations required for risk assessment of butyl series family of compounds. Using the models, equations were developed to allow human equivalent concentrations (HEC) of n-butanol and n-butyl acetate to be calculated corresponding to the rat exposures. The equations can be used with confidence in the range of the rat exposures (approximately 2000 ppm for either n-butanol or n-butyl acetate) or human exposures (100-200 ppm n-butanol). The HEC for n-butanol from the rat n-butyl acetate exposures is represented by the equation "HEC (a n-butanol exposure in ppm) = $(1x10^{-11} \times ppm^3_{butyl\ acetate} + 2x10^{-8} \times ppm^2_{butyl\ acetate} + 0.0022\ ppm_{butyl\ acetate})/0.0066$" Correspondingly, The HEC for n-butanol from the rat n-butanol exposures is represented by the equation "HEC (a n-butanol exposure in ppm) = $(1x10^{-8} \times ppm^2_{butanol} + 0.0016\ ppm_{butanol})/0.0066$" The reported error in the HEC by using these formulas rather than the PBPK model itself is less than 1%.

Reference: Teeguarden, J.G., P. J. Deisinger, T.S. Poet, J. C. English, W.D. Faber, H.A. Barton, R.A. Corley, and H. J. Clewell III (2005) "Derivation of a Human Equivalent Concentration for n-Butanol Using A Physiologically-Based Pharmacokinetic Model for n-Butyl Acetate and Metabolites n-Butanol and n-Butyric Acid" *Toxicological Sciences*, accepted for publication.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(A.) Remark: The Monell Chemical Senses Center has conducted studies of the odor and irritation thresholds for n-butanol in workers and naïve subjects (32 persons in each category). The lateralization technique used by this group is based on differences in the afferent pathways for odor and sensory irritation. The techniques provides objective determinations of threshold levels for olfaction and sensory irritation. The studies indicated a median odor threshold for n-butanol of 0.17 ppm, and a median irritation threshold of 2402 ppm. The lowest irritation threshold in any test subject was 289 ppm.

Reference: Wysocki, C.J. and Dalton, P. 1996. Odor and Irritation Thresholds for 1-Butanol in Humans. Monell Chemical Senses Center. Philadelphia, PA.

(B.) Remark: Subsequent to the Monell studies, similar lateralization techniques were used by Cometto-Muniz and Cain to determine the odor and irritation thresholds of a series of n-alcohols, including n-butanol, in normosmic and anosmic subjects. Little, if any, difference was noted between the responses of either subject group. The odor and nasal irritation thresholds for n-butanol were 28.8 and 4163 ppm, respectively, based upon mean values from nine subjects. The results of this study provide further evidence that the sensory irritation threshold lies substantially above the odor threshold.

Reference: Cometto-Muniz, J.E.; Cain, W.S. 1998. Trigeminal and Olfactory Sensitivity: Comparison of Modalities and Methods of Measurement. *Int. Arch. Occup. Environ. Health.* 71:105-110.

(C.) Remark: Circumstantial evidence indicates that 1-butanol vapor may cause a special vacuolar keratopathy in humans. Experimentally, this effect has not been duplicated with laboratory animals.

Reference: Grant W. M. Toxicology of the Eye 3rd ed., Charles C. Thomas, Springfield IL, 1985 pp. 162-163.

(D.) Remark: 1-Butanol has been alleged to produce audiologic impairment in workers (Velazquez, et al 1969) The study in which this result was obtained has been critically reviewed and found to be deficient in regard to measurements of concentrations to which workers were exposed and methodology of audiologic measurements (Royster,1993).

Reference: Velazquez, J. Escobar, R. Almaraz, A. Audiologic Impairment Due to n-Butyl Alcohol Exposition. In: Proceedings of the XVI International Congress on Occupational Health, pp.231-234 Excerpta Medica Foundation, Tokyo (Sept. 22-27, 1969).

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