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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 1--BUTANOL

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Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986c, respectively.

EXECUTIVE SUMMARY

1-Butanol is also known by the synonyms n-butanol, n-butyl alcohol, butan-1-ol, methylolpropane, propylcarbinol and propylmethanol (Chemline, 1988). It is a highly refractive colorless liquid with a vinous or wine-like odor (Windholz, 1983; Sherman, 1978; Hawley, 1981). Seven U.S. manufacturers at eight sites in Texas and Louisiana have a combined production capacity of 1.3 billion pounds of 1-butanol annually (SRI, 1988). Domestic production of 1-butanol in 1987 and 1986 has been reported to be 1.155 and 0.881 billion pounds, respectively (USITC, 1987, 1988). 1-Butanol is manufactured primarily by the oxo process, in which propylene is reacted with carbon monoxide and hydrogen to form butyraldehyde, which is subsequently reduced to butanol (Sherman, 1978). The use pattern for 1-butanol has been reported as follows (CMR, 1984): butyl acrylates and methacrylate, 30%; glycol ethers, 23%; butyl acetate, 12.5%; solvent, 12.5%; plasticizers, 8%; amino resins, 5%; amines, 1%; miscellaneous, 1%; export, 7%.

When released to the atmosphere, 1-butanol is expected to exist in the vapor phase, where it will degrade relatively rapidly by reaction with sunlight-formed hydroxyl radicals. Based upon an experimentally measured rate constant (Atkinson, 1985), the atmospheric half-life for this reaction in average air is ~2.2 days. When released to either the aquatic or soil environments, 1-butanol is expected to degrade primarily by microbial degradation. A number of biological screening studies have demonstrated that 1-butanol is readily biodegradable under aerobic conditions (Hammerton, 1955; Bridie et al., 1979a; Wagner, 1976; Price et al., 1974; Urano and Kato, 1986; Babeu and Vaishnav, 1987; Gellman and Heukelekian, 1955; Dias

and Alexander, 1971; Hatfield, 1957; Pitter, 1976; McKinney and Jeris, 1955; Gerhold and Malaney, 1966). A river die-away study that used only natural river water as a microbial inocula found that 56% of added 1-butanol was bio-oxidized in a 4-day period (Hammerton, 1955). Chou et al. (1979) found 1-butanol biodegradable under anaerobic conditions. Following a 4-day lag period, 100% of added 1-butanol was degraded at a rate of ~100 ppm/day. In a soil degradation study, 51-58% of added butanol was released from the soil as CO_2 (presumably from microbial degradation) over a 20-day period (Fairbanks et al., 1985). Although not as important as microbial degradation, volatilization from soil within the first day of addition can be a significant removal mechanism (Fairbanks et al., 1985). The K_{oc} of 1-butanol has been estimated to be ~10, which indicates that leaching in soil is expected (Roy and Griffin, 1985); however, concurrent microbial degradation may lessen the importance of leaching.

Human exposure to 1-butanol can occur from both natural and human sources. Natural sources of air release include animal wastes, microbes and insects; human sources include volatilization from solvents (such as used in paints), rendering, sewage treatment, starch manufacture, whiskey manufacture, wood pulping and turbine emissions (Graedel et al., 1986). Concentrations of 34-445 ppb detected in the ambient air at Point Barrows, AL, are thought to occur as a result of a fermentation process of the tundra cover (Cavanagh et al., 1969). 1-Butanol appears to occur naturally in volatile components of apples, pears, grapes, dried legumes and mountain cheese (Drawert et al., 1962; Stevens et al., 1965; Lovegren et al., 1979; Dumont and Adda, 1978). Release of 1-butanol to water can occur through wastewater emissions from chemical and textile plants, sewage treatment plants, oil refineries, landfill leaching and kraft pulp mills (Shackelford and Keith, 1976; Carlberg et al., 1986). 1-Butanol has been detected tentatively and

qualitatively in drinking water concentrates collected from Cincinnati, OH, Miami, FL, New Orleans, LA, Philadelphia, PA, and Seattle, WA (Lucas, 1984).

The 24-hour LC_{50} for creek chub exposed to 1-butanol would probably be between 1000 and 1400 ppm (Gillette et al., 1952). The threshold narcotic concentration for 1-butanol in frog tadpoles was 38 mmol/ℓ (Munch, 1972). Bridie et al. (1973, 1979b) reported a 24-hour TL_m of 1900 mg/ℓ for goldfish exposed to 1-butanol. Bresch and Spielhoff (1974) reported that the limits of toxicity to the 8-cell and gastrula stages of the sea urchin embryo were $\sim 8 \times 10^{-6}$ and $\sim 3 \times 10^{-5}$ mol/mℓ, respectively. Price et al. (1974) reported a 24-hour TL_m of 2950 mg/ℓ for brine shrimp exposed to n-butanol, although Hudson et al. (1981) reported the lack of mortality among brine shrimp exposed to <100 μM n-butanol (<7412 mg/ℓ) for 24 hours. The 96-hour LC_{50} for fathead minnows exposed to butanol ranged from 1510-1940 mg/ℓ (Mattson et al., 1976; Veith et al., 1983; Brooke et al., 1984). The 24-hour EC_{50} and LC_{50} for Daphnia magna exposed to butanol were 1880 and 1855 mg/ℓ, respectively (Bringmann and Kühn, 1977a, 1982). Juhnke and Luedemann (1978) reported that exposure of the Golden Orfe to n-butanol for 48 hours produced LC_{50} values of 1200 and 1770 mg/ℓ for studies conducted in two different laboratories. Linden et al. (1979) reported 96-hour LC_{50}s of 2100 and 2250-2400 mg/ℓ for copepods and bleaks exposed to 1-butanol, respectively.

Concentrations of butanol in brain tissue of goldfish exposed to 10 and 15 mM solutions of butanol reached equilibrium levels of 0.46 and 0.74 mg/g, respectively, within ~60 minutes (Hill et al., 1981). Concentrations of butanol in brain tissue from fish exposed to 20 mM solutions did not plateau within the first 30 minutes, ultimately reaching an equilibrium concentration of 0.95 mg/g. The investigators speculated that goldfish possessed the ability to metabolize butanol.

No measured steady-state BCF value for butanol was found in the literature. An estimated BCF value of 2.75 for this compound suggests that butanol will not bioaccumulate significantly in aquatic organisms.

Toxicity threshold levels for exposure of Microcystis aeruginosa to n-butanol were 100 and 312 mg/ℓ, while toxicity threshold levels for exposure of Scenedesmus quadricauda to n-butanol were 95 and 875 mg/ℓ (Bringmann, 1975; Bringmann and Kühn, 1976, 1977b, 1978, 1979, 1980). Haley et al. (1987) reported a 96-hour EC_{50} of 2000 mg/ℓ for the green alga, Chlorella pyrenoidosa. The toxicity thresholds for an aquatic bacterium, Pseudomonas putida, and a flagellated protozoan, Entosiphon sulcatum, exposed to butanol were 650 and 55 mg/ℓ, respectively (Bringmann and Kühn, 1976, 1977b, 1979, 1980, 1981). The toxicity threshold values for a holozoic bacteriovorous ciliated protozoan, Uronema parduczi Chatton-Lwoff, and a saprozoic ciliated protozoan, Chilomonas paramecium Ehrenberg, exposed to n-butanol were 8.0 and 27 mg/ℓ, respectively (Bringmann and Kühn, 1981).

The 15-minute log EC_{50} for Photobacterium phosphoreum exposed to n-butanol in the Microtox bacterial luminescence assay was 4.58 (~38,000 mg/ℓ) (Hermens et al., 1985). Tarkpea et al. (1986) reported 5-, 15- and 30-minute EC_{50} values of 3370, 3690 and 3710 mg/ℓ, respectively, for P. phosphoreum exposed to 1-butanol in the Microtox assay. Vaishnav (1986) reported an EC_{50} of 10,614 mg/ℓ for a mixed microbial culture from a wastewater sample exposed to 1-butanol.

Mallard duck eggs immersed in 100% solutions of butanol for 30 seconds failed to produce viable chicks by day 18 of incubation (Hoffman and Eastin, 1981). There were no effects on embryos in duck eggs exposed to distilled water or 10% butanol. Schafer et al. (1983) estimated an oral LD_{50} of <2500 mg/kg for starlings treated with butanol.

1-Butanol was taken up readily by the respiratory tracts of humans (Astrand et al., 1976) and dogs (DiVincenzo and Hamilton, 1979). Levels of 1-butanol in the blood of humans following inhalation exposure were lower than expected based on a measured blood/air partition coefficient and the disappearance of the compound from inhaled air (Astrand et al., 1976). This observation may reflect sequestration of 1-butanol in mucosal tissue water in the lung (Astrand et al., 1976) or rapid metabolism of the compound following absorption (DiVincenzo and Hamilton, 1979). 1-Butanol appears to be absorbed rapidly and virtually completely from the gastrointestinal tracts of rats (DiVincenzo and Hamilton, 1979).

In addition, 1-butanol is absorbed through oral mucosa (Siegel et al., 1976), intestines (Winne, 1978, 1979), skin (Scheuplein and Blank, 1973; Akhter et al., 1984; DiVincenzo and Hamilton, 1979; DelTerzo et al., 1986; Behl et al., 1983, 1984) and the cornea (Grass and Robinson, 1984). Following oral treatment of rats with 1-^{14}C-butanol, the largest amounts of radioactivity were located in the liver, kidney and blood. Unchanged 1-butanol levels in plasma were below detection limits at 4 hours after treatment (DiVincenzo and Hamilton, 1979). 1-Butanol was metabolized rapidly to carbon dioxide (~80% of the dose) (DiVincenzo and Hamilton, 1979), primarily by hepatic microsomal alcohol dehydrogenase (Brentzel and Thurman, 1977; Videla et al., 1982). Smaller amounts were excreted in the urine as sulfate and glucuronide conjugates and as urea.

At 24 hours after rats were treated orally with 1-^{14}C-butanol, ~14% of the dose of radioactivity was retained in the carcass, attributed to the incorporation of ^{14}C into the one-carbon pool (DiVincenzo et al., 1979).

1-Butanol is mildly toxic to humans and laboratory species. Human inhalation exposure to 1-butanol at levels of 25-50 ppm (75-150 mg/m^3) is irritating to the eyes, nose and throat, and can cause headaches, but no

systemic effects occur at this exposure level (Nelson et al., 1943; Amoore and Hautula, 1983; Tabershaw et al., 1944; Seitz, 1972). Sensory irritation and neurobehavioral toxicity have been noted in mice and rats exposed by inhalation to high levels of 1-butanol (DeCeaurriz et al., 1981, 1983; Alarie, 1981). Acute dermal contact with the liquid in oil is irritating to healthy human skin (Ba'inova and Madzhunov, 1984), and eye contact with the vapor can cause painful keratitis and conjunctivitis (Cogan and Grant, 1945).

Rabbits and male rats appear to be equally sensitive to acute oral doses of 1-butanol, but female rats are more sensitive; single-dose oral LD_{50} values ranged from 0.79-4.36 g/kg (Munch, 1972; Ciugudeanu et al., 1985; Smyth et al., 1951; Jenner et al., 1964; Purchase, 1969). Acute oral exposure to 1-butanol at 1200 mg/kg caused decreased ability of rats to retain balance (Wallgren, 1960). Dose-related hypothermia and impaired coordination of muscular activity occurred in mice treated by gavage at 1.0 or 2.0 g/kg (Maickel and Nash, 1985). Single oral 810 mg/kg doses administered to rats induced significant dose-related decreases in liver content of vitamins (Shehata and Saad, 1978). Sensitivity to intravenous or intraperitoneal injection is greater than sensitivity by the oral route among rats and mice, but very little difference in toxic response was found between these species (Tichy et al., 1985; Maickel and McFadden, 1979). Abnormal EEG and loss of righting reflex occur in rats exposed to a single intravenous (500 mg/kg) or intraperitoneal (600 mg/kg) injection of 1-butanol (Marcus et al., 1976).

Subchronic inhalation studies have been performed using rats and guinea pigs, and human epidemiology studies are available. Liver and kidney degeneration and hematologic effects were reported in guinea pigs intermittently exposed to 100 ppm (300 mg/m^3) for 9 weeks (Smyth and Smyth, 1928).

Foreign studies using rats reported no effects with continuous exposure to 0.09 mg/m³, but effects on the blood and CNS at concentrations of ≥0.8 mg/m³ (Savel'ev et al., 1975; Rumyantsev et al., 1976; Baikov and Khachaturyan, 1973). In an occupational study, no effects were reported at 100 ppm (300 mg/m³); ocular irritation was reported at 200 ppm (600 mg/m³) (Sterner et al., 1949).

Oral exposure data are limited to subchronic studies. Rats treated by gavage with 1-butanol at 30 mg/kg/day for 13 weeks showed no toxic effects; transitory effects on hematology (RBC, PCV) were noted among females but not males at 125 mg/kg/day, and 500 mg/kg/day caused ataxia and hypoactivity in the final 6 weeks of treatment among both sexes (U.S. EPA, 1986a). 1-Butanol administered in drinking water to rats for up to 3 months at a high dose (9660 mg/kg/day) caused structural alterations of liver mitochondria, accompanied by moderately decreased MAO and cytochrome oxidase activity (Wakabayashi et al., 1984).

Data regarding carcinogenicity to humans or animals were not located in the available literature. Results of mutagenicity and genotoxicity testing were mixed. 1-Butanol is not scheduled for testing by the NTP (1988).

1-Butanol, when administered by gavage, was not a developmental toxicant to rats at dosages up to 24% of the oral LD_{50} (Mankes et al., 1985). Inhalation exposure to 8000 ppm (24,250 mg/m³) resulted in mild maternal toxicity and decreased fetal body weight in rats, but teratogenicity was not evident (Brightwell et al., 1987). Reversible effects on testicular endocrine function were noted in rats intermittently exposed to 500 ppm (1516 mg/m³) (Cameron et al., 1985).

In vitro studies have demonstrated toxic effects of 1-butanol on cardiac and smooth muscle (Nakano and Moore, 1973; Madan et al., 1969) and on cellular structure and function (Walum and Peterson, 1983; Chen et al., 1984; Masamoto et al., 1974).

Because of the lack of cancer data for either humans or experimental animals, 1-butanol was assigned to EPA Group D -- not classifiable as to carcinogenicity to humans. Therefore, neither cancer potency factors nor a cancer-based RQ were derived.

Although inhalation data were available, they were insufficient for derivation of RfD values for either subchronic or chronic inhalation exposure. The NOAEL of 125 mg/kg/day from the 13-week gavage study sponsored by U.S. EPA (1986a) served as the basis for the RfD of 1 mg/kg/day for subchronic oral exposure. An RfD of 0.1 mg/kg/day for chronic oral exposure was derived from the same study.

An RQ for chronic toxicity of 1000 pounds based on ocular irritation in occupationally-exposed women (Velasquez, 1964; Velasquez et al., 1969) has been recommended to supersede that of the earlier analysis (U.S. EPA, 1987b) in which an RQ of 5000 pounds was derived.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biological oxygen demand
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
EEG	Electroencephalogram
GLC	Gas-liquid chromatography
GMAV	Genus mean acute value
GMCV	Genus mean chronic value
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration)
LD_{50}	Dose lethal to 50% of recipients (and all other subscripted dose levels)
LH	Luteinizing hormone
LOAEL	Lowest-observed-adverse-effect level
MAO	Monoamine oxidase
MED	Minimum effective dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NOAEL	No-observed-adverse-effect level
PCV	Packed cell volume
PEL	Permissible expsure level

ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cell
RD_{50}	Concentration associated with a 50% decrease in respiratory rate
RfD	Reference dose
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TL_m	Median tolerance limit
TLV	Threshold limit value
TOC	Total organic carbon
TWA	Time-weighted average
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1-Butanol is also known by the synonyms n-butanol, n-butyl alcohol, butan-1-ol, methylolpropane, propylcarbinol and propylmethanol (Chemline, 1988). The structure, molecular weight, empirical formula and CAS number for 1-butanol are as follows:

$$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OH$$

Molecular weight: 74.12

Empirical formula: $C_4H_{10}O$

CAS Registry number: 71-36-3

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1-Butanol is a highly refractive colorless liquid with a vinous or wine-like odor (Windholz, 1983; Sherman, 1978; Hawley, 1981). It is miscible with alcohol, ether and many other organic solvents (Windholz, 1983). Selected physical properties are as follows:

Melting point:	-90.2°C	Sherman, 1978
Boiling point:	117.7°C	Sherman, 1978
Specific gravity:	0.810 (20/4°C)	Windholz, 1983
Vapor pressure at 22.6°C: at 25.0°C: (using Antoine equation) at 30.9°C:	 5.5 mm Hg 6.64 mm Hg 10.3 mm Hg	 Kemme and Kreps, 1969

Water solubility at 25°C:	73,000 ppm	Amoore and Hautala, 1983
Log K_{ow}:	0.88	Hansch and Leo, 1985
TLV:	50 ppm (air)	Amoore and Hautala, 1983
Water odor threshold:	7.1 ppm	Amoore and Hautala, 1983
Conversion factor: (air at 20°C)	1 mg/m³ = 0.33 ppm 1 ppm = 3.03 mg/m³	Verschueren, 1983

The chemical reactivity of 1-butanol is based primarily on the hydroxyl function; therefore, the most important reactions are dehydration, dehydrogenation, oxidation and esterification (Sherman, 1978). 1-Butanol is flammable and has a flash point of 36-38°C (Windholz, 1983).

1.3. PRODUCTION DATA

Table 1-1 lists commercial manufacturers of 1-butanol and their annual capacities.

United States production of 1-butanol in 1987 and 1986 has been reported to be 1.155 and 0.881 billion pounds, respectively (USITC, 1987, 1988).

The primary method of manufacturing 1-butanol in the United States is the oxo process, which is used by all of the manufacturers cited in Table 1-1 except Ethyl Corp. and Vista Chemical (SRI, 1988). Ethyl Corp. and Vista Chemical produce 1-butanol by the Ziegler process (SRI, 1988). In the oxo process, propylene is reacted with carbon monoxide and hydrogen in the presence of an appropriate catalyst to yield n- and iso-butyraldehyde (Sherman, 1978). Reduction of the n-butyraldehyde yields 1-butanol. The Ziegler process involves reaction of ethylene with aluminum alkyls followed by oxidation and hydrolysis to yield 1-butanol (Gautreaux et al., 1978).

TABLE 1-1

Commercial Manufacturers of 1-Butanol*

Company	Location	Annual Capacity (millions of pounds)
BASF Corp.	Freeport, TX	130
Eastman Kodak (Texas Eastman)	Longview, TX	190
Ethyl Corp.	Pasadena, TX	5
Hoechst Celanese	Bay City, TX Bishop, TX	225 175
Shell Oil Co.	Deer Park, TX	180
Union Carbide Corp.	Texas City, TX	400
Vista Chemical	Lake Charles, LA	7

*Source: SRI, 1988

1.4. USE DATA

The following use pattern for 1-butanol has been reported (CMR, 1984):

Butyl acrylates and methacrylate	30%
Glycol ethers	23%
Butyl acetate	12.5%
Solvent	12.5%
Plasticizers	8%
Amino resins	5%
Amines	1%
Miscellaneous	1%
Exports	7%

As can be seen from the information above, 1-butanol is used mainly as a chemical intermediate in the manufacture of other chemicals. About 12.5% of production is consumed in solvent applications for fats, waxes, resins, shellac, varnishes, gums and other materials (Windholz, 1983).

1.5. SUMMARY

1-Butanol is also known by the synonyms n-butanol, n-butyl alcohol, butan-1-ol, methylolpropane, propylcarbinol and propylmethanol (Chemline, 1988). It is a highly refractive colorless liquid with a vinous or wine-like odor (Windholz, 1983; Sherman, 1978; Hawley, 1981). Seven U.S. manufacturers at eight sites in Texas and Louisiana have a combined production capacity of 1.3 billion pounds of 1-butanol annually (SRI, 1988). Domestic production of 1-butanol in 1987 and 1986 has been reported to be 1.155 and 0.881 billion pounds, respectively (USITC, 1987, 1988). 1-Butanol is manufactured primarily by the oxo process, in which propylene is reacted with carbon monoxide and hydrogen to form butyraldehyde, which is subsequently reduced to butanol (Sherman, 1978). The use pattern for 1-butanol has been reported as follows (CMR, 1984): butyl acrylates and methacrylate, 30%; glycol ethers, 23%; butyl acetate, 12.5%; solvent, 12.5%; plasticizers, 8%; amino resins, 5%; amines, 1%; miscellaneous, 1%; export, 7%.

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Based upon its relatively high vapor pressure of 5.5 mm Hg at 22.6°C (Kemme and Kreps, 1969), 1-butanol is expected to exist almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al., 1981). The dominant degradation process in ambient air is probably reaction with sunlight-formed hydroxyl radicals. Based upon an experimentally determined rate constant of 7.32×10^{-12} cm³/molecule-sec at 19°C and an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm³ (Atkinson, 1985), the half-life for this reaction can be estimated to be 2.2 days.

1-Butanol has a relatively high water solubility of 73,000 ppm (Amoore and Hautala, 1983), which suggests that physical removal from air by wet deposition (washout by rainfall, dissolution in clouds, etc.) is possible. The relatively fast degradation rate by hydroxyl radicals, however, is probably more important than physical removal for the general ambient air environment.

2.2. WATER

2.2.1. Hydrolysis. Experimental hydrolysis data regarding 1-butanol were not located. Because alcohols are generally resistant to environmental hydrolysis (Harris, 1982), hydrolysis of 1-butanol in the aquatic environment is not expected to be important.

2.2.2. Oxidation. The rate constant for the reaction between 1-butanol and hydroxyl radicals in water at room temperature is ~4×10^9/M-sec (Guesten et al., 1981). Assuming an ambient hydroxyl radical concentration of 1×10^{-17} M in brightly sunlit natural water (Mill et al., 1980), the half-life can be estimated to be ~200 days. Therefore, this reaction should have no environmental significance.

2.2.3. Photolysis. Pertinent data regarding the photolysis of 1-butanol in the aquatic environment were not located; however, 1-butanol does not contain any significantly active chromophores. Therefore, direct photolysis in the environment should not be important.

2.2.4. Microbial Degradation. 1-Butanol has been shown to biodegrade readily in a number of aerobic biological screening studies (Hammerton, 1955; Bridie et al., 1979a; Wagner, 1976; Price et al., 1974; Urano and Kato, 1986; Babeu and Vaishnav, 1987; Gellman and Heukelekian, 1955; Dias and Alexander, 1971; Hatfield, 1957; Pitter, 1976; McKinney and Jeris, 1955; Gerhold and Malaney, 1966). For example, Hammerton (1955) found that 1-butanol (3 ppm) was degraded readily by biochemical means in a natural river die-away test using only river water as inoculum. Graphical interpretation of results after 4 days of inoculation indicated that ~56% of initial 1-butanol had bio-oxidized. The rest of the screening studies cited above used inocula such as activated sludge or sewage and test methods such as standard dilution or respirometric methods. Typical test results for standard dilution studies are measured 5-day theoretical BODs of 42-86.8% (Wagner, 1976; Price et al., 1974; Bridie et al., 1979a; Urano and Kato, 1986).

Chou et al. (1979) found 1-butanol biodegradable under anaerobic conditions. Using the Hungate serum bottle technique, 1-butanol at an initial concentration of 500 ppm exhibited a 4-day lag period before 100% of initial substrate was degraded at a rate of ~100 ppm/day.

2.2.5. Volatilization. The Henry's Law constant for 1-butanol has been measured experimentally to be 7.89×10^{-6} atm-m^3/mole at 25°C (Snider and Dawson, 1985). A Henry's Law constant of this magnitude indicates that volatilization from environmental waters is generally slow, although

volatilization from shallow rivers may be significant (Thomas, 1982). Using a model river estimation method (Thomas, 1982), the volatilization half-life of 1-butanol from a river 1 m deep flowing 1 m/sec with a wind velocity of 3 m/sec can be estimated to be ~4.1 days. The volatilization half-life from a model environmental pond can be estimated to be ~44.5 days (U.S. EPA, 1987a). Based upon these estimates, volatilization from water does not appear to be as environmentally important as microbial degradation, with the possible exception of very shallow rivers.

2.2.6. **Adsorption.** The relatively high water solubility of 1-butanol (73,000 ppm at 25°C) suggests that partitioning from the water column to sediment and suspended material should not be important.

2.2.7. **Bioconcentration.** Experimental BCFs for 1-butanol in fish were not located. A BCF of 2.75 can be calculated using a log K_{ow} value of 0.88 (Hansch and Leo, 1985) and the following recommended equation (Bysshe, 1982): log BCF = 0.76 log K_{ow} - 0.23. This calculated BCF value indicates that bioconcentration in aquatic organisms is not significant.

2.3. SOIL

2.3.1. **Microbial Degradation and Volatilization.** Fairbanks et al. (1985) studied the degradation and volatilization of 14-radiolabeled 1-butanol in two agricultural soils from New Mexico under laboratory conditions. Total losses in both soils averaged 67% over a 20-day observation period with a majority of the loss occurring during the initial 2 days. Degradation losses of butanol to $^{14}CO_2$ (presumably by microbial means) were 2-17 times greater than losses by volatilization. Nearly all of the volatilization occurred within the first day as expected, since 1-butanol has a relatively high vapor pressure. The authors suggested that subsequent volatilization may be attenuated by sorption to clay particles. After 20

days, evolution of $^{14}CO_2$ averaged 51-58% of the total initial amounts added. The rates of CO_2 evolution indicate that 1-butanol biodegrades readily in the tested soils. This result is consistent with the results of the biological screening studies noted in Section 2.2.4.

2.3.2. Adsorption/Leaching. Based upon its water solubility and log K_{ow}, the K_{oc} for 1-butanol has been estimated to be ~10, which indicates that it should be very highly mobile in soil (Roy and Griffin, 1985). Detection of 1-butanol in leachate monitoring wells in the vicinity of a solid waste landfill and paint factory may demonstrate that 1-butanol is mobile in soil (Dewalle and Chian, 1981; Botta et al., 1984). Alcohols, such as butanol, can adsorb to clay surfaces (Fairbanks et al., 1985; Stul et al., 1979), which may retard the rate of leaching in some soils.

2.4. SUMMARY

When released to the atmosphere, 1-butanol is expected to exist in the vapor phase, where it will degrade relatively rapidly by reaction with sunlight-formed hydroxyl radicals. Based upon an experimentally measured rate constant (Atkinson, 1985), the atmospheric half-life for this reaction in average air is ~2.2 days. When released to either the aquatic or soil environments, 1-butanol is expected to degrade primarily by microbial degradation. A number of biological screening studies have demonstrated that 1-butanol is readily biodegradable under aerobic conditions (Hammerton, 1955; Bridie et al., 1979a; Wagner, 1976; Price et al., 1974; Urano and Kato, 1986; Babeu and Vaishnav, 1987; Gellman and Heukelekian, 1955; Dias and Alexander, 1971; Hatfield, 1957; Pitter, 1976; McKinney and Jeris, 1955; Gerhold and Malaney, 1966). A river die-away study that used only natural river water as a microbial inocula found that 56% of added 1-butanol was bio-oxidized in a 4-day period (Hammerton, 1955). Chou et al. (1979) found

1-butanol biodegradable under anaerobic conditions. Following a 4-day lag period, 100% of added 1-butanol was degraded at a rate of ~100 ppm/day. In a soil degradation study, 51-58% of added butanol was released from the soil as CO_2 (presumably from microbial degradation) over a 20-day period (Fairbanks et al., 1985). Although not as important as microbial degradation, volatilization from soil within the first day of addition can be a significant removal mechanism (Fairbanks et al., 1985). The K_{oc} of 1-butanol has been estimated to be ~10, which indicates that leaching in soil is expected (Roy and Griffin, 1985); however, concurrent microbial degradation may lessen the importance of leaching.

3. EXPOSURE

3.1. WATER

1-Butanol has been detected tentatively and qualitatively in drinking water concentrates collected from Cincinnati, OH (October 17, 1978), Miami, FL (February 3, 1976), New Orleans, LA (January 14, 1976), Philadelphia, PA (February 10, 1976) and Seattle, WA (November 5, 1976) (Lucas, 1984). Finished drinking water from Durham, NC, has also been reported to contain 1-butanol (Shackelford and Keith, 1976).

Reported detections of 1-butanol in environmental surface waters are limited. Qualitative detection of 1-butanol in a water sample from the western basin of Lake Ontario has been reported (Great Lakes Water Quality Board, 1983). Concentrations of 87-318 ppb were identified in water samples from the polluted Hayashida River in Japan in 1980 (Yasuhara et al., 1981) while levels <1 ppb were detected in water samples collected from the Lee River in England (Waggott, 1981).

1-Butanol can be released to water through various wastewater emissions. It has been detected in wastewater emissions from chemical manufacturing plants, textile plants, sewage treatment plants, oil refineries and landfill leachates (Shackelford and Keith, 1976). It has also been identified in wastewater from pulp mills making kraft paper (Carlberg et al., 1986).

3.2. FOOD

1-Butanol appears to occur naturally in various fruits. It has been detected qualitatively as a volatile component of apple and pear aroma (Drawert et al., 1962) and grape essence (Stevens et al., 1965). Lovegren et al. (1979) detected 1-butanol concentrations of 0-7 ppb in dried beans (lima, common, mung), 150 ppb in split peas and 120 ppb in lentils.

1-Butanol has also been identified in volatiles from mountain cheese (Dumont and Adda, 1978), roasted filberts (Kinlin et al., 1972) and fried bacon (Ho et al., 1983).

Pellizzari et al. (1982) qualitatively detected 1-butanol in 3/12 samples of human milk collected from volunteers in Bayonne, NJ, Jersey City, NJ, Bridgeville, PA, and Baton Rouge, LA.

3.3. INHALATION

1-Butanol can be released to air by both natural and human sources. Natural sources of release include animal wastes, microbes and insects; human sources include volatilization from solvents (such as used in paints), rendering, sewage treatment, starch manufacture, whiskey manufacture, wood pulping and turbine emissions (Graedel et al., 1986).

Monitoring data for 1-butanol in the ambient atmosphere are limited. Juttner (1986) qualitatively detected 1-butanol in forest air of the Southern Black Forest in Germany in 1983. Smoyer et al. (1971) detected maximum concentrations of 1-10 ppm (3.03-30.3 mg/m^3) in ambient air in the vicinity of a solvent reclamation plant in Maryland; the solvent plant was considered the source of exposure. Cavanagh et al. (1969) detected 1-butanol levels of 34-445 ppb (103-1348 µg/m^3) in air from Point Barrows, AL, in 1967, probably resulting from a fermentation process (various bacteria) of the tundra cover. 1-Butanol was not detected in marine air samples collected in Hawaii (Cavanagh et al., 1969).

An indoor air sample collected in 1983 from homes in Italy contained a 1-butanol level of 20 µg/m^3 (DeBortoli et al., 1986); the source of exposure was probably solvent evaporation.

The mean concentration of 1-butanol in the breathable air of workers involved with varnish spraying (varnish containing butanol solvent) in

various German plants was found to be 1.2 ppm (3.64 mg/m³) (Angerer and Wulf, 1985). A similar mean concentration of 1.6 mg/m³ (3.6 mg/m³ maximum) was determined for a group of Belgian workers exposed to solvents (Veulemans et al., 1987).

3.4. DERMAL

Pertinent monitoring data regarding the dermal exposure of 1-butanol were not located in the available literature cited in Appendix A.

3.5. SUMMARY

Human exposure to 1-butanol can occur from both natural and human sources. Natural sources of air release include animal wastes, microbes and insects; human sources include volatilization from solvents (such as used in paints), rendering, sewage treatment, starch manufacture, whiskey manufacture, wood pulping and turbine emissions (Graedel et al., 1986). Concentrations of 34-445 ppb detected in the ambient air at Point Barrows, AL, are thought to occur as a result of a fermentation process of the tundra cover (Cavanagh et al., 1969). 1-Butanol appears to occur naturally in volatile components of apples, pears, grapes, dried legumes and mountain cheese (Drawert et al., 1962; Stevens et al., 1965; Lovegren et al., 1979; Dumont and Adda, 1978). Release of 1-butanol to water can occur through wastewater emissions from chemical and textile plants, sewage treatment plants, oil refineries, landfill leaching and kraft pulp mills (Shackelford and Keith, 1976; Carlberg et al., 1986). 1-Butanol has been detected tentatively and qualitatively in drinking water concentrates collected from Cincinnati, OH, Miami, FL, New Orleans, LA, Philadelphia, PA, and Seattle, WA (Lucas, 1984).

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Gillette et al. (1952) exposed creek chub, Semotitus a. atromaculatus, to 1-butanol in covered 1-gallon glass jars for 24 hours at temperatures ranging from 15-21°C. Control and treatment solutions were aerated during the exposure phase. Dilution water was obtained directly from the East Channel of the Detroit River and was used untreated. Four fish were used per treatment. The authors gave no indication that the treatments were replicated. All fish survived exposure to 1000 ppm 1-butanol for 24 hours, but all fish died on exposure to 1400 ppm 1-butanol after 24 hours.

Munch (1972) assessed the narcotizing effects of 1-butanol in frog, Rana pipiens, tadpoles. Tadpoles were exposed to 1-butanol in 500 mℓ of tap water at 20°C. The duration of exposure was not specified. The threshold narcotic concentration was defined as the concentration at which tactile stimuli failed to cause movement by the tadpole. The threshold narcotic concentration for 1-butanol in frog tadpoles was 38 mmol/ℓ.

Bridie et al. (1973, 1979b) reported a 24-hour TL_m of 1900 mg/ℓ for goldfish, Carassius auratus, exposed to 1-butanol. Testing was conducted in all-glass aquaria with 25 ℓ of test solution at ~20°C. Diluent water was municipal tap water. The concentration of butanol was determined at the beginning and end of the test by measurement of TOC.

Bresch and Spielhoff (1974) assessed the toxic effects of n-butanol on early embryonic stages of the sea urchin, Sphaerechinus granularis. Various concentrations of the alcohol were added to preparations of embryos 20 minutes after fertilization. Stages of treated embryos were evaluated when control embryos had reached the 8-cell stage. Investigators also assessed

the toxic effects of n-butanol on embryos at the gastrula stage. The limit of toxicity was defined as the highest concentration of n-butanol that did not lead to morphological changes or inhibition of the swimming movements of the gastrula. Investigators reported that the limit of toxicity to the 8-cell stage was ~8×10^{-6} mol/mℓ and the limit of toxicity to the gastrula was ~3×10^{-5} mol/mℓ.

Price et al. (1974) exposed brine shrimp, Artemia salina, to n-butanol in artificial seawater at 24.5°C for 24 hours in static tests. The investigators reported a 24-hour TL_m of 2950 mg/ℓ.

Mattson et al. (1976) assessed the static acute toxicity of 1-butanol to fathead minnows in Lake Superior water and soft reconstituted water. Fish were exposed to 1-butanol in 3-ℓ cylindrical glass jars with 2 ℓ of test solution. Butanol concentrations were not measured. Test temperatures ranged from 18-22°C. Investigators reported 24-, 48-, 72- and 96-hour LC_{50}s of 1950, 1950, 1950 and 1910 mg/ℓ, respectively, for fish exposed to 1-butanol in Lake Superior water and 24- to 96-hour LC_{50}s of 1940 mg/ℓ for fish exposed to 1-butanol in soft reconstituted water.

Bringmann and Kühn (1977a) reported LC_0, LC_{50} and LC_{100} values for Daphnia magna exposed to 1-butanol for 24 hours of 300, 1855 and 5000 mg/ℓ, respectively. Subsequently, Bringmann and Kühn (1982) reported a 24-hour EC_{50} for D. magna exposed to 1-butanol of 1880 mg/ℓ, with 95% confidence limits of 1747-2024 mg/ℓ. The EC_0 and EC_{100} values were 1411 and 2500 mg/ℓ, respectively.

Juhnke and Luedemann (1978) reported the results of studies conducted in two laboratories with the Golden Orfe, Leuciscus idus melanotus. Exposure of the Golden Orfe to n-butanol for 48 hours produced LC_{50} values of 1200 and 1770 mg/ℓ. The respective LC_0 values were 1170 and 1620 mg/ℓ, and the respective LC_{100} values were 1220 and 1980 mg/ℓ.

Linden et al. (1979) assessed the acute toxicity of 1-butanol to the harpacticoid copepod, Nitocra spinipes, and the bleak, Alburnus alburnus. Copepods were exposed to 1-butanol in 15-mℓ test tubes containing 10 mℓ of filtered brackish water. Fish were exposed to 1-butanol in 70ℓ glass aquaria containing 60 ℓ of brackish water filtered through a 300 µm filter. Salinity and temperature of test solutions in both studies were 7 o/oo and 10°C, respectively. The investigators reported 96-hour LC_{50}s of 2100 and 2250-2400 mg/ℓ for copepods and bleaks, respectively. The 95% confidence limits for the copepod LC_{50} were 1900-2300 mg/ℓ.

Hudson et al. (1981) assessed the acute toxicity of n-butanol to brine shrimp, Artermia. Nauplius larvae were taken up from culture in a 100 µℓ micropipet, counted, and transferred to a glass shell vial containing 0.9 mℓ seawater. The toxic endpoint was the lack of movement by larvae. Tests were conducted at 30°C for 24 hours. No toxic effects were observed among larvae exposed to <100 µM concentrations of n-butanol.

Veith et al. (1983) reported the results of flowthrough toxicity tests in which fathead minnows, Pimephales promelas, were exposed to 1-butanol at 25±1°C. Diluent water was soft (hardness = 56.3 mg/ℓ as $CaCO_3$) and drawn from Lake Superior. Alcohol concentrations were measured in each tank throughout the test. The investigators reported a 96-hour LC_{50} of 1730 mg/ℓ.

Brooke et al. (1984) assessed the toxicity of butanol to fathead minnows, P. promelas, in dynamic acute tests. Fish were exposed to butanol in soft water (hardness = 47.7 mg/ℓ) at 24.7°C using a cycling proportional diluter with duplicate exposures for each concentration. Butanol concentrations were measured by GLC. Investigators reported a 24- to 96-hour EC_{50} of 1510 mg/ℓ. The 48- to 96-hour LC_{50} (and 95% confidence limits) was 1730 mg/ℓ (1630-1840).

de Zwart and Slooff (1987) assessed the toxicity of butanol to larvae of the clawed toad, Xenopus laevis. Larvae were exposed to butanol in 1 ℓ of reconstituted water in glass aquaria at 20°C. Toxicant concentrations were not measured and solutions were not renewed. The 48-hour LC_{50} for toad larvae exposed to 1-butanol was 1200 mg/ℓ.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. **TOXICITY** -- Pertinent data regarding the effects of chronic exposure of aquatic fauna to butanol were not located in the available literature cited in Appendix A.

4.1.2.2. **BIOACCUMULATION/BIOCONCENTRATION** -- Hill et al. (1981) presented limited data regarding short-term accumulation of butanol in brain tissues of goldfish exposed to aerated solutions containing 10, 15 or 20 mM butanol. Pseudo steady-state levels of butanol in brain tissues were reached within ~60 minutes for fish exposed to the two lower concentrations (~0.5 and 0.7 mg/g for 10 and 20 mM, respectively). Data for time periods >30 minutes were not presented for fish exposed to the highest concentration. The authors stated that butanol concentration in brain tissues declined during exposure periods lasting >4 hours, but data were not presented in the paper. From the unpublished data, the authors speculated that goldfish can metabolize butanol.

No measured steady-state BCF value for butanol was found in the literature. Based on the regression equation, log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982) and a log K_{ow} value of 0.88 (see Section 1.2.), a BCF value of 2.75 is estimated for this compound, suggesting that butanol will not bioaccumulate significantly in aquatic organisms.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Effects of exposure of a green alga, Scenedesmus quadricauda, and a blue-green alga, Microcystis aeruginosa, to 1-butanol were reported by Bringmann (1975) and Bringmann and Kühn (1976, 1977b, 1978, 1979, 1980). Cultures were incubated with a series of 1-butanol solutions for 8 days at 27°C to determine the toxicity threshold. The toxicity threshold was defined as the concentration of toxicant that inhibited multiplication of cells in suspension. The inhibition was measured turbidimetrically as a ≥3% extinction of the primary light of monochromatic radiation at 436 nm for a layer of cells 10 mm thick. Toxicity threshold levels for exposure of M. aeruginosa to n-butanol were 100 and 312 mg/ℓ. Toxicity threshold levels for exposure of S. quadricauda to n-butanol were 95 and 875 mg/ℓ.

Haley et al. (1987) reported a 96-hour EC_{50} of 2000 mg/ℓ for the green alga, Chlorella pyrenoidosa.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of butanol in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria and Other Microorganisms. Effects of exposure of an aquatic bacteria, Pseudomonas putida, and a flagellated protozoan, Entosiphon sulcatum, to butanol were reported by Bringmann and Kühn (1976, 1977b, 1979, 1980, 1981). Effects on bacterial suspensions were determined turbidimetrically by the extinction of primary light at 436 nm for a layer 10 mm thick. The toxicity threshold was defined as the concentration of toxicant having an extinction value of ≥3% below the mean value of extinction for nontoxic dilutions of the test cultures. Effects on protozoa were determined by cell counts on a Coulter counter. The toxicity threshold with

protozoa was defined as a 5% reduction in cell counts obtained mathematically from regressions between n-butanol concentrations and cell counts. Bacterial suspensions were exposed to n-butanol for 16 hours at 25°C and protozoan cultures for 72 hours at 25°C. The investigators reported toxicity thresholds of 650 and 55 mg/ℓ for the bacteria and protozoa, respectively. Subsequently, Bringmann and Kühn (1981) assessed the effects of exposure of a holozoic bacteriovorous ciliated protozoan Uronema parduczi Chatton-Lwoff, and a saprozoic ciliated protozoan, Chilomonas paramecium Ehrenberg, to n-butanol. They reported toxicity threshold values of 8.0 and 27 mg/ℓ, respectively.

Hermens et al. (1985) assessed the toxicity of n-butanol to Photobacterium phosphoreum by the Microtox bacterial luminescence assay. Tests were conducted in accordance with procedures recommended by the manufacturer, Beckman Instruments Inc. Bacteria were incubated in five concentrations of n-butanol for 15 minutes at 15°C. The EC_{50} was based on a reduction in bacterial luminescence. The investigators reported a 15-minute log EC_{50} for n-butanol of 4.58 (~38000 mg/ℓ). Subsequently, Tarkpea et al. (1986) reported 5-, 15- and 30-minute EC_{50} values of 3370, 3690 and 3710 mg/ℓ, respectively, for P. phosphoreum exposed to 1-butanol in the Microtox assay.

Vaishnav (1986) assessed the effects of 1-butanol on bacterial respiration rates in a mixed microbial culture from a wastewater sample. Respiration studies were conducted on a Warburg apparatus at 30°C. Oxygen consumption of cultures was monitored at 15-minute intervals for 75 minutes. The toxic endpoint represented the concentration of 1-butanol that would reduce the maximum observed biodegradation rate by 50%. The investigators reported an EC_{50} of 10,614 mg/ℓ.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Hoffman and Eastin (1981) assessed the toxicity of butanol to mallard duck, Anas platyrhynchos, eggs. On days 3 and 8 of incubation, eggs were immersed for 30 seconds in distilled water or in 10 and 100% solutions of butanol. Eggs were examined by the candle method daily until day 18 of incubation. There were no effects on embryos exposed to distilled water or 10% butanol. There were no surviving chicks within eggs immersed in 100% butanol for either the 3- or 8-day-old embryos by day 18 of incubation.

Schafer et al. (1983) determined the acute oral toxicity of 1-butanol to starling, Sturnus vulgaris. Birds were trapped in the wild and preconditioned to captivity for a period of 2-6 weeks before the initiation of testing. The investigators estimated an oral LD_{50} of <2500 mg/kg.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to butanol were not located in the available literature cited in Appendix A.

4.3. FIELD STUDIES

Pertinent data regarding the effects of butanol on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. AQUATIC RISK ASSESSMENT

Insufficient data prevented the development of a criterion for the protection of freshwater life exposed to 1-butanol (Figure 4-1) by the method of U.S. EPA/OWRS (1986). Development of a freshwater criterion requires the results of acute assays with a salmonid fish species, a benthic crustacean, an insect, a non-Athropod/Chordate, and a new insect or phylum representative. Results from chronic assays required for the development of a freshwater criterion include assays with two species of fauna and at least one bioconcentration study.

Family	TEST TYPE		
	Acute*	Chronic*	BCF*
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	1,757*	NA	NA
#3 Chordate (fish or amphibian)	1,200*	NA	NA
#4 Crustacean (planktonic)	1,867*	NA	NA
#5 Crustacean (benthic)	NA	NA	NA
#6 Insectan	NA	NA	NA
#7 Non-Arthropod/-Chordate	NA	NA	NA
#8 New insectan or phylum representative	NA	NA	NA
#9 algae	NA	2,000*	NA
#10 vascular plant	NA	NA	NA

*NA=Not Available *96-hour EC_{50}/LC_{50} in mg/L for fathead minnows Pimephales promelas *48-hour LC_{50} in mg/L for toad larvae Xenopus laevis *24-hour EC_{50}/LC_{50} in mg/L for Daphnia magna *96-hour EC_{50} in mg/L for Chlorella pyrenoidosa.

FIGURE 4-1

Organization Chart for Listing GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria by the Method of U.S. EPA/OWRS (1986) for the Protection of Freshwater Aquatic Life from Exposure to Butanol

Available data regarding the effects of exposure of marine fauna and flora to butanol were inappropriate for use in the development of a saltwater criterion by the method of U.S. EPA/OWRS (1986).

4.5. SUMMARY

The 24-hour LC_{50} for creek chub exposed to 1-butanol would probably be between 1000 and 1400 ppm (Gillette et al., 1952). The threshold narcotic concentration for 1-butanol in frog tadpoles was 38 mmol/ℓ (Munch, 1972). Bridie et al. (1973, 1979b) reported a 24-hour TL_m of 1900 mg/ℓ for goldfish exposed to 1-butanol. Bresch and Spielhoff (1974) reported that the limits of toxicity to the 8-cell and gastrula stages of the sea urchin embryo were ~$8x10^{-6}$ and ~$3x10^{-5}$ mol/mℓ, respectively. Price et al. (1974) reported a 24-hour TL_m of 2950 mg/ℓ for brine shrimp exposed to n-butanol, although Hudson et al. (1981) reported the lack of mortality among brine shrimp exposed to <100 µM n-butanol (<7412 mg/ℓ) for 24 hours. The 96-hour LC_{50} for fathead minnows exposed to butanol ranged from 1510-1940 mg/ℓ (Mattson et al., 1976; Veith et al., 1983; Brooke et al., 1984). The 24-hour EC_{50} and LC_{50} for Daphnia magna exposed to butanol were 1880 and 1855 mg/ℓ, respectively (Bringmann and Kühn, 1977a, 1982). Juhnke and Luedemann (1978) reported that exposure of the Golden Orfe to n-butanol for 48 hours produced LC_{50} values of 1200 and 1770 mg/ℓ for studies conducted in two different laboratories. Linden et al. (1979) reported 96-hour LC_{50}s of 2100 and 2250-2400 mg/ℓ for copepods and bleaks exposed to 1-butanol, respectively.

Concentrations of butanol in brain tissue of goldfish exposed to 10 and 15 mM solutions of butanol reached equilibrium levels of 0.46 and 0.74 mg/g, respectively, within ~60 minutes (Hill et al., 1981). Concentrations of butanol in brain tissue from fish exposed to 20 mM solutions did not plateau

within the first 30 minutes, ultimately reaching an equilibrium concentration of 0.95 mg/g. The investigators speculated that goldfish possessed the ability to metabolize butanol.

No measured steady-state BCF value for butanol was found in the literature. An estimated BCF value of 2.75 for this compound suggests that butanol will not bioaccumulate significantly in aquatic organisms.

Toxicity threshold levels for exposure of Microcystis aeruginosa to n-butanol were 100 and 312 mg/ℓ, while toxicity threshold levels for exposure of Scenedesmus quadricauda to n-butanol were 95 and 875 mg/ℓ (Bringmann, 1975; Bringmann and Kühn, 1976, 1977b, 1978, 1979, 1980). Haley et al. (1987) reported a 96-hour EC_{50} of 2000 mg/ℓ for the green alga, Chlorella pyrenoidosa. The toxicity thresholds for an aquatic bacterium, Pseudomonas putida, and a flagellated protozoan, Entosiphon sulcatum, exposed to butanol were 650 and 55 mg/ℓ, respectively (Bringmann and Kühn, 1976, 1977b, 1979, 1980, 1981). The toxicity threshold values for a holozoic bacteriovorous ciliated protozoan, Uronema parduczi Chatton-Lwoff, and a saprozoic ciliated protozoan, Chilomonas paramecium Ehrenberg, exposed to n-butanol were 8.0 and 27 mg/ℓ, respectively (Bringmann and Kühn, 1981).

The 15-minute log EC_{50} for Photobacterium phosphoreum exposed to n-butanol in the Microtox bacterial luminescence assay was 4.58 (~38,000 mg/ℓ) (Hermens et al., 1985). Tarkpea et al. (1986) reported 5-, 15- and 30-minute EC_{50} values of 3370, 3690 and 3710 mg/ℓ, respectively, for P. phosphoreum exposed to 1-butanol in the Microtox assay. Vaishnav (1986) reported an EC_{50} of 10,614 mg/ℓ for a mixed microbial culture from a wastewater sample exposed to 1-butanol.

Mallard duck eggs immersed in 100% solutions of butanol for 30 seconds failed to produce viable chicks by day 18 of incubation (Hoffman and Eastin, 1981). There were no effects on embryos in duck eggs exposed to distilled water or 10% butanol. Schafer et al. (1983) estimated an oral LD_{50} of <2500 mg/kg for starlings treated with butanol.

5. PHARMACOKINETICS

5.1. ABSORPTION

Uptake by 12 humans exposed to 300 or 600 mg/m³ (100 and 200 ppm, respectively) of 1-butanol in air for four 30-minute periods of rest or exercise was studied by Astrand et al. (1976). The amount of uptake was measured as the difference between amounts in inspired and expired air. The percentage taken up at rest ranged from ~46-48%. During exercise, the percentage taken up ranged from ~37-41%. Therefore, percentage of uptake decreased with exercise; however, total uptake increased because ventilation (ℓ/minute) increased during exercise. The percentage of uptake appeared to be independent of the concentration of 1-butanol in air and independent of the intensity of exercise (estimated at 50-150 watts). Measured arterial blood concentrations after 30 minutes of exposure ranged from 0.5-1.3 mg/kg, proportional to exposure concentration and intensity of exercise.

The investigators observed that the arterial concentrations measured were lower than expected, based on an experimentally determined blood/air partition coefficient of 1200 and based on the disappearance of the compound from inhaled air. They hypothesized that because 1-butanol is readily soluble in water, the compound was taken up by the water in the mucosa of the lung during inspiration, thereby reducing the amount available for absorption by the blood.

The concentration of 1-butanol in the expired air of four male beagle dogs exposed to 50 ppm (150 mg/m³) for 6 hours remained relatively stable, averaging ~22 ppm during the exposure period (DiVincenzo and Hamilton, (1979). From this value, the investigators estimated that 55% of the inhaled vapor was absorbed through the lungs. In addition, they observed

that blood levels of 1-butanol were below detection limits both during and after exposure, and attributed this to the rapid metabolism of 1-butanol to carbon dioxide (Section 5.3.).

DiVincenzo and Hamilton (1979) studied the fate of 1-^{14}C-butanol administered in corn oil by gavage to groups of 2 or 4 fasted adult male Charles River CD rats at single doses of 4.5, 45 or 450 mg/kg. At 24 hours after treatment, 78.3-83.3% of the dose of radioactivity had been recovered as expired $^{14}CO_2$, 0.27-0.56% as unchanged compound in the expired air, 2.6-5.0% in the urine and 0.6-1.1% in the feces; 12.1-16.3% remained in the carcass. These data suggest that absorption of radiolabel from the gastrointestinal tract was virtually complete. Within the range tested, absorption from the gastrointestinal tract appeared to be independent of the magnitude of the dose. In rats treated with 450 mg/kg, 44.4 and 69.3% of the dose was recovered as $^{14}CO_2$ at 4 and 8 hours, respectively, indicating that absorption was rapid. Total recovery in these experiments ranged from 97.5-102.8% of the dose.

An *in vitro* study indicated that 1-butanol is absorbed through the oral mucosa of dogs. Siegel et al. (1976) studied the transfer of 1-^{14}C-butanol across a preparation of the lingual frenulum. A mean permeability constant of 10^{-4} cm/sec was calculated from 12 preparations. Winne (1978, 1979) demonstrated that radioactivity from 1-^{14}C-butanol is rapidly absorbed into the blood in perfusion experiments using *in situ* rat jejunal preparations.

1-Butanol is also absorbed through skin. Scheuplein and Blank (1973) exposed human adult abdominal skin samples obtained at autopsy to 1-butanol placed on the donor side of standard pyrex diffusion cells; the receptor side was filled with distilled water that was stirred continuously. A

permeability constant for 1-butanol in an aqueous system of 2.5×10^{-3} cm/hour was reported for the epidermis, and the stratum corneum was determined to be the diffusion rate limiter; 3×10^{-2} cm/hour was the permeability constant for the dermis. Akhter et al. (1984) reported similar findings for human skin absorption of 1-butanol (permeability constant = 3.0×10^{-3} cm/hour). DiVincenzo and Hamilton (1979) measured the dermal uptake of 1-butanol *in vivo* in young male beagle dogs, then extrapolated their findings to humans. Their data showed that 29.08 mg was absorbed at 1 hour at a rate of 8.7 $\mu g\ min^{-1}\ cm^{-2}$. Assuming that the rate of absorption through the skin of humans was approximately equal to that of the dog, the authors calculated that if 4% of the body surface area (approximately equal to the surface area of the hands) were immersed in 1-butanol for 1 hour, ~390 mg would be absorbed.

DelTerzo et al. (1986) estimated a permeability constant of 2.4×10^{-3} cm/hour for 1-butanol using a nude rat skin model, and noted that the results were comparable with those obtained for human skin by Scheuplein and Blank (1973). Behl et al. (1984) measured permeability constants for 1-butanol in skin preparations of 3.7×10^{-3} cm/hour to 23.7×10^{-3} cm/hour for nude mice, with variations depending on anatomical site (dorsal vs. abdominal) and age of the mouse. Dorsal skin appeared to be somewhat more permeable than abdominal skin, particularly at 4-25 days of age. Behl et al. (1983) investigated the effect of aqueous contact on rat skin permeability to 1-butanol and determined that the permeability coefficient increased by a small fraction (~15%) through the first 5 hours of hydration, and that it remained at this value (~6.0×10^{-3} cm/hour) for the remaining 80 hours of exposure.

Grass and Robinson (1984) applied doses of 25 µℓ of a 92.23 M solution of 1-butanol to corneas of both eyes of male albino rabbits (number not reported), the rabbits were sacrificed at various intervals afterward, and the aqueous humor of the eyes was analyzed for 1-butanol. At 10 minutes the aqueous humor concentration of 1-butanol was 56.43×10^{-9} M, and at 20 minutes, 35.57×10^{-9} M, suggesting that 1-butanol is absorbed through the cornea of rabbits' eyes.

5.2. DISTRIBUTION

Distribution of single gavage doses of 450 mg/kg 1-^{14}C-butanol in male CD rats was investigated by DiVincenzo and Hamilton (1979). The results, presented in terms of the percentage of the dose of radioactivity located in each of several tissues and organs, are presented in Table 5-1. The largest amounts were located in the liver, blood, kidneys and lungs; peak levels in these organs occurred 8 hours after treatment. It is not possible to identify tissue affinities because the results were not presented as concentrations in the tissues. The plasma concentration of 1-butanol vs. time plot showed a peak at 1 hour followed by a rapid, biphasic decline. The plasma concentration of 1-butanol was below detection limits at 4 hours after treatment.

5.3. METABOLISM

The most complete <u>in vivo</u> investigation of the metabolism of 1-^{14}C-butanol was the oral rat study by DiVincenzo and Hamilton (1979) (see Section 5.1.). The metabolism of 1-butanol was rapid and nearly complete, with <1% of the dosage eliminated as unchanged compound in expired air. From 78.3-83.3% of the dose was eliminated as $^{14}CO_2$, and 2.6-5.1% of the radioactivity was eliminated in the urine. Of the radioactivity eliminated in the urine, treatment with hydrochloric acid or β-glucuronidase

TABLE 5-1

Tissue Distribution of Radioactivity in Rats Dosed by Gavage with 450 mg/kg of 1-^{14}C-Butanol[a]

Tissue	Percentage of Administered Dose[b]		
	4 Hours	8 Hours	24 Hours
Liver	2.64 ± 0.34	3.88 ± 0.40	2.65 ± 0.2
Kidney	0.24 ± 0.01	0.18 ± 0.01	0.11 ± 0.01
Lung	0.11 ± 0.008	0.12 ± 0.004	0.07 ± 0.009
Heart	0.05 ± 0.004	0.02 ± 0.002	0.02 ± 0.004
Brain	0.03 ± 0.004	0.04 ± 0.001	0.04
Adrenal glands	0.006 ± 0.002	0.009 ± 0.002	0.009 ± 0.001
Fat[c]	0.05 ± 0.02	0.09 ± 0.01	0.06 ± 0.008
Blood	0.51 ± 0.05	0.74 ± 0.11	0.38 ± 0.04

[a]Source: DiVincenzo and Hamilton, 1979

[b]Values are expressed as the mean ± SE for four rats.

[c]Percentage of administered dose per gram of fat.

indicated that 44.4% was present as the O-sulfate and 30.7% was present as the O-glucuronide conjugates of 1-butanol. The remainder of the radioactivity present in the urine (24.9%) was identified as urea. The investigators suggested that radioactivity retained in the carcass (12.1-16.3% of the dose) represented incorporation of single ^{14}C-atoms into normal metabolic pathways.

DiVincenzo and Hamilton (1979) administered 1-^{14}C-butanol at 1 mg/kg intravenously to 3 young male beagle dogs and collected expired air and urine for 8 hours following treatment. Expired $^{14}CO_2$ accounted for 12-16% of the dose of radioactivity; 2.2-2.9% was excreted in the urine (total recovery accounted for 14-19% of the dose). These data suggest that metabolism of 1-butanol by dogs is qualitatively similar to rats. Kamil et al. (1953) administered a single 16 mmol (395 mg/kg) dose of 1-butanol in water by gavage to large chinchilla rabbits and measured the increase in glucuronic acid excretion in the urine until excretion of glucuronic acid above pretreatment levels appeared to be complete. Glucuronic acid conjugation accounted for an average of 1.8% of the dose in the three treated rabbits.

In an investigation of the elimination of 1-butanol by the isolated perfused rat liver, Auty and Branch (1976) found that the concentration in the recycled perfusate decreased as a zero-order process above 0.8 mmol, and as a first-order process below this level. These data suggest that a metabolic pathway was saturated at concentrations above 0.8 mmol. Because 1-butanol decreased the rate of metabolism of ethanol when the two alcohols were combined, the investigators concluded that alcohol dehydrogenase, the enzyme primarily responsible for the metabolism of ethanol, was also responsible for the metabolism of 1-butanol. In a review of the literature,

von Oettingen (1943) stated that 1-butanol appeared to follow the general metabolic pathway for primary alcohols: oxidation to the aldehyde, then to the acid, and finally to carbon dioxide and water. Brentzel and Thurman (1977) presented supporting evidence that oxidation of 1-butanol to aldehyde occurs in the liver by way of alcohol dehydrogenase, an NADPH-dependent process carried out in the hepatic microsomes. Teschke et al. (1974, 1975) did not find evidence that 1-butanol is a substrate for catalase, as is ethanol. 1-Butanol is oxidized more rapidly than ethanol; this is apparently due to the high substrate affinity of 1-butanol for alcohol dehydrogenase (Videla et al., 1982).

5.4. EXCRETION

DiVincenzo and Hamilton (1979) administered 1-^{14}C-butanol in corn oil by gavage to male Charles River CD rats, and measured excretion rates. At doses of 4.5-450 mg/kg, 78.3-83.3% of the dose was excreted as labeled CO_2 within 24 hours, 2.6-5.1% was eliminated in the urine, 0.69-1.1% was excreted in feces, and 12.1-16.3% remained in the carcass. Although kinetic data were not provided, it appears that excretion was rapid.

Rumyantsev et al. (1975) adminstered ^{14}C-labeled 1-butanol orally to rats and noted decreased organ levels of radioactivity at 3 hours post-treatment; 95% of the radioactivity was eliminated from the body after 3 days. Excreta in urine and feces accounted for 2.8% of the radioactivity. No further details were available. Kamil et al. (1953) noted that 1.8% of the dose administered by stomach tube to chinchilla rabbits was excreted in the urine as glucuronide.

5.5. SUMMARY

1-Butanol was taken up readily by the respiratory tracts of humans (Astrand et al., 1976) and dogs (DiVincenzo and Hamilton, 1979). Levels of

1-butanol in the blood of humans following inhalation exposure were lower than expected based on a measured blood/air partition coefficient and the disappearance of the compound from inhaled air (Astrand et al., 1976). This observation may reflect sequestration of 1-butanol in mucosal tissue water in the lung (Astrand et al., 1976) or rapid metabolism of the compound following absorption (DiVincenzo and Hamilton, 1979). 1-Butanol appears to be absorbed rapidly and virtually completely from the gastrointestinal tracts of rats (DiVincenzo and Hamilton, 1979).

In addition, 1-butanol is absorbed through oral mucosa (Siegel et al., 1976), intestines (Winne, 1978, 1979), skin (Scheuplein and Blank, 1973; Akhter et al., 1984; DiVincenzo and Hamilton, 1979; DelTerzo et al., 1986; Behl et al., 1983, 1984) and the cornea (Grass and Robinson, 1984). Following oral treatment of rats with 1-^{14}C-butanol, the largest amounts of radioactivity were located in the liver, kidney and blood. Unchanged 1-butanol levels in plasma were below detection limits at 4 hours after treatment (DiVincenzo and Hamilton, 1979). 1-Butanol was metabolized rapidly to carbon dioxide (~80% of the dose) (DiVincenzo and Hamilton, 1979), primarily by hepatic microsomal alcohol dehydrogenase (Brentzel and Thurman, 1977; Videla et al., 1982). Smaller amounts were excreted in the urine as sulfate and glucuronide conjugates and as urea.

At 24 hours after rats were treated orally with 1-^{14}C-butanol, ~14% of the dose of radioactivity was retained in the carcass, which was attributed to the incorporation of ^{14}C into the one-carbon pool (DiVincenzo et al., 1979).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Smyth and Smyth (1928) tested the toxicity of 1-butanol by exposing a group of three guinea pigs to 0 or 100 ppm (300 mg/m^3) daily (schedule not stated) for 2 weeks, followed by exposure periods of 4 hours/day, 6 days/week for another 7 weeks. Effects noted were decreased red blood cell counts and a relative and absolute lymphocytosis. Two of the three treated guinea pigs had hemorrhagic areas in the lungs and a transient albuminuria. Follow-up studies at the same concentrations resulted in reduced red blood cell counts, reduced blood hemaglobin concentrations, lymphocytosis and liver and kidney degeneration.

Savel'ev et al. (1975) exposed rats to inhalation levels of 212 mg/m^3 1-butanol, 5 hours/day for 2 months, and reported decreased oxygen consumption and delayed restoration of normal body temperature after cooling. Continuing this exposure for another 4 months led to increased oxygen consumption and accelerated return to normal body temperature after cooling. The authors concluded that these data indicate high adaptability of rats to low doses of 1-butanol. Rumyantsev et al. (1976) exposed male rats and mice to 1-butanol inhalation concentrations of 0, 0.8, 6.6 or 40 mg/m^3 continuously for 4 months. Rats at 6.6 and 40 mg/m^3 had decreases in hexobarbital sleeping time, CNS subliminal impulses, work capacity and oxygen requirements. Pathologic lesions reported in rats at 6.6 and 40 mg/m^3 included dilation of blood vessels with diapedesis of erythrocytes, pulmonary edema and atalectasis, and necrotic changes in the parenchyma of the intestines. Some of the vascular changes were also seen at lesser intensity in rats at 0.8 mg/m^3. Increased reflex activity and thyroid activity, and

a concentration-related increase in blood cholinesterase levels occurred in rats in all exposed groups. The only effects reported in mice included decreased hexobarbital sleeping time and CNS subliminal impulses at 6.6 and 40 mg/m³, and increased reflex activity at all concentrations. Baikov and Khachaturyan (1973) administered 0.09 or 21.8 mg/m³ by inhalation to rats continuously for 92 days and noted no toxic effects at 0.09 mg/m³, but at 21.8 mg/m³, decreased RNA and DNA were noted in blood, along with alterations in enzyme activity, increased leukocyte luminescence and increased penetration of 1-butanol across blood-tissue barriers in testis, spleen and thyroid. In another part of this study, 18 volunteers were exposed to 1-butanol at concentrations of 0.3-15 mg/m³ by an unspecified schedule for an unreported duration. Altered sensitivity to light in the dark-adapted eye and altered electrical activity of the brain were reported at 1.2 mg/m³. No effects were reported at 1 mg/m³.

6.1.1.2. CHRONIC -- Sterner et al. (1949) conducted a 10-year study of occupational exposure to butyl alcohol, examining hematological effects, liver, lung and kidney function, ophthalmological health and absenteeism from work among butanol-exposed men vs. all men in the plant. The level of exposure in air was determined to be 100 ppm (300 mg/m³) during most of the study period, but was as high as 200 ppm (600 mg/m³) in the early phases of the study. The initial exposed group consisted of 16 men, but was gradually increased to ~100. No effects were noted among men exposed to 100 ppm. With concentrations averaging $\geq$200 ppm, transient corneal inflammation, with associated lacrimation, burning sensation and photophobia, was encountered occasionally among exposed workmen.

Velasquez (1964) and Velasquez et al. (1969) reported hearing loss in 9/11 workers simultaneously exposed to 1-butanol at 80 ppm (240 mg/m³) and

industrial noise (unquantified) without personal hearing protection. The affected workers, 20-39 years of age, were exposed for 3-11 years. The extent of hearing loss correlated positively with duration of exposure. The control group consisted of 47 workers exposed to industrial noise at 90-100 dB without exposure to 1-butanol.

Human occupational exposure to 1-butanol at six manufacturing plants was studied through site visits by Tabershaw et al. (1944), who determined that eye inflammation resulted when air concentrations of butanol exceeded 50 ppm. No systemic effects were noted from concentrations <100 ppm. Cogan and Grant (1945) reported that 19 of ~75 female workers exposed to 1-butanol in a gluing operation complained of ocular irritation. The complaints began <2 months after various solvents had been replaced with 1-butanol that contained varying amounts of diacetone alcohol and denatured ethanol. Ophthalmological examination revealed the presence of characteristic corneal lesions in 17/19 workers who registered complaints and in 9 others who worked in the same area. The concentration of 1-butanol in the air was measured at several locations and found to vary from 15-100 ppm (45-300 mg/m^3). The largest number of affected employees was found in the area of greatest contamination. Absence from work for 5-7 days resulted in nearly complete reversal of the ocular effects in the majority of affected workers.

Seitz (1972) reported three cases of severe and persistent vertigo in laboratory workers after handling 1-butanol and isobutanol for 1 year. Two of the seven exposed workers showed no ill effects, and another two showed transitory and brief periods of vertigo. Exposure was in a poorly ventilated photographic laboratory that was intensely illuminated, producing heat that evaporated the substances. Improvement of working conditions reportedly prevented recurrences of these problems. Concentrations of the solvents in workroom air were not quantified.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- The U.S. EPA (1986a) sponsored a study in which groups of 30 Charles river CD rats/sex were treated with 1-butanol in water by gavage at dose levels of 0, 30, 125 or 500 mg/kg/day for 13 weeks. After 6 weeks, an interim sacrifice of 10 rats/sex was conducted to determine clinicopathologic, biochemical and gross morphological effects. Survivors were sacrificed on days 92 or 93; endpoints examined were body and organ weight changes, food consumption, moribundity, mortality, ophthalmology, and gross and clinical histopathology. In the final 6 weeks of treatment, males and females in the high-dose group showed ataxia and hypoactivity within minutes of treatment. Reduced erythrocyte count and blood hemoglobin concentration were noted in females from the middle- and high-dose groups at the time of the interim sacrifice, but these were not found at the final sacrifice, suggesting that the effects were transitory rather than adverse. No compound-related differences were noted between control and treated animals with respect to any of the other endpoints evaluated. No effects were noted at 30 mg/kg/day.

Wakabayashi et al. (1984) administered 1-butanol in drinking water to groups of 30 male Wistar rats at concentrations of 0 or 6.9% for up to 3 months; some of the rats were sacrificed at 5, 9 or 13 weeks. Liver mitochondria were examined for effects on ultrastructure and oxidative coupling efficiency. Megamitochondria, often appearing elongated, constricted or cup-shaped, were noted in treated rats. The number of cristae membranes per mitochondrion decreased significantly. Activities of monoamine oxidase and cytochrome oxidase decreased moderately compared with controls, but there was no effect on coupling efficiency with either succinate or glutamate as the substrate.

6.1.2.2. CHRONIC -- Pertinent data regarding the chronic oral toxicity of 1-butanol were not located in the available literature cited in Appendix A.

6.1.3. Other Relevant Information. Data regarding the acute toxicity in animals of 1-butanol are presented in Table 6-1. Oral LD_{50} values for rats ranged from 0.7-4.36 g/kg. Female rats appear to be more sensitive than males (Ciugudeanu et al., 1985; Smyth et al., 1951; Jenner et al., 1964; Purchase, 1969), and the sensitivity of rabbits is similar to that of male rats (Munch, 1972). Little difference in response to intravenous administration of 1-butanol was noted between mice and rats (Tichy et al., 1985; Maickel and McFadden, 1979).

Nelson et al. (1943) exposed an average of 10 humans (male and female) to vapor concentrations of 1-butanol (and other solvents under study) for 3-5 minutes. Subjects were not informed of the concentrations used, or whether they were being administered in increasing or decreasing levels. After the exposure, subjects classified the effect of the vapor on eyes, nose and throat, and described the odor as absent, definite, moderate, strong or overpowering. 1-Butanol at 25 ppm (75 mg/m^3) produced mild irritation to eyes, nose and throat; 50 ppm (150 mg/m^3) was judged objectionable because of pronounced throat irritation and later onset of mild headaches. Amoore and Hautala (1983) determined that 50-90% of distracted persons can perceive the odor of 50 ppm 1-butanol in workplace air.

Ba'inova and Madzhunov (1984) noted that 24-hour contact with $\geq$7.8% 1-butanol in plant oil irritated the skin of healthy humans. Details of the study were not available.

DeCeaurriz et al. (1981) exposed six Swiss F_1 mice/group to four concentrations (500-1100 ppm) of 1-butanol for 5 minutes, noting respiratory

TABLE 6-1

Acute Lethal Toxicity of 1-Butanol

Species/Strain	Sex	Route	LD_{50} (g/kg)	Reference
Rat/NR	NR	oral (gavage)	3.83	Ciugudeanu et al., 1985
Rat/NR	NR	oral (food)	4.36	Smyth et al., 1951
Rat/Osborne-Mendel	male	oral (gavage)	2.51	Jenner et al., 1964
Rat/NR	male	oral (gavage)	2.02	Purchase, 1969
Rat/NR	female	oral (gavage)	0.79	Purchase, 1969
Rabbit/NR	NR	oral (gavage)	3.484	Munch, 1972
Rat/Wistar	male	intravenous	0.310	Tichey et al., 1985
Mouse/strain H	male	intravenous	0.450	Tichey et al., 1985
Mouse/SW	male	intraperitoneal	0.254	Maickel and McFadden, 1979

NR = Not reported

rates as an indicator of sensory irritation (assuming that expiratory rate decreases reflexively in the presence of an irritant). The concentration-response relationship (percentage decrease in respiratory rate vs. the logarithm of the exposure concentration) was linear, and 1268 ppm (3844 mg/m³) was determined to be the RD_{50}. In a similar study by Alarie (1981), the RD_{50} was reported to be 4784 ppm (14,503 mg/m³). Concentrations tested ranged from 1000 to ~15,000 ppm. Length of exposure was not reported.

Carpenter and Smyth (1946) investigated the ocular irritation caused by applying 0.005 mℓ 1-butanol to the center of one cornea of each of five albino rabbits, retracting the eyelids for 1 minute, then scoring the injuries on a scale of 1-10. Pure 1-butanol and 40% 1-butanol solution caused serious injury (necrosis).

Shehata and Saad (1978) noted significant dose-related decreases in liver content of thiamine, riboflavin, pyridoxine, niacin and pantothenic acid after daily oral administration to rats of 1-butanol in doses of 1 and 2 mℓ/kg (810 and 1620 mg/kg) for 7 days. Weese (1928) noted liver toxicity in three mice after an inhalation dose of 24,624 mg/m³ was administered "for several days." Reversible fatty infiltrations of liver and kidneys, along with narcosis but no deaths, were noted.

Wallgren (1960) studied the intoxicating effects on rats of several alcohols and determined, by a performance test that measured ability to retain balance on a rising slope, that a dose of 1-butanol of 0.0163 mol/kg (1208 mg/kg) administered orally reduced the performance rate as much as 45% (approximately), to an average of 73% of the performance measured before dosing. Marcus et al. (1976) administered 1-butanol to male Sprague-Dawley rats (number/group unclear) and found that a single intravenous injection of 6.7 mmol/kg (497 mg/kg) or an intraperitoneal injection of 8.1 mmol/kg (600 mg/kg) induced abnormal EEG and behavioral effects (loss of righting reflex).

DeCeaurriz et al. (1983) examined the neurobehavioral toxicity of 1-butanol in male Swiss OF_1 mice by noting effects on duration of the period of immobility in the "behavioral despair" swimming test. 1-Butanol, delivered as single 4-hour inhalation exposures ranging from 470-965 ppm (1425-2925 mg/m^3) to groups of 10 naive mice, significantly decreased total duration of immobility during a 3-minute postexposure observation period. The authors suggested that this may be the result of a nonspecific neurotoxic action. Maickel and Nash (1985) observed impairment of coordinated muscular activity among male Swiss-Cox mice, compared with controls treated by oral intubation with 1.0 or 2.0 g/kg doses of 1-butanol. This effect was not observed at 0.5 g/kg. The investigators reported that hypothermia occurred in a dose-related fashion, but statistical analysis was not performed.

Several studies have reported toxic effects of 1-butanol from <u>in vitro</u> tissue exposures. Nakano and Moore (1973) noted dose-dependent decreases in the contractile force of isolated guinea pig myocardial strips. Madan et al. (1969) reported relaxation of rat intestine smooth muscle without increased tonicity, and reversible contracture of the frog rectus abdominis muscle with exposure to 1-butanol. Walum and Peterson (1983) tested the effects of 790 mg/kg 1-butanol on cultured mouse neuroblastoma cells (C1300), clone 41 A_3, and noted 25% cell detachment and morphological changes (flattened and bearing short processes). Chen et al. (1984) reported positive results for 1-butanol in tests on the effects of a series of common solvents for their ability to inhibit metabolic cooperation in Chinese hamster cells. Masamoto et al. (1974) noted MAO inhibition in a concentration-dependent manner by treating rat liver mitochondria with

1-butanol. Swollen mitochondria and lack of matrix and cristae were noted following treatment with 0.1-1.0% 1-butanol; at a concentration of 10%, mitochondrial structure disappeared.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of 1-butanol were not located in the available literature cited in Appendix A.

6.2.2. Oral. Pertinent data regarding the oral carcinogenicity of 1-butanol were not located in the available literature cited in Appendix A.

6.2.3. Other Relevant Information. Pertinent data regarding other relevant information on carcinogenicity of 1-butanol by other routes of exposure were not located in the available literature cited in Appendix A.

6.3. MUTAGENICITY

1-Butanol has been tested for mutagenicity in prokaryotes and eukaryotes, including several mammalian test systems, with mixed results (Table 6-2). Tests using Salmonella typhimurium have consistently yielded negative results (Connor et al., 1985; McCann et al., 1975; Nakamura et al., 1987), while a test using Escherischia coli gave weakly positive results (Yoshiyama et al., 1973). A chick embryo cytotoxicity test proved negative (Bloom, 1982), and mammalian test results were both negative (Lasne et al., 1984) and positive (Oenfelt, 1987).

6.4. TERATOGENICITY

Without providing additional data or documentation, Ritter et al. (1985) stated that 1-butanol is a member of a class of chemical compounds that exhibit teratogenic properties. Mankes et al. (1985) treated pregnant Long-Evans rats with 1-butanol (presumably in water) by gavage at doses of 0.02-24% of the oral LD_{50} on days 6-15 of gestation. Controls were

TABLE 6-2

Mutagenicity Testing of 1-Butanol

Assay	Indicator/ Organism	Compound Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA100 TA1535 TA1537 TA98	purest commercial grade available	plate incorporation	NR	+ (S-9) -	- -	NC	McCann et al., 1975
DNA repair	S. typhimurium TA100 TA98 UTH8413 UTH8414	99%	plate incorporation	50-2000 µg/plate	± (S-9) ± ± ±	= = = =	Positive controls responded appropriately	Connor et al., 1985
UMU test	S. typhimurium TA1535/pSK1002	purest commercial grade available	suspension	27,000 µg/mL	+ -	- -	NC	Nakamura et al., 1987
DNA synthesis inhibition	Escherischia coli	NR	suspension	NR	-	+	1-Butanol did not inhibit completion of DNA-replication begun prior to addition of these agents to medium	Yoshiyama et al., 1973
Sister chromatid exchange (chick embryo cytogenetic test)	chick embryo	NR	injection	1-10 µL/egg	NR	-	NC	Bloom, 1982
Sister chromatid exchange	Chinese hamster ovary cells	NR	cell culture	0.1% v/v	NR	-	NC	Obe and Ristow, 1977
Micronucleus induction	Chinese hamster lung V79	NR	cell culture	50 µL/mL	-	-	NC	Lasne et al., 1984
Spindle disturbance	Chinese hamster cells/V79	NR	cell culture	NR	NR	+	Good qualitative coupling observed between spindle disturbance and aneuploidy	Oenfelt, 1987

NC = No comment; NR = not reported

treated similarly with distilled water. No effects on the incidence of malformations or embryolethality were attributed specifically to 1-butanol in this brief report.

Brightwell et al. (1987) administered 1-butanol to groups of 15 pregnant Sprague-Dawley rats for 7 hours/day throughout gestation at inhalation concentrations of 0, 3500, 6000 or 8000 ppm (0, 10,610, 18,190 or 24,250 mg/m^3). Previous data showed that a concentration of 8000 ppm produced maternal toxicity (reduced food consumption and body weight gain) without mortality. On gestation day 20, dams were sacrificed and fetuses were divided into two groups for teratological examination of skeletal and soft-tissues. Although fetal weights were reduced at 8000 ppm, no teratogenic effects were noted.

6.5. OTHER REPRODUCTIVE EFFECTS

The effects of 1-butanol on testicular function in Sprague-Dawley rats were studied by Cameron et al. (1985). Groups of five rats were exposed to 0 or 500 ppm (0 or 1516 mg/m^3) 1-butanol in inhalation chambers for 6 hours/day, for up to 1 week. Blood serum samples collected from the heart were analyzed for effects on testosterone, LH and corticosterone levels. After the first 6-hour exposure, circulating testosterone levels were significantly depressed and remained so after 18 hours of posttreatment rest. These changes were not associated with altered levels of circulating LH. A significant increase in corticosterone levels found after the first 6-hour exposure suggested this to be a result of adrenocortical stimulation, which the authors suggested may explain the decrease in concentration of circulating testosterone. The rats appeared to adapt after exposure for 1 week, when hormone levels return to near-normal levels. The change may be a result of increased breakdown of the alcohol or its metabolites over time, or to decreased sensitivity of testicular or adrenal gland cells.

6.6. SUMMARY

1-Butanol is mildly toxic to humans and laboratory species. Human inhalation exposure to 1-butanol at levels of 25-50 ppm (75-150 mg/m^3) is irritating to the eyes, nose and throat, and can cause headaches, but no systemic effects occur at this exposure level (Nelson et al., 1943; Amoore and Hautula, 1983; Tabershaw et al., 1944; Seitz, 1972). Sensory irritation and neurobehavioral toxicity have been noted in mice and rats exposed by inhalation to high levels of 1-butanol (DeCeaurriz et al., 1981, 1983; Alarie, 1981). Acute dermal contact with the liquid in oil is irritating to healthy human skin (Ba'inova and Madzhunov, 1984), and eye contact with the vapor can cause painful keratitis and conjunctivitis (Cogan and Grant, 1945).

Rabbits and male rats appear to be equally sensitive to acute oral doses of 1-butanol, but female rats are more sensitive; single-dose oral LD_{50} values ranged from 0.79-4.36 g/kg (Munch, 1972; Ciugudeanu et al., 1985; Smyth et al., 1951; Jenner et al., 1964; Purchase, 1969). Acute oral exposure to 1-butanol at 1200 mg/kg caused decreased ability of rats to retain balance (Wallgren, 1960). Dose-related hypothermia and impaired coordination of muscular activity occurred in mice treated by gavage at 1.0 or 2.0 g/kg (Maickel and Nash, 1985). Single oral 810 mg/kg doses administered to rats induced significant dose-related decreases in liver content of vitamins (Shehata and Saad, 1978). Sensitivity to intravenous or intraperitoneal injection is greater than sensitivity by the oral route among rats and mice, but very little difference in toxic response was found between these species (Tichy et al., 1985; Maickel and McFadden, 1979). Abnormal EEG and loss of righting reflex occur in rats exposed to single intravenous (500 mg/kg) or intraperitoneal (600 mg/kg) injections of 1-butanol (Marcus et al., 1976).

Subchronic inhalation studies have been performed using rats and guinea pigs, and human epidemiology studies are available. Liver and kidney degeneration and hematologic effects were reported in guinea pigs intermittently exposed to 100 ppm (300 mg/m³) for 9 weeks (Smyth and Smyth, 1928). Foreign studies using rats reported no effects with continuous exposure to 0.09 mg/m³, but effects on the blood and CNS at concentrations of $\geq$0.8 mg/m³ (Savel'ev et al., 1975; Rumyantsev et al., 1976; Baikov and Khachaturyan, 1973). In an occupational study, no effects were reported at 100 ppm (300 mg/m³); ocular irritation was reported at 200 ppm (600 mg/m³) (Sterner et al., 1949).

Oral exposure data are limited to subchronic studies. Rats treated by gavage with 1-butanol at 30 mg/kg/day for 13 weeks showed no toxic effects; transitory effects on hematology (RBC, PCV) were noted among females but not males at 125 mg/kg/day, and 500 mg/kg/day caused ataxia and hypoactivity in the final 6 weeks of treatment among both sexes (U.S. EPA, 1986a). 1-Butanol administered in drinking water to rats for up to 3 months at a high dose (9660 mg/kg/day) caused structural alterations of liver mitochondria, accompanied by moderately decreased MAO and cytochrome oxidase activity (Wakabayashi et al., 1984).

Data regarding carcinogenicity to humans or animals were not located in the available literature. Results of mutagenicity and genotoxicity testing were mixed. 1-Butanol is not scheduled for testing by the NTP (1988).

1-Butanol, when administered by gavage, was not a developmental toxicant to rats at dosages up to 24% of the oral LD_{50} (Mankes et al., 1985). Inhalation exposure to 8000 ppm (24,250 mg/m³) resulted in mild maternal toxicity and decreased fetal body weight in rats, but no evidence of

teratogenicity (Brightwell et al., 1987). Reversible effects on testicular endocrine function were noted in rats intermittently exposed to 500 ppm (1516 mg/m^3) (Cameron et al., 1985).

In vitro studies have demonstrated toxic effects of 1-butanol on cardiac and smooth muscle (Nakano and Moore, 1973; Madan et al., 1969) and on cellular structure and function (Walum and Peterson, 1983; Chen et al., 1984; Masamoto et al., 1974).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1988) recommended a ceiling limit TWA-TLV for 1-butanol of 50 ppm (150 mg/m^3), and warned that dermal absorption may contribute significantly to the body burden. These recommendations are based on data showing hearing impairment in workers between the ages of 20 and 39 years (Velasquez, 1964; Velasquez et al., 1969), and impairment of vestibular function (vertigo) (Seitz, 1972). OSHA (1985) has established a PEL in air of 100 ppm (300 mg/m^3).

The U.S. EPA (1988a) has established a verified RfD of 0.1 mg/kg/day for chronic oral exposure to 1-butanol, based on an oral subchronic study sponsored by U.S. EPA (1986a).

1-Butanol is approved for human use both as a direct and an indirect food additive (CFR, 1984).

The RQ for 1-butanol is 5000 based on application of the secondary criterion of biodegradation to the primary criterion RQ of 1000, which is determined by its ignitability (U.S. EPA, 1988b).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to butanol were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential business information (CBI), which this document could not address, are not in existence. From examination of the bibliographies of the CBI data, however, it was determined that CBI data that would alter the approach to risk assessment or the risk assessment values presented herein do not exist.

8.1. CARCINOGENICITY

8.1.1. All Routes. Pertinent data regarding the carcinogenicity of 1-butanol by inhalation, oral or other routes of exposure were not located in the available literature cited in Appendix A.

8.1.2. Weight of Evidence. No data are available concerning the carcinogenicity of 1-butanol to animals or humans. The most appropriate classification according to the U.S. EPA (1986c) classification scheme for this substance is Group D, not classifiable as to human carcinogenicity.

8.1.3. Quantitative Risk Estimates. Lack of data precludes derivation of estimates of carcinogenic potency by any route of exposure.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Smyth and Smyth (1928) reported hematologic effects, pulmonary hemorrhage and liver and kidney degeneration in guinea pigs intermittently exposed to 100 ppm (300 mg/m^3), the only concentration tested, for 9 weeks. Rumyantsev et al. (1976) reported histopathologic lesions in the blood vessels, lungs and intestines of rats exposed continuously to 6.6 or 40 mg/m^3 for 4 months.

Subtle nervous system effects were reported in rats and mice at 0.8 mg/m³, the lowest concentration tested. Baikov and Khachaturyan (1973) reported biochemical changes in the blood and increased passage of 1-butanol into the testis, spleen and thyroid of rats exposed continuously to 21.8 mg/m³ for 92 days. No effects were reported at 0.09 mg/m³. The toxicological significance of the effects in rats reported by Baikov and Khachaturyan (1973) is unclear. Baikov and Khachaturyan (1973) also reported changes in vision and in the electrical activity of the brain in humans exposed to 1.2 mg/m³ by an unspecified schedule. No effects were reported at 1.0 mg/m³.

The subchronic inhalation studies in animals and humans discussed above were all insufficiently reported for critical evaluation and, therefore, the data are judged insufficient for derivation of an RfD for subchronic inhalation exposure to 1-butanol. Furthermore, the data do not clearly identify a target organ or suggest a specific syndrome for the toxicity of 1-butanol. These data are included, however, in the generation of dose/duration-effect graphs presented in Appendix C.

8.2.1.2. **CHRONIC EXPOSURE** -- Data regarding chronic inhalation exposure of animals to 1-butanol were not located. Human occupational data suggest that the central and peripheral nervous system and the eyes may be targets for the toxicity of 1-butanol. Sterner. et al. (1949) reported no effects on hematology, liver, lung or kidney function, ophthalmological health or absenteeism in workers exposed to 100 ppm (300 mg/m³). Ocular irritation was reported at 200 ppm (600 mg/m³). Ocular irritation was also reported by Tabershaw et al. (1944) at concentrations >50 ppm (150 mg/m³) and by Cogan and Grant (1945) at concentrations ranging from 15-100 ppm (45-300 mg/m³). Velasquez (1964) and Velasquez et al. (1969) reported

hearing loss in workers exposed to 1-butanol at 80 ppm (240 mg/m³). Seitz (1972) reported vertigo in workers exposed to (presumably) high but unquantified levels of 1-butanol in workroom air.

These data suggest that ocular irritation may be the critical effect in humans exposed to 1-butanol in air. The lowest level associated with ocular involvement was 15 ppm (45 mg/m³) in the Cogan and Grant (1945) study with female workers exposed to 1-butanol and other chemicals. This study is not a suitable basis for an RfD for inhalation exposure, however, because symptoms were reported after less than 2 months of exposure and because exposure involved a mixture of chemicals. Furthermore, the ocular effects reported were probably the result of local contact with the vapor, and therefore were dependent upon concentration rather than duration of exposure or absorbed dose.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Two studies are available for consideration in the derivation of an RfD for subchronic oral exposure to 1-butanol. Wakabayashi et al. (1984) reported adverse effects on liver mitochondrial structure and function in male Wistar rats treated with 6.9% 1-butanol in the drinking water for up to 13 weeks. Assuming rats drink 0.049 ℓ of water/day and weigh 0.35 kg (U.S. EPA, 1986b), this concentration is equivalent to a dosage of 9660 mg/kg/day. No other dose was tested.

A verified RfD for chronic oral exposure of 0.1 mg/kg/day has been derived by the U.S. EPA (1988a) using data from a 13-week study sponsored by U.S. EPA (1986a). Gavage doses of 1-butanol in deionized water at levels of 0, 30, 125 and 500 mg/kg/day were given to groups of 30 CDR(SD)B rats/sex.

Females showed slightly reduced red blood cell, hematocrit and blood hemoglobin concentration at 125 and 500 mg/kg/day at the end of 6 weeks, but this was not found at 13 weeks and was not noted in males at any time. The researchers did not consider this an adverse effect. At 500 mg/kg/day, ataxia and hypoactivity were noted in both sexes within minutes of treatment, which was probably due to the bolus nature of gavage administration during the final 6 weeks of the experiment. The NOAEL is therefore 125 mg/kg/day for CNS effects in rats, and the LOAEL is 500 mg/kg/day.

The NOAEL of 125 mg/kg/day is the most appropriate basis for deriving an RfD for subchronic oral exposure to 1-butanol. Applying an uncertainty factor of 100, 10 to extrapolate from rats to humans and 10 to provide for individual variations in sensitivity among humans, results in an RfD of 1.25 mg/kg/day, which is rounded to 1 mg/kg/day. The key study was a well designed and performed comprehensive toxicological experiment; therefore, confidence in the study is high. Confidence in the data base is low, because adequate developmental and reproductive toxicity studies are lacking. Confidence in the RfD, therefore, is low.

8.2.2.2. **CHRONIC EXPOSURE** -- No reports of chronic experiments with orally administered 1-butanol were located in the available literature. U.S. EPA (1988a) derived an RfD for chronic oral exposure from the 13-week gavage experiment in rats sponsored by U.S. EPA (1986a). Applying an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for individual human variation and 10 to expand from subchronic to chronic exposure) to the NOAEL of 125 mg/kg/day resulted in an RfD of 0.125 mg/kg/day, which was rounded to 0.1 mg/kg/day. This value is adopted as the RfD for chronic oral exposure to 1-butanol for the purposes of this document. U.S. EPA (1988a) considered confidence in the study to be high, and confidence in the data base and RfD to be low.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of 1-butanol was discussed in Chapter 6. Animal inhalation data for 1-butanol consist of a number of subchronic studies that are considered inadequate for risk assessment because of technical limitations (Smyth and Smyth, 1928) or because they were available only as abstracts of the foreign literature (Savel'ev et al., 1975; Rumyantsev et al., 1976; Baikov and Khachaturyan, 1973). Most human occupational studies identify levels associated with local irritation (Tabershaw et al., 1944; Cogan and Grant, 1945; Sterner et al., 1949). These endpoints are inappropriate for consideration in deriving an RQ based on chronic toxicity. Seitz (1972) associated vertigo with exposure to high but unquantified levels of 1-butanol. Velasquez (1964) and Velasquez et al. (1969) associated hearing loss with occupational exposure to 1-butanol at 80 ppm (243 mg/m^3). The hearing loss reported by Velasquez (1964) and Velasquez et al. (1969) is presented in Table 9-1 and considered for calculation of a candidate CS for 1-butanol.

Table 9-1 also presents data from oral exposure studies considered for derivation of CSs. Pertinent chronic oral exposure data are lacking for 1-butanol. Two subchronic oral exposure studies provide data suitable for deriving candidate CSs. U.S. EPA (1986a) reported a study in which rats were administered gavage doses of 0, 30, 125 or 500 mg/kg/day 1-butanol in deionized water for 13 weeks. Ataxia and hypoactivity were noted in both sexes at 500 mg/kg/day. Transitory decreases in RBC, hematocrit and blood hemoglobin concentration at 125 and 500 mg/kg/day (noted at 6 weeks, but not at 13 weeks) were not considered adverse effects. Wakabayashi et al. (1984)

TABLE 9-1

Toxicity Summary for 1-Butanol

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Inhalation	human/NA	NR	30/sex/ group	70[a]	NR	NR	80 ppm occupational	NA	24.8[b]	Hearing loss	Velasquez, 1964; Velasquez et al., 1969
Oral (gavage)	rat/ CDR(SD)B	both	30/sex/ group	0.35[a]	deionized H_2O	"acceptable"	0	0	0	None	U.S. EPA, 1986a
Oral (gavage)	rat/ CDR(SD)B	both	30/sex/ group	0.35[a]	deionized H_2O	"acceptable"	30 mg/kg/day for 13 weeks	30	5.13[c]	None	U.S. EPA, 1986a
Oral (gavage)	rat/ CDR(SD)B	both	30/sex/ group	0.35[a]	deionized H_2O	"acceptable"	125 mg/kg/day for 13 weeks	125	21.4[c]	Transient hematologic effects	U.S. EPA, 1986a
Oral (gavage)	rat/ CDR(SD)B	both	30/sex/ group	0.35[a]	deionized H_2O	"acceptable"	500 mg/kg/day for 13 weeks	500	85.5[c]	Ataxia, hypoactivity	U.S. EPA, 1986a
Oral	rat/ Wistar	male	30/group	0.35[a]	drinking water	NR	0	0	0	None	Wakabayashi et al., 1984
Oral	rat/ Wistar	male	30/group	0.35[a]	drinking water	NR	6.9 ppm for 3 months	9660[d]	1652[c]	Liver ultrastructural and biochemical changes	Wakabayashi et al., 1984

[a]Reference value from U.S. EPA (1986b) assumed.

[b]Assumed: workers inhale 10 m^3 during the workday, work 5 days/week and weigh 70 kg.

[c]Calculated by multiplying the animal dose expressed as mg/kg/day by the cube root of the ratio of the animal body weight to the reference body weight for humans of 70 kg.

[d]Assuming a water consumption value of 0.049 ℓ/day and a body weight of 0.35 kg (U.S. EPA, 1986b).

NA = Not applicable; NR = not reported

fed male Wistar rats 0 or 6.9 ppm (9660 mg/kg/day) 1-butanol in drinking water for 3 months and noted morphological and functional changes in liver mitochondria.

Composite scores and RQ values for the effects listed in Table 9-1 are computed in Table 9-2. Reportable quantities of 5000 are derived for transient hematologic effects in rats treated by gavage at 125 mg/kg/day for 13 weeks (U.S. EPA, 1986a) and for ultrastructural and biochemical changes in the livers of rats that consumed 9660 mg/kg/day in drinking water (Wakabayashi et al., 1984). Reportable quantities of 1000 were derived for CNS signs in rats treated by gavage at 500 mg/kg/day for 13 weeks (U.S. EPA, 1986a) and for hearing loss in humans occupationally exposed to 80 ppm (243 mg/m^3) (Velasquez, 1964; Velasquez et al., 1969). The RQ of 1000 associated with hearing loss in humans is chosen to represent the chronic toxicity of 1-butanol. The Velasquez (1964) and Velasquez et al. (1969) data in humans are selected over the U.S. EPA (1986a) data in rats to avoid the uncertainties associated with interspecies extrapolation. The well-designed and conducted experiment in rats is considered to support the human data. The RQ of 1000 based on the Velasquez (1964) and Velasquez et al. (1969) data is presented in Table 9-3.

The RQ for chronic toxicity derived in this document differs from that of U.S. EPA (1987b), in which an RQ of 5000 was derived based on unspecified effects in mice, reported in an abstract of a Russian study by Rumyantsev et al. (1975). This appears to be the same study cited herein as Rumyantsev et al. (1976). It is unclear what, if any, other data were considered by U.S. EPA (1987b) in deriving the RQ. The U.S. EPA (1986a) gavage study using rats probably was not available at the time the U.S. EPA (1987b) analysis was made. Because more complete supporting documentation is provided for

TABLE 9-2

Composite Scores for 1-Butanol

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation	*human*	NA	1736	1	*Hearing loss*	7	7	1000	Velasquez, 1964; Velasquez et al., 1969
Oral (gavage)	rat	125	149.8[b]	2.2	Transient hematologic effects	1	2.2	5000	U.S. EPA, 1986a
Oral (gavage)	rat	500	598.5[b]	1.3	Ataxia, hypoactivity	7	9.1	1000	U.S. EPA, 1986a
Oral (drinking water)	rat	9660	115.64[b]	1	Megamitochondria, altered mitochondrial enzyme levels	2	2	5000	Wakabayashi et al., 1984

[a]Calculated by multiplying the human equivalent dose by 70 kg to present the MED in terms of mg/day for a 70 kg human.

[b]The dose was divided by an uncertainty factor of 10 to expand from subchronic to chronic exposure.

NA = Not applicable

TABLE 9-3

1-Butanol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose:	1155 mg/day
Effect:	hearing loss
RV_d:	1
RV_e:	7
Composite Score:	7
RQ:	1000
Reference:	Velasquez, 1964; Velasquez et al., 1969

the RQ for chronic toxicity derived herein, it is recommended that the RQ of 1000 based on the Velasquez (1964) and Velasquez et al. (1969) data supersede that of the earlier (U.S. EPA, 1987b) analysis.

9.2. BASED ON CARCINOGENICITY

Data regarding the carcinogenicity of 1-butanol to humans or laboratory animals by any route of exposure were not located. The compound was assigned to EPA Group D: unable to be classified as to carcinogenicity to humans. Hazard ranking is not possible for chemicals assigned to EPA Group D; therefore, an RQ based on carcinogenicity cannot be derived for 1-butanol.

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in May, 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for 1-Butanol

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
	ID	ID	ID	ND	NA
Oral Exposure					
Subchronic	rat	125 mg/kg/day by gavage for 13 weeks	NOAEL for effects on erythrocyte	1 mg/kg/day	U.S. EPA, 1986a
Chronic	rat	125 mg/kg/day by gavage for 13 weeks	NOAEL for effects on erythrocyte	0.1 mg/kg/day	U.S. EPA, 1986a
Carcinogenicity	ID	ID	ID	ND	NA
REPORTABLE QUANTITIES					
Based on chronic toxicity:		1000			Velasquez, 1964; Velasquez et al., 1969
Based on carcinogenicity:		ND			NA

ID = Insufficient data; NA = not applicable; ND = not derived

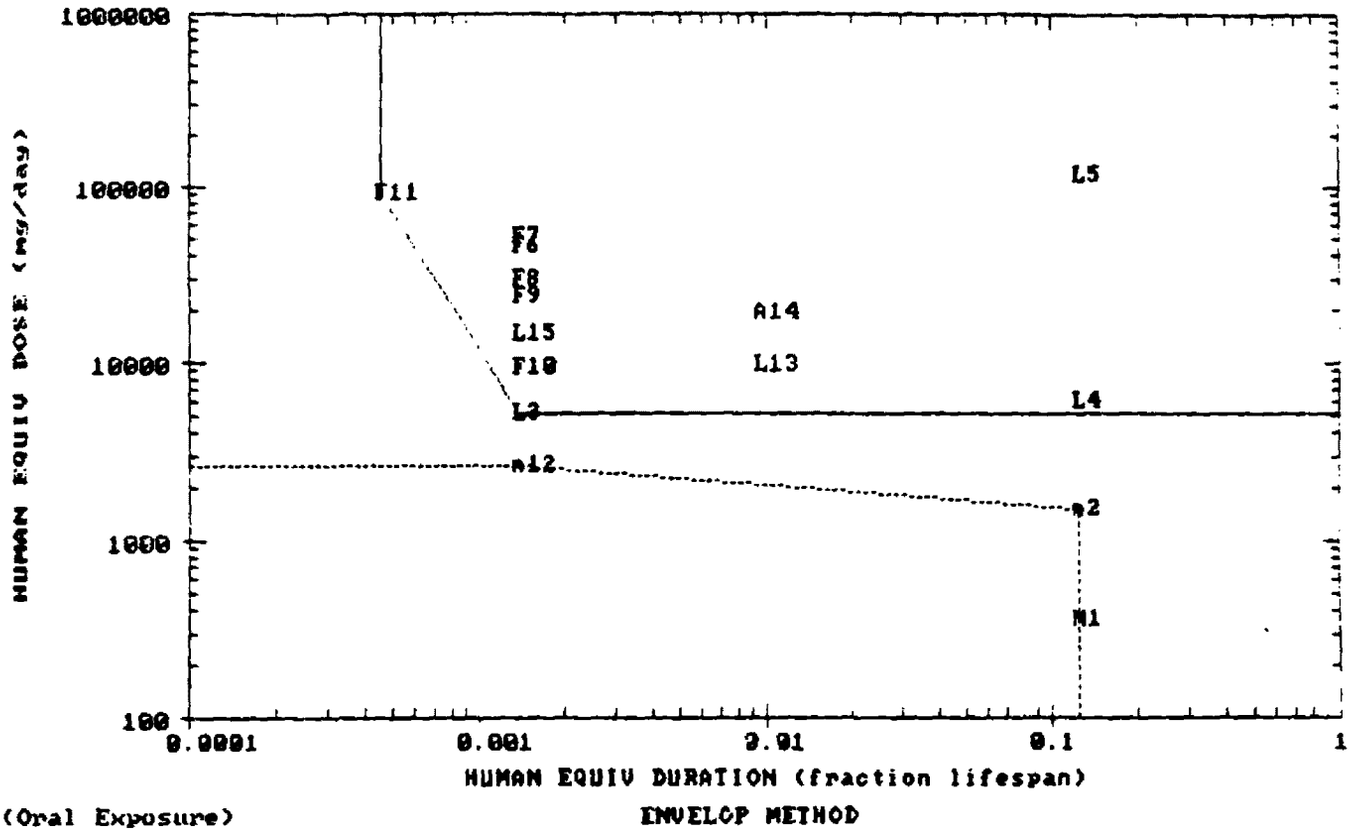
APPENDIX C

DOSE/DURATION RESPONSE GRAPHS FOR EXPOSURE TO 1-BUTANOL

C.1. DISCUSSION

Dose/duration-response graphs for oral and inhalation exposure to 1-butanol generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) are presented in Figures C-1 through C-5. Data used to generate these graphs are presented in Section C.2. In the generation of these figures, all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. For oral exposure, the ordinate expresses dosage expressed as human equivalent dose. The animal dosage expressed as mg/kg/day is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human. For inhalation exposure, the ordinate expresses concentration in either of two ways. In Figures C-2 and C-3, the experimental concentration expressed as mg/m^3 was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In Figures C-4 and C-5, the expanded experimental concentration was multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975) to estimate an equivalent human or scaled concentration [scaled conc (mg/m^3)].

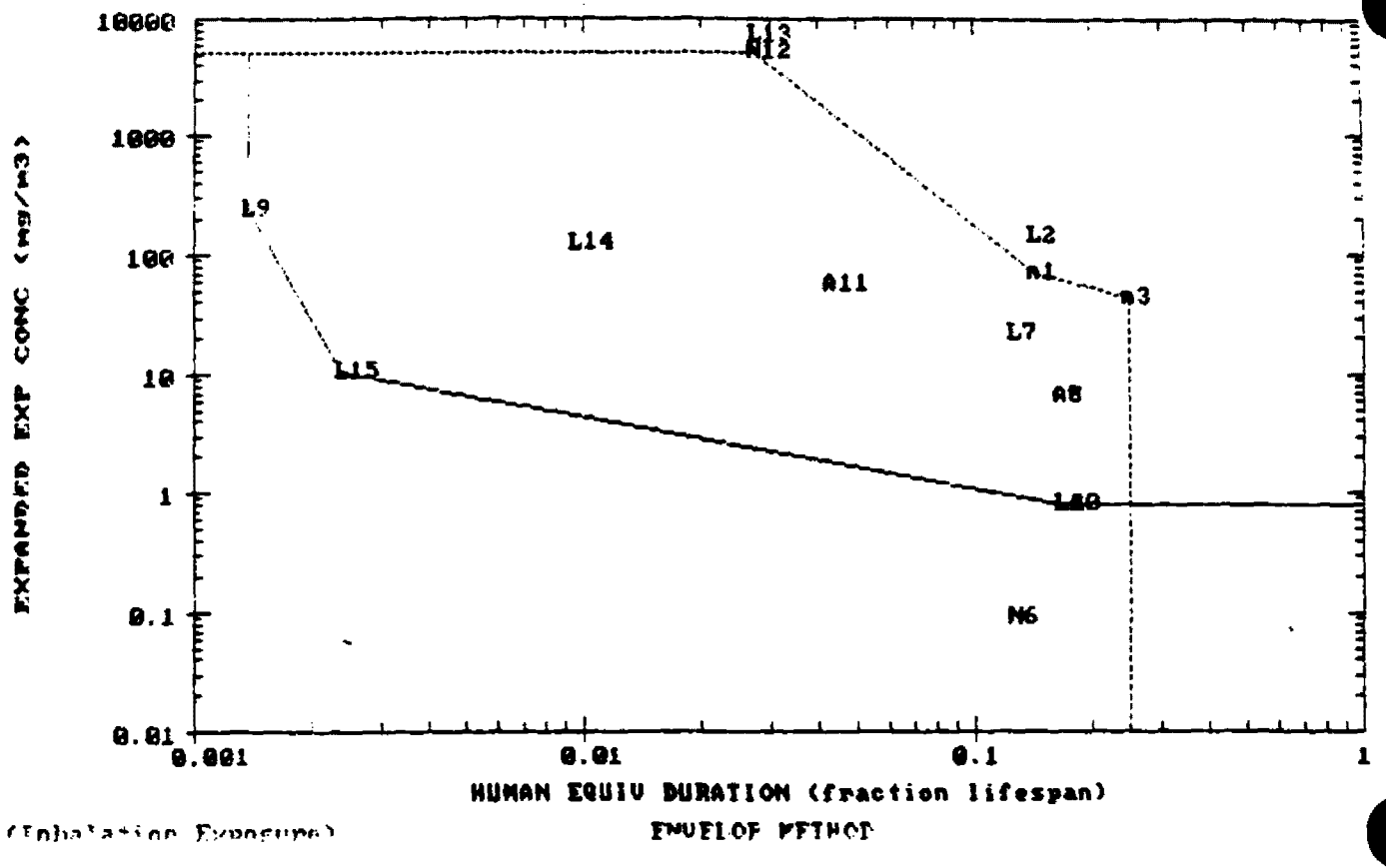
The boundary for adverse effects (solid line) is drawn by identifying the lowest adverse effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point, an infinite



Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL
Solid line = Adverse effects boundary
Dashed line = No adverse effects boundary

FIGURE C-1

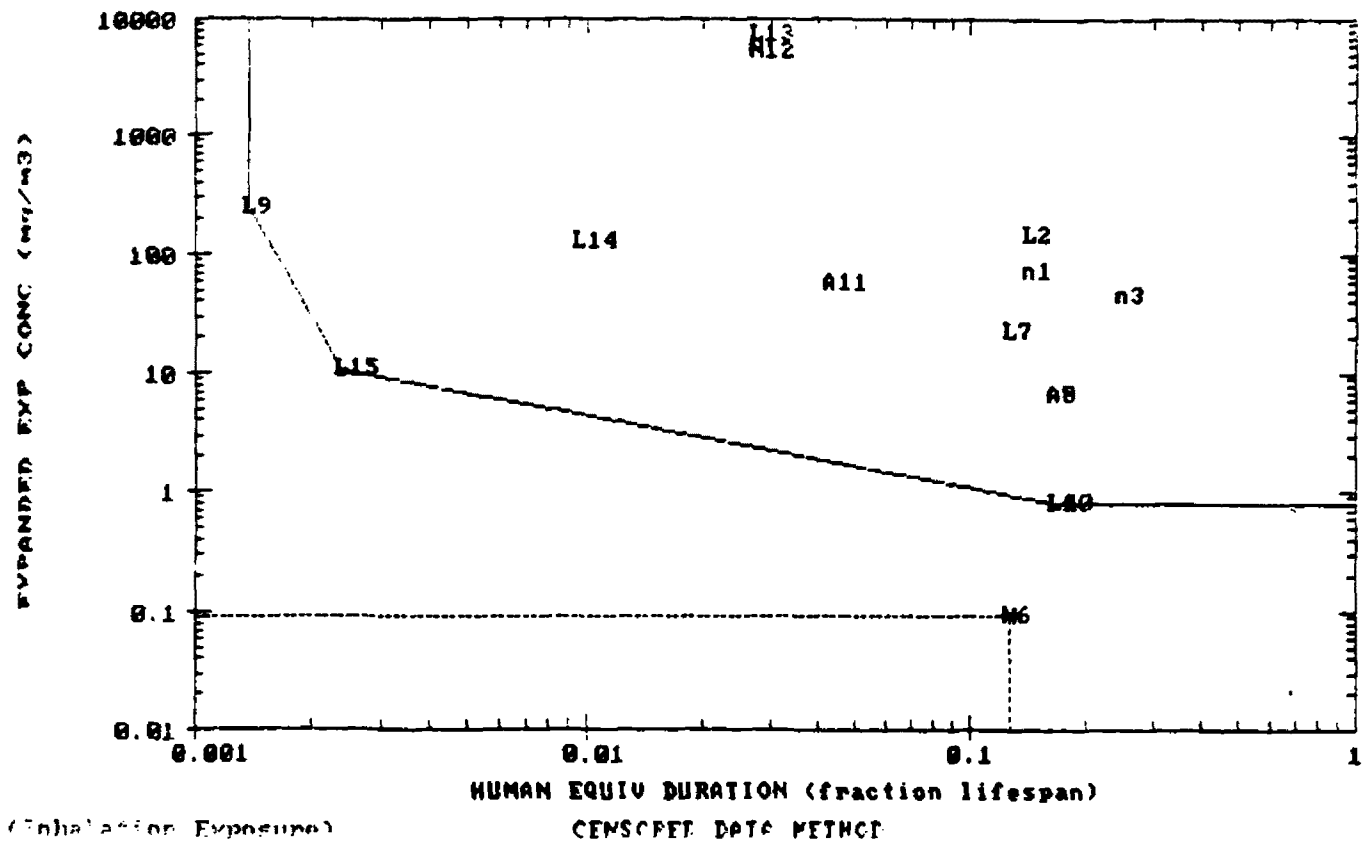
Dose/Duration - Response Graph for Oral Exposure to 1-Butanol:
Envelope Method



Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL
Solid line = Adverse effects boundary
Dashed line = No adverse effects boundary

FIGURE C-2

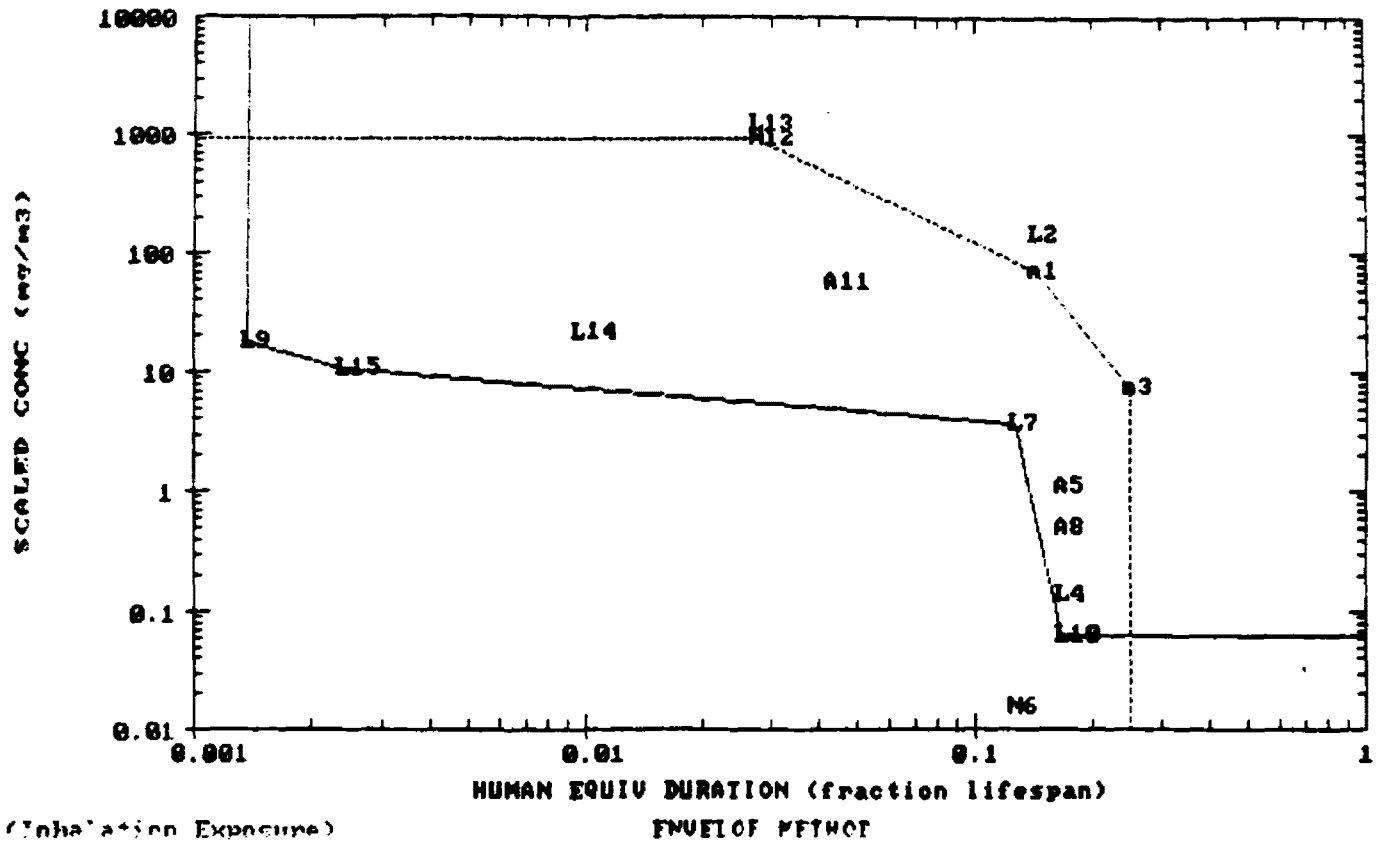
Dose/Duration - Response Graph for Oral Exposure to 1-Butanol, Expanded Experimental Concentration: Envelope Method



Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL
Solid line = Adverse effects boundary
Dashed line = No adverse effects boundary

FIGURE C-3

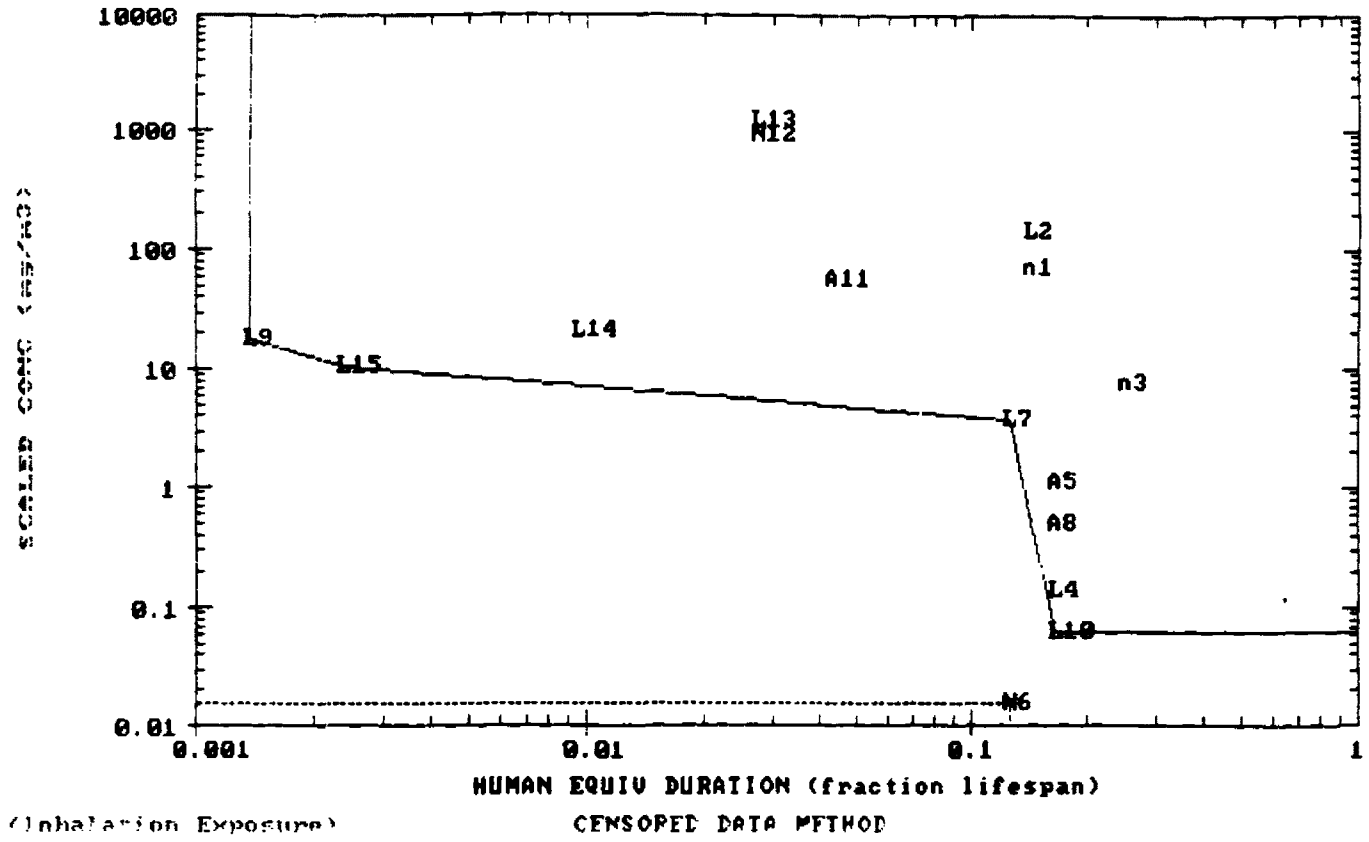
Dose/Duration - Response Graph for Inhalation Exposure to 1-Butanol, Expanded Experimental Concentration: Censored Data Method



Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL
Solid line = Adverse effects boundary
Dashed line = No adverse effects boundary

FIGURE C-4

Dose/Duration - Response Graph for Inhalation Exposure to 1-Butanol, Scaled Concentration: Envelope Method



Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL
Solid line = Adverse effects boundary
Dashed line = No adverse effects boundary

FIGURE C-5

Dose/Duration - Response Graph for Inhalation Exposure to 1-Butanol, Scaled Concentration: Censored Data Method

line is extended upward parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point, a line is extended to the right parallel to the duration axis. The region of adverse effects lies above the adverse effects boundary.

Using the envelope method, the boundary for no adverse effects (dashed line) is drawn by identifying the highest no adverse effects dose or concentration. From this point, a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next highest or equal no adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The region of no adverse effects lies below the no adverse effects boundary. At either ends of the graph between the adverse effects and no adverse effects boundaries are regions of ambiguity. The area (if any) resulting from intersection of the adverse effects and no adverse effects boundaries is defined as the region of contradiction.

In the censored data method, all no adverse effect points located in the region of contradiction are dropped from consideration, and the no adverse effect boundary is redrawn so that it does not intersect the adverse effects boundary and no region of contradiction is generated. This method results in the most conservative definition of the no adverse effects region.

The dose/duration-response graph for oral exposure to 1-butanol generated by the envelope method is presented in Figure C-1. The adverse effects boundary is defined by an LD_{50} value in rabbits (Munch, 1972, Rec.

#11) and a LOAEL for CNS effects in mice given a single gavage treatment (Maickel and Nash, 1985, Rec. #3). The no adverse effect boundary is defined by a NOAEL for CNS effects in mice in the study cited above (Rec. #12) and a NOAEL associated with mild and transient effects on hematology in rats treated by gavage for 13 weeks (U.S. EPA, 1986a, Rec. #2). The latter data point served as the basis for the RfD values for subchronic and chronic oral exposure to 1-butanol. Because of the absence of a region of contradiction, a graph generated by the censored data method would be identical to Figure C-1.

Figures C-2 and C-3 present dose/duration-response graphs for inhalation exposure to 1-butanol using the envelope method and censored data method, respectively, with the ordinate expressed in terms of expanded experimental concentration. The adverse effects boundary is defined by a LOAEL for CNS effects in mice following one exposure (De Ceaurriz et al., 1983, Rec. #9), a LOAEL for ocular irritation in occupationally exposed women (Cogan and Grant, 1945, Rec. #15) and a LOAEL for CNS effects in mice exposed continuously for 4 months (Rumyantsev et al., 1976, Rec #10). The boundary for no adverse effects is defined by a NOEL for developmental toxicity in rats (Brightwell et al., 1987, Rec. #12), a NOAEL in occupationally exposed men (Sterner et al., 1949, Rec. #1) and a NOAEL for systemic effects in rats exposed for 6 months (Savel'ev et al., 1975, Rec. #3). The large region of contradiction in Figure C-2 probably reflects the unreliability of the data base, as discussed in Section 8.2.1. When graphed by the censored data method, the only point defining the no adverse effects boundary is a NOEL for hematological effects in rats exposed for 92 days (Baikov and Khachaturyan, 1973, Rec. #6).

Figures C-4 and C-5 present the inhalation data using the scaled concentration. The large region of contradiction observed in Figure C-2 also appears in Figure C-4, which is generated by the envelope method. The region of contradiction disappears in Figure C-5, generated by the censored data method.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

Oral Exposure

Chemical Name: 1-Butanol
CAS Number: 71-36-3
Document Title: Health and Environmental Effects Document for 1-Butanol
Document Number: SRC-TR-88-189
Document Date: 03/09/89
Document Type: HEED

RECORD #1:	Species:	Rats	Dose:	30.000
	Sex:	Both	Duration Exposure:	13.0 weeks
	Effect:	NOEL	Duration Observation:	13.0 weeks
	Route:	Gavage		
	Number Exposed:	30	30	
	Number Responses:	0	0	
	Type of Effect:	HEMAT	BEHAV	
	Site of Effect:	BLOOD	CNS	
	Severity Effect:	6	8	

Comment: No effects on RBC, PCV averages; no ataxia or hypoactivity.

Citation: U.S. EPA, 1986a

RECORD #2:

Species:	Rats	Dose:	125.000
Sex:	Female	Duration Exposure:	13.0 weeks
Effect:	NOAEL	Duration Observation:	13.0 weeks
Route:	Gavage		

Number Exposed:	30
Number Responses:	NR
Type of Effect:	HEMAT
Site of Effect:	BLOOD
Severity Effect:	6

Comment: Reversible effect: RBC and PCV slightly reduced at 6 weeks, but effect not noted at 13 weeks.

Citation: U.S. EPA, 1986a

RECORD #3:

Species:	Mice	Dose:	1000.000
Sex:	Male	Duration Exposure:	1.0 days
Effect:	LOAEL	Duration Observation:	1.0 days
Route:	Gavage		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	FUNS
Site of Effect:	CNS
Severity Effect:	6

Comment:

Citation: Maickel and Nash, 1985

RECORD #4:

Species:	Rats	Dose:	500.000
Sex:	Both	Duration Exposure:	13.0 weeks
Effect:	LOAEL	Duration Observation:	13.0 weeks
Route:	Gavage		

Number Exposed:	60	60
Number Responses:	16	16
Type of Effect:	MOTOR	MOTOR
Site of Effect:	CNS	PNS
Severity Effect:	7	7

Comment: Ataxia and hypoactivity noted in both sexes during final 6 weeks of test.

Citation: U.S. EPA, 1986a

RECORD #5:

Species:	Rats	Dose:	9660.000
Sex:	Male	Duration Exposure:	3.0 months
Effect:	LOAEL	Duration Observation:	3.0 months
Route:	Water		

Number Exposed:	30
Number Responses:	NR
Type of Effect:	SUBCC
Site of Effect:	LIVER
Severity Effect:	1

Comment: Megamitochondrial formation in liver cells; significantly increased cristae membranes per mitochondrion; reduced MAO and cytochrome oxidase activity.

Citation: Wakabayashi et al., 1984

RECORD #6:

Species:	Rats	Dose:	3830.000
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	7.0 days
Route:	Gavage		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	MORTL
Site of Effect:	HEART
Severity Effect:	9

Comment: LD_{50} value. Rumanian study. Abstract available.

Citation: Ciugudeanu et al., 1985

RECORD #7:

Species:	Rats	Dose:	4360.000
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Food		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: Range-finding LD_{50} value.

Citation: Smyth et al., 1951

RECORD #8:

Species:	Rats	Dose:	2510.000
Sex:	Both	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Gavage		

Number Exposed:	10
Number Responses:	5
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value; death occurred within 4-18 hours.

Citation: Jenner et al., 1964

RECORD #9:

Species:	Rats	Dose:	2020.000
Sex:	Male	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	7.0 days
Route:	Gavage		

Number Exposed:	4
Number Responses:	2
Type of Effect:	DEGEN
Site of Effect:	LIVER
Severity Effect:	9

Comment: LD_{50} value; kidney lesions as well as liver lesions. Earliest deaths were from congestion, with degenerative changes noted in later deaths.

Citation: Purchase, 1969

RECORD #10:

Species:	Rats	Dose:	790.000
Sex:	Female	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	7.0 days
Route:	Gavage		

Number Exposed:	4
Number Responses:	2
Type of Effect:	DEGEN
Site of Effect:	LIVER
Severity Effect:	9

Comment: LD_{50} value; degenerative changes in liver and kidney.

Citation: Purchase, 1969

RECORD #11:

Species:	Rabbits		Dose:	3484.000
Sex:	Both		Duration Exposure:	1.0 days
Effect:	FEL		Duration Observation:	1.0 days
Route:	Gavage			
Number Exposed:	100			
Number Responses:	50			
Type of Effect:	DEATH			
Site of Effect:	NR			
Severity Effect:	9			

Comment: LD_{50} value.

Citation: Munch, 1972

RECORD #12:

Species:	Mice		Dose:	500.000
Sex:	Male		Duration Exposure:	1.0 days
Effect:	NOAEL		Duration Observation:	1.0 days
Route:	Gavage			
Number Exposed:	NR	0		
Number Responses:	NR	0		
Type of Effect:	FUNS	NOS		
Site of Effect:	CNS	NR		
Severity Effect:	6	1		

Comment:

Citation: Maickel and Nash, 1985

RECORD #13:

Species:	Rats		Dose:	810.000
Sex:	NR		Duration Exposure:	7.0 days
Effect:	LOAEL		Duration Observation:	7.0 days
Route:	Oral (NOS)			
Number Exposed:	NR			
Number Responses:	NR			
Type of Effect:	ENZYM			
Site of Effect:	LIVER			
Severity Effect:	1			

Comment: Significant decrease in vitamin content of liver, proportional to dose administered.

Citation: Shehata and Saad, 1978

RECORD #14:

Species:	Rats	Dose:	1620.000
Sex:	NR	Duration Exposure:	7.0 days
Effect:	AEL	Duration Observation:	7.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	ENZYM
Site of Effect:	LIVER
Severity Effect:	1

Comment: Significant dose-related decrease in liver content of vitamins.

Citation: Shehata and Saad, 1978

RECORD #15:

Species:	Rats	Dose:	1208.000
Sex:	Both	Duration Exposure:	1.0 days
Effect:	LOAEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	10	10
Number Responses:	NR	NR
Type of Effect:	MOTOR	MOTOR
Site of Effect:	CNS	PNS
Severity Effect:	6	6

Comment: Decrease in ability to maintain balance on a rising slope; average decrease of 73% that measured prior to dosing.

Citation: Wallgren, 1960

Inhalation Exposure

RECORD #1:

Species:	Rats	Dose:	30.000
Sex:	Both	Duration Exposure:	13.0 weeks
Effect:	NOEL	Duration Observation:	13.0 weeks
Route:	Gavage		

Number Exposed:	30	30
Number Responses:	0	0
Type of Effect:	HEMAT	BEHAV
Site of Effect:	BLOOD	CNS
Severity Effect:	6	8

Comment: No effects on RBC, PCV averages; no ataxia or hypoactivity.

Citation: U.S. EPA, 1986a

RECORD #2:

Species:	Rats	Dose:	125.000
Sex:	Female	Duration Exposure:	13.0 weeks
Effect:	NOAEL	Duration Observation:	13.0 weeks
Route:	Gavage		

Number Exposed:	30
Number Responses:	NR
Type of Effect:	HEMAT
Site of Effect:	BLOOD
Severity Effect:	6

Comment: Reversible effect: RBC and PCV slightly reduced at 6 weeks, but effect not noted at 13 weeks.

Citation: U.S. EPA, 1986a

RECORD #3:

Species:	Mice	Dose:	1000.000
Sex:	Male	Duration Exposure:	1.0 days
Effect:	LOAEL	Duration Observation:	1.0 days
Route:	Gavage		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	FUNS
Site of Effect:	CNS
Severity Effect:	6

Comment:

Citation: Maickel and Nash, 1985

RECORD #4:

Species:	Rats	Dose:	500.000
Sex:	Both	Duration Exposure:	13.0 weeks
Effect:	LOAEL	Duration Observation:	13.0 weeks
Route:	Gavage		

Number Exposed:	60	60
Number Responses:	16	16
Type of Effect:	MOTOR	MOTOR
Site of Effect:	CNS	PNS
Severity Effect:	7	7

Comment: Ataxia and hypoactivity noted in both sexes during final 6 weeks of test.

Citation: U.S. EPA, 1986a
