Toxicology of 2-Butyne-1,4-diol [110-65-6]

Review of Literature

Prepared for

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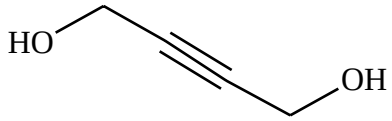
TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Chemical Identification

2-Butyne-1,4-diol



2-Butyne-1,4-diol ($C_4H_8O_2$, CASRN 110-65-6, mol. wt. = 88.11) is also called:

2-Butyne-1,4-diol (8CI9CI)

Agrisynth b3d

Bis(hydroxymethyl)acetylene

Butynediol

1,4-Butynediol (VAN)

2-Butynediol

But-2-yne-1,4-diol

1,4-Dihydroxy-2-butyne

2-Butyne-1,4-diol has the designation for shipping UN 2716.

1.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Plate crystals	Weast and Astle (1980)
Melting Point, °C	58	Weast and Astle (1980)
Boiling Point, °C	238	Weast and Astle (1980)
Solubility:		

Water at 20 °C	Soluble	Weast and Astle (1980)
Organic Solvents	Soluble in ethyl alcohol and acetone	Weast and Astle (1980)

2.0 PRODUCTION PROCESS ANALYSIS

2-Butyne-1,4-diol is generally manufactured from acetylene and formaldehyde and usually contains 10% propargyl alcohol as a byproduct (Malten, 1980).

3.0 PRODUCTION AND IMPORT VOLUMES

Circa 1977, 4 plants reported production of 2-butyne-1,4-diol, and 3 plants reported importation of 2-butyne-1,4-diol (TSCAPP, 1983). One of the importers (Aceto Chem.) reported an import volume of 10,000 to 100,000 lb (4,535 to 22,680 metric tons [Mg])/year. Only 2 (BASF and DuPont) of the 4 U.S. producers reported production volumes (4,535 to 22,680 Mg/yr and 45,350 to 226,800 Mg/yr, respectively, or 50,000 to 250,000 Mg/yr, combined). In 1981, GAF Corporation began operation of a 2-butyne-1,4-diol plant in Seadrift, TX. The compound was then transported to Texas City, TX and Calvert City, KY for processing into butanediol and derivatives (SRI, 1996a). For 1986 through 1989, U.S. ITC (1986-1989) listed BASF Corporation and GAF Corporation as U.S. manufacturers of 2-butyne-1,4-diol, while BASF Corporation and ISP Chemicals, Inc. (International Specialty Products) were listed as manufacturers in 1992 (U.S. ITC, 1992). U.S. ITC (1994) and SRI Int. (1996b) listed only ISP Chemicals, Inc. as a U.S. manufacturer, while BASF Corporation was listed as a supplier of 2-butyne-1,4-diol in 1995 (Kuney, 1994).

4.0 USES

2-Butyne-1,4-diol has been used in the manufacture of plant protection agents and pesticides, textile additives, corrosion inhibitors, plasticizers, synthetic resins, stabilizers (Baadsgaard and Jrrgensen, 1985), and pharmaceuticals (type not specified) (Malten, 1980); as a stabilizer for halogenated hydrocarbons (Anonymous, 1990); as a mordant retarder (Malten, 1980); and as an additive to nickel-electroplating baths to improve the gloss of plated objects (Malten, 1980). When used for this latter purpose, it may contain a stabilizer such as sodium dithiobutyrate.

2-Butyne-1,4-diol, diluted to 0.7%, has also been used as a corrosion inhibitor in a metal cleaning agent (Baadsgaard and Jrrgensen, 1985).

2-Butyne-1,4-diol has been used also as an intermediate in the production of butanediol and derivatives (e.g., 2-butene-1,4-diol, 1,4-butanediol, tetrahydrofuran) (Anonymous, 1990; SRI Int., 1996a).

5.0 ENVIRONMENTAL OCCURRENCE

No data were found.

6.0 HUMAN EXPOSURE

Dermal and inhalation exposure to 2-butyne-1,4-diol may occur during its use in manufacturing processes, and with exposure to some types of metal cleaning agents. Exposure may also occur in workers involved with the use of nickel electroplating baths (Malten, 1980).

A National Occupational Exposure Survey (NOES) for 1983 (cited by RTECS, 1996) concluded that the total number of U.S. workers occupationally exposed to 2-butyne-1,4-diol was 17,571 (4,756 females). **Table 6-1** provides information on the number of exposed workers by occupation, while **Table 6-2** provides exposure information by industry.

Table 6-1. Exposure to 2-Butyne-1,4-diol by Occupation[a]

Occupation/Industry	Number of Plants	Number of Employees	Number of Female Employees
Engineering Technicians, N.E.C.	27	27	27
Freight, Stock, and Material Movers, Hand, N.E.C.	203	1411	
Grinding, Abrading, Buffing, and Polishing Machine Operators	147	434	
Hand Packers and Packagers	69	347	347
Heating, Air Conditioning, Refrigeration Mechanics	174	1042	
Hoist and Winch Operators	27	214	
Inspectors, Testers, and Graders	3	14	
Janitors and Cleaners	168	218	
Machine Operators, not specified	86	350	
Machine Feeders and Offbearers	171	1290	1209
Metal Plating Machine Operators	632	8206	2315
Millwrights	27	135	
Miscellaneous Machine Operators, N.E.C.	17	796	6
Miscellaneous Material Moving Equipment Operators	131	131	
Mixing and Blending Machine Operators	156	180	
Science Technicians, N.E.C.	24	48	
Special Trade Contractors	174	1042	
Stationary Engineers	24	95	
Supervisors, Production Occupations	80	106	
Technicians, N.E.C.	3	1196	852
Vehicle Washers and Equipment Cleaners	144	289	
Total	2487	17571	4756

Abbreviations: N.E.C. = not elsewhere classified
[a]NOES, 1983; cited by RTECS, 1996

Table 6-2. Exposure to 2-Butyne-1,4-diol by Industry[a]

Industry	Number of Plants	Number of Employees	Number of Female Employees
Electrical and Electronic Equipment	188	868	6
Fabricated Metal Products	548	8444	2760
Food and Kindred Products	24	96	
Furniture and Fixtures	12	60	
Instruments and Related Products	9	3035	1801
Machinery, except Electrical	22	316	
Miscellaneous Manufacturing Industries	103	1802	181
Primary Metal Industries	57	703	7
Transportation by Air	3	162	
TOTAL	966	15486	4755

[a]NOES, 1983; cited by RTECS, 1996

7.0 REGULATORY STATUS

REGULATIONS

EPA Regulatory Action	Effect of Regulation/Other Comments
40 CFR 60CStandards of Performance for New Stationary Sources; Volatile Organic Compound (VOC) Emissions From the Synthetic Organic Chemical Manufacturing Industry (SOCMI). Subpart NNNC Distillation Operations. Subpart RRRCReactor Processes.	These standards implement section 111 of the Clean Air Act (CAA), and requires all new, modified, and reconstructed SOCMI distillation and reactor process facilities achieve an emission reduction that reflects the capabilities of the best demonstrated system of continuous emission reduction, considering costs, nonair quality health and environmental impacts, and energy requirements. The chemicals (including 2-butyne-1,4-diol) affected for distillation operations are listed in 60.667 and those affected for reactor processes are listed in 60.707.

8.0 TOXICOLOGICAL DATA

Summary: The odor threshold for 2-butyne-1,4-diol in humans is 200 mg/L water (2000 :M). Two case reports were located which attributed contact sensitization to 2-butyne-1,4-diol. One involved a female cleaner using a cleaning agent that contained 0.7% of 2-butyne-1,4-diol. The other involved a male worker in an electroplating department of a factory, who occasionally prepared 10% aqueous solutions of 2-butyne-1,4-diol.

Metabolically, 2-butyne-1,4-diol appears to be activated to a toxic metabolite *in vivo* by liver alcohol dehydrogenase (ADH). In Wistar rats, 2-butyne-1,4-diol hen administered i.p. induced mortality in a dose-dependent manner, while pretreatment with pyrazole (an inhibitor of liver ADH) prevented death. Pretreatment with pyrazole prevented also the induction of marked behavioral effects. Using rat liver extract, it was shown that 2-butyne-1,4-diol was a substrate for ADH, and that pyrazole competitively inhibited the oxidation and, therefore, the metabolism of 2-butyne-1,4-diol. It was proposed that inactivation of alcohol oxidase by 2-butyne-1,4-diol was due to the enzymatic production of 4-hydroxy-2-butynal, a potent electrophile which could function as an affinity label for the enzyme.

2-Butyne-1,4-diol has been extensively evaluated for acute and subchronic toxicity in different species (mouse, rat, rabbit, guinea pig, cat) using different routes of exposure (dermal, oral, i.p., ocular, inhalation). The 7-day acute oral LD_{50} for mice, rats, rabbits, and guinea pigs were between 100 and 200 mg/kg bw (1200 to 2400 :mol/kg bw). For i.p. administration, the 7-day acute LD_{50} in mice was also about 100 mg/kg bw (1200 :mol/kg bw), while the 24-hour acute LD_{50} in rats was approximately 50 mg/kg bw (609 to 635 :mol/kg bw). The 2-hour inhalation LCLo (lowest lethal concentration) for mice and rats exposed to 2-butyne-1,4-diol was 150 mg/m^3 (1700 :mol/m^3). Treatment with 2-butyne-1,4-diol acutely or subchronically resulted in irritation and/or systemic toxicity, the latter primarily involving damage to the liver and kidneys and, depending on the route of exposure, to the skin and lungs. Administration of 2-butyne-1,4-diol i.p. to rats also induced hypothermia.

In the only reproductive study located, 2-butyne-1,4-diol administered by gavage at 653 :mol/kg to male Coturnix quail (*Coturnix coturnix*) did not induce a sufficient decrease in fertility or testis weight to be classified as a avian chemosterilant.

No carcinogenicity data were found.

The only genotoxicity information on 2-butyne-1,4-diol reports it as negative for the both the induction of gene mutations in *Salmonella typhimurium*

and chromosome aberrations in Chinese hamster V79 cells, in the presence or absence of metabolic activation.

8.1 Human Data

The odor threshold for 2-butyne-1,4-diol in humans is 200 mg/L water (2000 :M) (Knyshova, 1968; cited by Anonymous, 1990). No other details were given.

In one case report, a 41-year-old female cleaner developed a Ared, pruritic, papular, sometimes urticaria-like eruption on the face, hands, and the distal part of the arms@ after using a cleaning agent that contained 0.7% of 2-butyne-1,4-diol for a few months (Baadsgaard and Jrrgensen, 1985). A positive patch test with aqueous 2-butyne-1,4-diol (0.01% vol/vol; > 99.9% pure) indicated it as the active agent.

In another case report (Malten, 1980), a 54-year-old male who had worked for an unspecified number of years in the storage room of an electroplating department developed an itchy dermatitis on his hands and lower arms. His job included the occasional preparation of solutions of 2-butyne-1,4-diol, and merely opening the drum in which the flakes of 2-butyne-1,4-diol were stored aggravated his symptoms.

8.2 General Toxicology

8.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

Results from a study conducted by Taberner and Pearce (1974) indicate that 2-butyne-1,4-diol is activated to a toxic metabolite *in vivo* by liver alcohol dehydrogenase (ADH). Male and female adult albino Wistar rats (320-360 g) were administered either a single dose of 0.558, 0.614, 0.675, 0.743, or 0.817 mmol 2-butyne-1,4-diol/kg i.p.; or treated with a single dose of 1.116 mmol 2-

butyne-1,4-diol/kg i.p. 10 minutes after treatment with 2.9 mmol pyrazole/kg i.p. (an inhibitor of liver ADH). When mortality was assessed 36 hours after treatment, there was a dose-related increase in response to 2-butyne-1,4-diol alone, with no survivors at doses of 0.743-mmol/kg and greater. Pretreatment with pyrazole prevented 2-butyne-1,4-diol induced mortality at a dose of 1.116 mmol 2-butyne-1,4-diol/kg. In addition, while administration of 2-butyne-1,4-diol alone produced marked behavioral effects (e.g., sedation, coughing, diarrhea, loss of spontaneous motor activity, and fall in body temperature) in the rats, pretreatment with pyrazole prevented these effects from occurring. Pretreatment with pyrazole also prevented the induction of toxicity and adverse behavioral effects by butane-1,4-diol and 2-butene-1,4-diol.

To further investigate the role of ADH in 2-butyne-1,4-diol-induced toxicity and behavioral effects in rats, Taberner and Pearce (1974) tested the ability of partially purified rat liver ADH to oxidize the diol. This was done to determine whether inhibition of ADH could explain the protective effect of pyrazole. The Michaelis constant (K_m) for the oxidation of 2-butyne-1,4-diol by ADH was 8.2×10^{-4} M (for ethanol it was 7.9×10^{-4} M). Based on these results, the authors concluded that 2-butyne-1,4-diol was a substrate for ADH, and that pyrazole inhibited the metabolism of 2-butyne-1,4-diol by competitively inhibiting the oxidation of the diol.

Bradbury and Christensen (1991) proposed that ADH may activate 2-butyne-1,4-diol to an electrophile capable of reacting with Abiologically relevant@ nucleophiles. The ability of 2-butyne-1,4-diol to inhibit ADH activity in horse and rainbow trout liver cytosol ADH preparations was investigated. Horse (0.2 mg/mL) or trout (6.0 mg/mL) protein was incubated with 50 mM pyrophosphate buffer (pH 8.0) and 100 mM 2-butyne-1,4-diol in a 5-mL total reaction volume,

with ethanol (100 mM) as the substrate. Reactions were initiated by adding 2.0 mM NAD. At 0.25, 1, 24, 48, 72, and 96 hours, aliquots of the preparations were withdrawn and assayed for ADH activity. After 48 hours, the mean ADH activities remaining in the horse and trout liver preparations were 57.2 " 3.22% and 99.0 " 17.6%, respectively, with this value remaining essentially the same at 72 and 96 hours. The authors speculated that the lack of inhibition of ADH activity in the trout liver preparations was due to the presence of nucleophiles with greater solubility in these preparations than in the horse liver preparations.

To test whether the horse or trout liver ADH preparations were producing electrophilic products after incubation with 2-butyne-1,4-diol (Bradbury and Christensen, 1991), reduced glutathione (GSH) was used as a nucleophilic trap. In both the horse and trout liver preparations, mean ADH activity (mmol/min/mg) was significantly increased in the presence of 100 mM GSH (horse liver: 216 " 24.0 [no GSH] and 397 " 10.0 [GSH]; trout liver: 14.0 " 0.907 [no GSH] and 18.7 " 2.82 [GSH]). It was concluded that reactive aldehyde products were formed by the metabolism of 2-butyne-1,4-diol, perhaps via a Michael addition reaction. The identities of the reactive aldehyde products produced from 2-butyne-1,4-diol were not discussed.

The molecular mechanism of 2-butyne-1,4-diol activation was also investigated by Nichols and Cromartie (1980; for review see Veith et al., 1989). 2-Butyne-1,4-diol was shown to be a substrate and an irreversible inactivator of alcohol oxidase (isolated from the yeast *Candida boidinii* grown on methanol) (K_m = 36 mM; V_{max} = 1.9 :mol/min/mg). The inactivation did not occur under anaerobic conditions, was prevented by the presence of GSH, and showed saturation kinetics with respect to increasing concentrations of 2-butyne-1,4-diol. It was proposed that the inactivation of alcohol oxidase by 2-butyne-1,4-diol was

due to the enzymatic production of 4-hydroxy-2-butynal, a potent electrophile which could function as an affinity label for the enzyme. 4-Hydroxy-2-butynal was shown to be a substrate and inactivator of alcohol oxidase (K_m = 0.44 mM; V_{max} = 0.25 :mol/min/mg).

At a low concentration (0.07 mM), 4-hydroxy-2-butynal caused partial loss of alcohol oxidase activity, while at higher concentrations (0.15 or 0.23 mM), there was complete, irreversible loss of activity in a pseudo-first-order process. Since there was a close correspondence between the K_m and the K_I for 4-hydroxy-2-butynal, Nichols and Cromartie (1980) suggested that the inactivation of alcohol oxidase by 4-hydroxy-2-butynal occurred at the active site with the aldehyde bound in the same manner for oxidation and for inactivation. Also, since there was no time lag for the inactivation, and the rates of inactivation under anaerobic and aerobic conditions were within a factor of 2, the authors proposed that the inactivation of alcohol oxidase by 4-hydroxy-2-butynal occurred without further oxidation of the inactivator. They also proposed that 4-hydroxy-2-butynal dissociates alcohol oxidase into solution, after which 4-hydroxy-2-butynal returns to the enzyme and binds with the alcohol moiety in the position at the active site where oxidation can occur. Thus, 4-hydroxy-2-butynal functions as an affinity label based on the substrate alcohol rather than on the product aldehyde.

8.2.2 Acute Exposures

Studies described in this section are presented in **Table 8-1**.

8.2.2.1 Dermal Application

Jedrychowski et al. (1992a) applied 2-butyne-1,4-diol (5000 mg/kg bw [60000 :mol/kg bw]) as either a solid or a 40% aqueous solution to the intact

dorsum of female Wistar Imp:DAK rats (213"17 g; age not given) for 24 hours and sacrificed rats in each dose group after 2 or 14 days. 2-Butyne-1,4-diol, applied as a solid, was not lethal. Eight of 16 rats that received the aqueous solution, however, died within 2 days of dosing (no deaths occurred thereafter). In dead rats, primarily the liver and kidneys were adversely affected with severe hyperemia and different stages of degeneration, including necrosis observed. Pathological lesions in surviving rats were detected only in the liver and skin. Diffuse hepatic necrotic foci were observed in 3/5 rats 2 days after application of solid 2-butyne-1,4-diol. Vacuolar degeneration of hepatocytes, and numerous binuclear and mitotic cells were observed in the other 2 of 5 rats 2 days after application of solid 2-butyne-1,4-diol. After 14 days, the most apparent condition in rats that received either treatment was extensive cytoplasmic vacuolation in the liver parenchyma. Skin alterations, observed in rats sacrificed 2 days after treatment, consisted of thickening of collagen fibers, signs of basophilic collagen degeneration, and dispersed infiltrations with mononuclear cells in the papillae and deeper layers of the dermis.

In rabbits (strain and age not specified), application of undiluted 2-butyne-1,4-diol for 4 hours to dorsal skin produced skin reddening, with some hemorrhaging and moderate to severe edema (Ullmann, 1975, 1985; both cited by Anonymous, 1990). When a 30% aqueous solution of 2-butyne-1,4-diol was applied to rabbit skin for up to 20 hours, it caused no irritation (BASF, 1986; cited by Anonymous, 1990).

In White Vienna rabbits (3.8-4.2 kg; age not given), 2-butyne-1,4-diol (0.3 g [3000 :mol]), on gauze patches moistened with water or in 20% and 40% aqueous solutions, was applied to intact and abraded skin for 24 hours (Jedrychowski et al., 1992a). Rabbits were observed at 1, 24, 48, and 72 hours

after the cessation of treatment. Dermal irritation was not observed in rabbits with intact skin. Slight reddening was observed on the abraded skin of 1/4 rabbits after application of solid 2-butyne-1,4-diol and the 40% solution, but not after application of the 20% solution.

In a study that evaluated the potential of 2-butyne-1,4-diol to induce allergic contact dermatitis in male and female Hartley albino guinea pigs (403 " 48 g; age not given), a 2% solution of 2-butyne-1,4-diol was injected intradermally and a 20% solution was applied topically. Challenge was done with 5% and 20% solutions of 2-butyne-1,4-diol. None of the guinea pigs sensitized with 2-butyne-1,4-diol developed contact dermatitis (Jedrychowski et al., 1992a).

8.2.2.2 Oral Administration

The oral LD_{50} for both mice and rats (strain and age not specified) administered 2-butyne-1,4-diol was reported by Knyshova (1968; cited by Anonymous, 1990) to be approximately 104 mg/kg bw (~1200 :mol/kg bw). In subsequent studies, the 7-day oral LD_{50} in rats (strain and age not specified) was determined to be approximately 100 mg/kg bw (1200 :mol/kg bw) by Ullmann (1975, 1985; cited by Anonymous, 1990) and 135 mg/kg bw (1570 :mol/kg bw) by BASF (1986; cited by Anonymous, 1990).

In Wistar Imp:DAK rats (209"21 g males, 322"43 g females; age not specified) administered a single dose of 100, 150, 180, 200, or 250 mg 2-butyne-1,4-diol/kg bw (1200-2900 :mol/kg bw) by gavage and observed for up to 14 days, the LD_{50} was 132 mg/kg (1530 :mol/kg) for males and 176 mg/kg (2040 :mol/kg) for females (Jedrychowski et al., 1992a). Gross pathological findings in rats that died included diarrhea, fluid-filled gastrointestinal tract, and congestion of internal

organs. Histopathological examinations revealed perivascular edema and extensive bronchopneumonia in lungs, passive hyperemia, and focal to diffuse centrilobular and midzonal necrosis in liver and nephrosis. Nephrosis was seen in all dead rats and was characterized by degeneration, necrosis, and sloughing of the epithelium of convoluted proximal tubules. The tubules showed dilations and hyaline and granular casts.

An additional group of male and female Wistar Imp:DAK rats were administered 2-butyne-1,4-diol at 100-mg/kg bw to assess pathological lesions (Jedrychowski et al., 1992a). The primary site of toxicity in unscheduled deaths was liver and kidneys. After 48 hours, hepatic changes ranged from vacuolar degeneration through centrilobular and midzonal focal necrosis to panlobular necrosis. The necrotic foci were accompanied by infiltration with reactive mononuclear cells and single granulocytes. Fatty changes at the edges of the necrotic foci were also seen, as were numerous mitotic cells in the intact parenchyma. In the renal cortex, 3/5 males exhibited sloughing of tubular epithelium. After 14 days, liver lesions were characterized by periportal cytoplasmic vacuolation, slight lymphocytic infiltrations, numerous polynucleated hepatocytes, and single cells in mitosis. In the renal cortex, epithelial regeneration was detected in 1/5 males.

In rabbits (strain and age not specified), the oral LD_{50} was 150 mg/kg bw (1700 :mol/kg bw) (Knyshova, 1968; cited by Anonymous, 1990).

In cats (strain and age not specified), administration of 50 mg 2-butyne-1,4-diol/kg bw (600 :mol/kg bw) orally in a single dose was lethal. When this same dose was administered either once or twice to rabbits (age and strain not specified), mortality was not induced. In the rabbit, however, a single dose of 100 mg/kg bw (1200 :mol/kg bw) led to death of the animals (BASF, 1986; cited by

Anonymous, 1990).

In guinea pigs, the oral LD_{50} was 130 mg/kg bw (1500 :mol/kg bw) (Knyshova, 1968; cited by Anonymous, 1990).

8.2.2.3 Intraperitoneal Injection

The LD_{50} for mice administered 2-butyne-1,4-diol i.p. and observed for 7 days was approximately 100 mg/kg bw (1200 :mol/kg bw) (BASF, 1986; cited by Anonymous, 1990).

In male and female adult Wistar albino rats (320-360 g) administered a single i.p. dose of 558, 614, 675, 743, or 817 :mol 2-butyne-1,4-diol/kg in 0.9% (w/v) saline, and observed for up to 24 hours, the LD_{50} was 609-635 :mol/kg (95% confidence limits) (Taberner and Pearce, 1974). After 15 minutes, a marked increase in parasympathetic activity occurred at all doses; the rats salivated excessively and coughed; there was a marked piloerection; severe diarrhea; and the rats felt cold and damp to the touch. Rats lost spontaneous motor activity and exhibited bradycardia (decrease in heart beat) and analgesia. This sedation increased until the rats lost their righting reflex. Death usually occurred within 30 minutes after loss of righting reflex. The clinical effects of 2-butyne-1,4-diol lasted approximately 6 to 8 hours; survivors appeared normal 24 hours after the dose was administered. Pretreatment with the ADH-inhibitor pyrazole (2900 :mol/kg) prevented the occurrence of the deleterious behavioral changes associated with 2-butyne-1,4-diol. Pretreatment with scopolamine at a dose sufficient to inhibit parasympathetic activity (1.5 mg/kg) did not affect the time course or effect of 2-butyne-1,4-diol.

In a follow-up experiment, Taberner and Pearce (1974) evaluated the body temperature of the rats, since many of them felt cold to the touch in the original

experiment. The rats were administered 408, 817, or 1634 :mol 2-butyne-1,4-diol/kg in 0.9% (w/v) saline, i.p. Body temperature was monitored at 30-minute intervals for 12 hours. Mid-dose and high-dose rats did not survive beyond 4 hours post-injection. Low-dose rats had a significant decrease in body temperature 2.5 hours post-injection, as compared to saline controls; body temperature returned to normal by 4 hours post-injection. Mid- and high-dose rats had a significant decrease in body temperature 1 hour and 30 minutes post-injection, respectively. These decreases were sustained until death.

In another follow-up experiment, Taberner and Pearce (1974) evaluated whether the deaths that occurred in the experiment described above were due to the significant decreases in body temperature that occurred. Rats were administered 70 mg (810 :mol) 2-butyne-1,4-diol/kg, in 0.9% (w/v) saline by i.p. injection, at room temperature or in an elevated-temperature environment [32EC], or at room temperature following pretreatment with pyrazole or scolopamine. Body temperature was monitored at 30-minute intervals for 12 hours. Neither an elevated-temperature environment nor pretreatment with scopolamine significantly altered the time course or magnitude of the fall in body temperature or the time at which death occurred, as compared to rats given 2-butyne-1,4-diol alone at room temperature. In rats pretreated with pyrazole, body temperature did not differ significantly from saline controls.

8.2.2.4 Ocular Application

In rabbits (strain and age not specified), application to the eyes of a 30% aqueous solution of 2-butyne-1,4-diol was not irritating while undiluted 2-butyne-1,4-diol induced only slight irritation (slight reddening of the conjunctiva) (BASF, 1986; cited by Anonymous, 1990).

In another study that evaluated ocular irritation, White New Zealand rabbits (weight and age not given) were administered a single dose of 100 mg (1200 :mol) 2-butyne-1,4-diol in the conjunctival sac of one eye (Jedrychowski et al., 1992a). The cornea, iris, and conjunctiva were scored for irritation from 1 hour to 7 days post-exposure. Marked lacrimation and slightly closed lids were observed in all rabbits 1 hour after dosing. Minimal conjunctival erythema was observed 24 and 48 hours after dosing. No ocular abnormalities were observed at later time points.

8.2.2.5 Inhalation Exposure

The 2-hour inhalation LCLo (lowest lethal concentration) for mice and rats (strain and age not specified) exposed to 2-butyne-1,4-diol was 150 mg/m^3 (1700 :mol/m^3) (Ismerov, 1982; cited by Anonymous, 1990).

8.2.3 Short-term and Subchronic Exposures

Studies described in this section are presented in **Table 8-2**.

8.2.3.1 Dermal Application

In male and female White Vienna rabbits (3.8-4.2 kg; age not given) which had the internal area of one ear painted daily with a 40% aqueous solution of 2-butyne-1,4-diol for 10 days, no dermal irritation was observed on day 11 of the study (Jedrychowski et al., 1992a).

8.2.3.2 Oral Administration

In a study to evaluate oral toxicity, young adult male and female Sprague-Dawley rats were administered 1, 10, or 100 mg 2-butyne-1,4-diol/kg bw/day (12,

120, or 1200 :mol/kg bw/day) by gavage for 14 days and were sacrificed on day 15 of the study (Komsta et al., 1989). No treatment-related deaths occurred, but some high-dose rats (sex not specified) had blood-tinged nasal discharges, piloerection, and diarrhea. In addition, the increase in body weight of high-dose males (but not females) was significantly depressed as compared to controls. Liver weight, but not spleen or kidney weight, in high-dose males and high-dose females was significantly increased.

Biochemical and hematological parameters were also evaluated in the rats. There was an increase in serum cholesterol levels in high-dose males and high-dose females. High dose females also had increased serum calcium levels and aminopyrine deethylase activities, decreased GOT and glucose levels, and decreased red blood cell counts, hemoglobin contents, and hematocrits. Hematological parameters were not affected in males.

In a longer-term study conducted by Jedrychowski et al. (1992b), male and female Wistar Imp:DAK rats were administered 1, 10, or 50 mg 2-butyne-1,4-diol/kg/day (12, 120, or 580 :mol/kg/day) by gavage for 28 days beginning at 6- to 8-weeks of age. Surviving animals were sacrificed on day 29 of the study. Three of 8 males and 3/8 females in the high-dose group died before the end of the study (males on days 26, 27, 28; females on days 7, 7, 26). In rats that died before the end of the study, histopathologic evaluation revealed congested internal organs, lung edema, and severe liver and kidney changes. Their livers exhibited parenchymal necrosis, mainly centrilobular and midzonal. Reactive mononuclear cells and granulocyte infiltration and extensive fatty changes were observed in the intact parenchyma. In the kidneys, the main effect observed was renal tubular degeneration and interstitial mononuclear cell infiltrations. The severity of hepatic and renal damage was similar in all animals.

In rats that survived the treatment period, liver lesions were detected in mid- and high-dose rats. These lesions included swelling of the parenchymal cells, mainly around central veins, and increased polymorphism of the hepatocyte nuclei. There were also some parenchymal cells with large nuclei and chromatin margination, and numerous binuclear cells. While all animals in the high-dose groups (8 males, 8 females) exhibited these changes, only 2/8 males and 3/8 females in the mid-dose groups were affected. The intensity of the increases in nuclear differentiation, number of binuclear cells, and intraparenchymal infiltrations was comparable in mid- and high-dose rats. No hepatic changes were detected in low-dose rats. Also, in rats that survived the treatment period, mononuclear cell infiltrations and numerous megakaryocytes in the red pulp of spleen were detected (mid-dose: 2/8 males, 1/8 females; high-dose: 2/5 males, 3/5 females). Changes in body weight, liver and kidney weights, and chemical and hematological parameters were also detected in some rats (see **Table 8-2** for details).

8.2.4 Chronic Exposures

The study described in this section is presented in **Table 8-3**.

In male rats (strain and age not specified) orally administered 0.04, 0.2, or 2 mg 2-butyne-1,4-diol/kg bw (0.5, 2, or 20 :mol/kg bw) for 6 months, there were no changes in general behavior, body weight, or blood parameters (hemoglobin content, number of erythrocytes, leukocytes, and thrombocytes, and coagulation time) (Knyshova, 1968; cited by Anonymous, 1990). The highest dose, however, caused a delay in conditioned reflexes, with a 40% increase in latency time. With the high dose, there was also a reduction in the activities of cholinesterase and SH-enzyme and an increase in transaminase activity, and an alteration in the serum

protein profile. In the brain, the highest dose caused a reduction in the number of Nissl=s bodies, an increase in the neuroglia, and a reduction in SH-enzyme activity. In the liver, the highest dose caused fatty degeneration, sclerotic zones, and reduced glycogen levels. In other, unspecified organs, the highest dose caused localized hyperemia.

8.2.5 Reproductive Effects

The study described in this section is presented in **Table 8-4**.

In a study (Schafer et al., 1982) that evaluated the potential use of a number of chemicals as male avian chemosterilants, fertile male Coturnix quail (*Coturnix coturnix*; age not specified) were administered a single dose of 56.2 mg 2-butyne-1,4-diol/kg (653 :mol/kg [about 50% of the estimated LD_{50}]) by gavage. Thirty to 35 days after dosing, the testes were removed and weighed, and female mates were evaluated for fertility by assessing the percent of eggs laid that were fertile. Based on the results obtained, 2-butyne-1,4-diol was not classified to be a chemosterilant.

8.2.6 Carcinogenicity

No data were found.

8.3 Genetic Toxicology

Studies described in this section are presented in **Table 8-5**.

8.3.1 Prokaryotic Mutations

2-Butyne-1,4-diol at 200 to 5000 Fg/plate (2-60 FM/plate) was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA1538, TA 98, or

TA100 either with or without metabolic activation (Anonymous, 1990 citing unpublished data by BASF, 1986).

8.3.2 *In Vitro* Mammalian Chromosomal Damage

2-Butyne-1,4-diol at 50, 300, and 860 :g/mL (600, 3000, and 10000 FM, respectively) in the absence of S9 and 10, 100, and 300 :g/mL (100, 1000, and 3000 FM, respectively) in the presence of S9 was not clastogenic in Chinese hamster V79 cells (Anonymous, 1990 citing an unpublished report by Heidemann, 1989). Treatment was for 4 hours followed by harvests at 7 hours (high dose only), 18 hours (low, medium, and high doses), and 28 hours (high dose only) later. Toxicity, as demonstrated by a decline in the mitotic index, was induced by 2-butyne-1,4-diol at the highest doses tested.

8.4 Immunotoxicity

No data were found.

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
8.2.2.1 Dermal Application								
Wistar Imp:DAK rats (213_17 g), age not given	27F (11F received solid substance; 16F received aqueous solution [see _ Dose_ column])	none	2-butyne-1,4-diol, ~ 99% pure	5000 mg/kg bw (60000 _mol/kg bw), either as solid substance moistened with water (0.05 g/cm$^{2;}$ 600 _mol/cm^2), or as 40% aqueous solution (0.15 mL/cm^2) applied to intact dorsum	24 h exposure; 2 or 14 days observation period	2-Butyne-1,4-diol, applied as a solid, was not lethal. Eight of 16 rats that received the aqueous solution, however, died within 2 days of dosing (no deaths occurred thereafter).	In dead rats, primarily liver and kidneys were adversely affected: Severe hyperemia and different stages of degeneration, including necrosis, were observed. Pathological lesions in surviving rats were detected only in the liver and skin. Diffuse necrotic foci in the liver were observed in 3/5 rats 2 days after application of solid 2-butyne-1,4-diol. Vacuolar degeneration of hepatocytes, and numerous binuclear and mitotic cells were observed in the other 2 rats 2 days after application of solid 2-butyne-1,4-diol. In rats that received the aqueous solution, liver damage was severe 2 days after treatment, and resembled that observed in rats that died. After 14 days, the most apparent condition in rats that received either treatment was extensive cytoplasmic vacuolation in the liver parenchyma. Skin alterations, observed in rats sacrificed 2 days after treatment, consisted of thickening of collagen fibers, signs of basophilic collagen degeneration, and dispersed infiltrations with mononuclear cells in the papillae and deeper layers of the dermis.	Jedrychowski et al. (1992a)
rabbits (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	undiluted 2-butyne-1,4-diol applied to dorsal skin	4 h; rabbits assessed immediately after exposure	n.g.	Exposure to undiluted 2-butyne-1,4-diol produced skin reddening with some hemorrhaging and moderate to severe edema.	Ullmann (1975, 1985; both cited by Anonymous, 1990)
rabbits (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	30% aqueous solution applied to skin (region not specified)	up to 20 h; observation period not specified	n.g.	Exposure did not induce irritation.	BASF (1986; cited by Anonymous, 1990)
White Vienna rabbits (3.8-4.2 kg), age not given	4 (sex not specified)	4 (sex not specified; see _ Dose_ column)	2-butyne-1,4-diol, ~ 99% pure	0.3 g (3000 _mol) on gauze patches moistened with water, and 20% and 40% aqueous solutions; applied	24 h exposure; 1, 24, 48, or 72 h observation period after cessation of exposure	n.g.	Dermal irritation was not observed in rabbits with intact skin. Slight reddening was observed on the abraded skin of 1 rabbit after application of 40% and 100% 2-butyne-1,4-diol, but not after application of the 20% solution.	Jedrychowski et al. (1992a)

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
				to intact (right side) and abraded (left side) skin Adjacent areas of untreated and water-treated skin of each rabbit served as controls				
Hartley albino guinea pigs (403_48 g), age not given	22 (M and F, not separated by sex)	8 (M and F, not separated by sex)	2-butyne-1,4-diol, ~ 99% pure	2% 2-butyne-1,4-diol was injected intradermally and 20% was applied topically. Challenge was with 5% and 20% 2-butyne-1,4-diol. No other details about dosing were given.	n.g.	n.g.	Guinea pigs were evaluated solely for allergic contact dermatitis. This condition was not detected in any of the guinea pigs sensitized with 2-butyne-1,4-diol.	Jedrychowski et al. (1992a)
8.2.2.2 Oral Administration								
mice (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; no observation period	LD_{50} = 105 mg/kg bw (1200 _mol/kg bw)	No other details were given.	Knyshova (1968; cited by Anonymous, 1990)
rats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; no observation period	LD_{50} = 104.5 mg/kg bw (1210 _mol/kg bw)	No other details were given.	Knyshova (1968; cited by Anonymous, 1990)
rats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; 7 day observation period	LD_{50} = 135 mg/kg bw (1570 _mol/kg bw)	No other details were given.	BASF (1986; cited by Anonymous, 1990)

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
rats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; 7 day observation period	LD_{50} = ~ 100 mg/kg bw (1200 _mol/kg bw)	No other details were given.	Ullmann (1975, 1985) and BASF (1986); all cited by Anonymous (1990)
Wistar Imp:DAK rats (322_21 g M; 209_43 g F), age not given	5M, 5F per dose	none	2-butyne-1,4-diol, ~ 99% pure	100, 150, 180, 200, or 250 mg/kg bw (1200-2900 _mol/kg bw) by gavage in 10% aqueous solution	single dose; 14 day observation period	LD_{50} (M) = 132 mg/kg (1530 _mol/kg) LD_{50} (F) = 176 mg/kg (2040 _mol/kg)	Gross pathological finding in rats that died included diarrhea, fluid-filled gastrointestinal tract, and congestion of internal organs. Histopathological examination revealed perivascular edema and extensive bronchopneumonia in lungs, passive hyperaemia, and focal to diffuse centrilobular and midzonal necrosis in liver and nephrosis. Nephrosis occurred in all dead rats and was characterized by degeneration, necrosis, and sloughing of the epithelium of convoluted proximal tubules. There were dilations and hyaline and granular casts in the tubules.	Jedrychowski et al. (1992a)
Wistar Imp:DAK rats (322 g M; 209 g F), age not given	10M, 10F	none	2-butyne-1,4-diol, ~ 99% pure	100 mg/kg bw (1200 _mol/kg bw) by gavage in 10% aqueous solution	single dose; 2 or 14 day observation period	n.g.	Rats were dosed to assess pathological lesions induced by 2-butyne-1,4-diol. In dead rats, primarily liver and kidneys were adversely affected. After 2 day, hepatic changes ranging from vacuolar degeneration through centrilobular and midzonal focal necrosis to panlobular necrosis were observed. The necrotic foci were accompanied by infiltration with reactive mononuclear cells and single granulocytes. Fatty changes at the edges of the necrotic foci were also observed. There were numerous mitotic cells in the intact parenchyma. In the renal cortex, 3/5 males exhibited sloughing of tubular epithelium. After 14 days, liver lesions were characterized by periportal cytoplasmic vacuolation, slight lymphocytic infiltrations, numerous polynucleated hepatocytes, and single cells in mitosis. In the renal cortex, epithelial regeneration was detected in 1 male.	Jedrychowski et al. (1992a)
rabbits (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; no observation period	LD_{50} = 150 mg/kg bw (1700 _mol/kg bw)	No other details were given.	Knyshova (1968; cited by

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
								Anonymous, 1990)
rabbits (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	50 mg/kg bw (600 μmol/kg bw), injected once or twice; or 100 mg/kg bw (1200 μmol/kg bw), injected once	n.g.	The low dose, administered once or twice, was not lethal. The high dose was lethal.	No other details were given.	BASF (1986; cited by Anonymous, 1990)
cats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	50 mg/kg bw (600 μmol/kg bw)	single dose; no observation period	The dose was lethal	No other details were given.	BASF (1986; cited by Anonymous, 1990)
guinea pigs (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single oral dose; no observation period	LD_{50} = 130 mg/kg bw (1500 μmol/kg bw)	No other details were given.	Knyshova (1968; cited by Anonymous, 1990)
8.2.2.3 Intraperitoneal Injection								
mice (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	single dose; 7 day observation period	LD_{50} = ~ 100 mg/kg bw (1200 μmol/kg bw)	No other details were given.	BASF (1986; cited by Anonymous, 1990)
adult Wistar albino rats (320-360 g)	6 rats per dose (not separated by sex)	none	2-butyne-1,4-diol, purity not specified	558, 614, 675, 743, or 817 μmol/kg , or 1116 μmol/kg + 2900 μmol pyrazole[1]/kg, in 0.9% (w/v) saline, i.p. [1] Pyrazole is an inhibitor of alcohol	single dose; mortality determined after 18 h (survivors were observed for an additional 24 h)	dose (μmol/kg) / dead/total 558 1/6 614 2/6 675 5/6 743 6/6 817 6/6 1116 + pyrazole 0/6	At all doses, after 15 min., a marked increase in parasympathetic activity occurred; the rats salivated excessively and coughed. There was marked piloerection and severe diarrhea and the rats felt cold and damp to the touch. Rats lost spontaneous motor activity, bradycardia (decrease in heart beat), and analgesia. This sedation increased until the rats lost their righting reflex. Death usually occurred within 30 min. after loss of righting reflex. The clinical effects of 2-butyne-1,4-diol lasted approximately 6-8 h; survivors appeared normal 24 h after the dose was administered. Rats were not necropsied.	Taberner and Pearce (1974)

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
				dehydrogenase. Pyrazole was administered i.p. 10 min. before 2-butyne-1,4-diol and mortality was determined at 36 h.		LD_{50}: 609-635 _mol/kg (95% confidence limits)	Pretreatment with pyrazole prevented the occurrence of deleterious behavioral changes associated with 2-butyne-1,4-diol. Pretreatment with scopolamine at a dose sufficient to inhibit parasympathetic activity (1.5 mg/kg i.p.) did not affect the time course or effect of 2-butyne-1,4-diol (no other details given).	
adult Wistar albino rats (320-360 g)	_6 rats per dose (not separated by sex)	_6 rats (saline alone)	2-butyne-1,4-diol, purity not specified	408, 817, or 1634 _mol/kg in 0.9% (w/v) saline, i.p.	single dose; body temp. was monitored at 30-min. intervals for 12 h	MD and HD rats did not survive beyond 4 h post-injection (no other details given)	This experiment was conducted to determine whether 2-butyne-1,4-diol induces hypothermia in rats. All rats were maintained at room temperature (22_ C) throughout the experiment. Controls maintained a body temp. within 37.2-37.9_ C over 5 h. LD rats had a significant decrease in body temp. 2.5 h post-injection ($p < 0.02$); this returned to normal by 4 h post-injection. MD and HD rats had significant decreases in body temp. 1 h and 30 min post-injection, respectively. These decreases were sustained until death. Statistical comparisons of body temp. were not made between LD, MD, and HD groups.	Taberner and Pearce (1974)
adult Wistar albino rats (320-360 g)	6 rats per dose (not separated by sex)	6 rats (saline alone)	2-butyne-1,4-diol, purity not specified	70 mg/kg (810 _mol/kg); or 1.5 mg/kg scopolamine 5 min before 70 mg/kg; or 225 mg/kg pyrazole 10 min before 70 mg/kg; or 70 mg/kg administered in an elevated-temp. environment (32_ C); in 0.9% (w/v) saline, i.p.	single dose; body temp. was monitored at 30-min. intervals for 12 h	Some rats pretreated with scolopamine, and some rats treated with 2-butyne-1,4-diol alone (maintained at room temp. and maintained at 32_ C) died before the end of 12 h, but the numbers were not specified.	This experiment was conducted to determine whether the deaths that occurred in the experiment described above were due to the significant decreases in body temp. Neither an elevated-temp. environment nor pretreatment with scopolamine significantly altered the time course or magnitude of the fall in body temp. or the time at which death occurred, as compared to rats given 2-butyne-1,4-diol alone at room temperature. In rats pretreated with pyrazole, body temp. did not differ significantly from saline controls.	Taberner and Pearce (1974)

Table 8-1. Acute Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
8.2.2.4 Ocular Application								
rabbits (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	undiluted or 30% aqueous solution applied to eye	n.g.	n.g.	Undiluted 2-butyne-1,4-diol induced only slight irritation; there was a slight reddening of the conjunctiva. The 30% aqueous solution produced no irritation.	BASF (1986; cited by Anonymous, 1990)
White New Zealand rabbits (age not given)	4 (sex not specified)	4 (sex not specified; see _ Dose_ column)	2-butyne-1,4-diol, ~ 99% pure	100 mg (1200 _mol) in conjunctival sac of one eye of each rabbit. Other eye served as control.	single dose; 1, 24, 48, and 72 h, and up to 7 days after exposure	n.g.	The cornea, iris, and conjunctiva were scored. Marked lacrimation and slightly closed lids were observed in all rabbits 1 h after dosing. Minimal conjunctival erythema was observed 24 and 48 h after dosing. No abnormalities were observed at later time points.	Jedrychowski et al. (1992a)
8.2.2.5 Inhalation Exposure								
mice (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	2 h inhalation; no observation period	LCLo (lowest lethal concentration) = 150 mg/m^3 (1700 _mol/m^3)	No other details were given.	Ismerov (1982; cited by Anonymous, 1990)
rats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	n.g.	2 h inhalation; no observation period	LCLo = 150 mg/m^3 (1700 _mol/m^3)	No other details were given.	Ismerov (1982; cited by Anonymous, 1990)

Abbreviations: bw = body weight; F= female; M = male; n.g. = not given; LD = low dose; MD = mid dose; HD = high dose

Table 8-2. Short-term and Subchronic Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
8.2.3.1 Dermal Application								
White Vienna rabbits (3.8-4.2 kg; age not given)	4 (sex not specified)	4 (sex not specified; see _Dose_ column)	2-butyne-1,4-diol, ~ 99% pure	40% aqueous solution painted on left ear. Right ear (control) was painted with water.	10 days; rabbits were examined the day after cessation of exposure (day 11 of study)	n.g.	No dermal irritation was detected.	Jedrychowski et al. (1992a)
8.2.3.2 Oral Administration								
young adult Sprague-Dawley rats	10M, 10F per dose	10M, 10F (tap water alone)	2-butyne-1,4-diol, purity not specified (between 97 and 99%)	1, 10, or 100 mg/kg bw (12, 120, or 1200 _mol/kg bw) in water, daily by gavage	14 days; rats sacrificed on day 15 of study	No treatment-related deaths occurred	**Clinical Effects:** Some HD rats had blood-tinged nasal discharges, piloerection, and diarrhea (incidences not given). **Growth:** Growth of HD males was significantly depressed. **Organ Weight**: Mean liver weight (expressed as percent bw) was significantly increased in HD males and females. **Chemistry:** There was an increase in serum cholesterol levels in HD males and females (HD males: 77.1 mg/100 mL vs. 60.0 in male controls; HD females: 112.1 mg/100 mL vs. 65.3 in female controls). There was an increase in serum calcium levels and aminopyrine deethylase (APDM) activity and a decrease in GOT and glucose levels in HD females (calcium: 11.2 mg/100 mL vs. 10.6 in controls; APDM: 14.8 nmol HCHO/h/mg protein vs. 11.0 in controls; GOT: 106.5 mU/100 mL vs. 144.8 in controls; glucose: 154.6 mg/100 mL vs. 177.5 in controls). **Hematology**: There was a decrease in red blood cell (rbc) counts, hemoglobin (Hb) content, and hematocrit in HD females (rbc: 6.8 x 10^6/_L vs. 7.5 x 10^6/_L in controls; Hb: 13.1 g/dL vs. 14.4 in controls; hematocrit: 37.5% vs. 40.9% in controls). Hematological parameters were not affected in males.	Komsta et al. (1989)
6- to 8-wk-old Wistar Imp:DAK rats	8M, 8F per dose	8M, 8F (distilled water alone)	2-butyne-1,4-diol, ~ 99% pure	1, 10, or 50 mg/kg (12, 120, or 580 _mol/kg), daily by gavage	28 days; rats were killed on day 29 of study	3/8 M and 3/8 F HD-rats died (M on days 26, 27, 28; F on days 7,	Histopathological evaluation was performed on the following tissues: adrenals, duodenum, heart, ovaries, testes, small and large intestine, kidneys, liver, lungs, pancreas, spleen, and stomach. **Histopathology:** In rats that died before the end of the study, histopathologic evaluation revealed congested internal organs, pulmonary edema, and severe changes in liver and kidneys. Diffuse hepatic parenchymal necrosis, mainly centrilobular and midzonal, accompanied by reactive mononuclear cells and granulocyte infiltration and extensive	Jedrychowski et al. (1992b)

Table 8-2. Short-term and Subchronic Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
						7, 26)	fatty changes in the intact parenchyma were detected. In the kidneys, the main effect observed was renal tubular degeneration and interstitial mononuclear cell infiltrations. The severity of hepatic and renal damage was similar in all animals. In rats that survived the treatment period, liver lesions were detected in MD and HD rats. These were swelling of the parenchymal cells, mainly around central veins, and increased polymorphism of the hepatocyte nuclei. There were also some parenchymal cells with large nuclei and chromatin margination, and numerous binuclear cells. While all animals in the HD groups had these changes, only 2 males and 3 females in the MD groups were affected. The intensity of the increases in nuclear differentiation, number of binuclear cells, and intraparenchymal infiltrations was comparable in MD and HD rats. No hepatic changes were detected in LD rats. Also in rats that survived the treatment period, mononuclear cell infiltrations and numerous megakaryocytes in the red pulp of spleen were detected (MD: 2/8 males, 1/8 females; HD: 2/5 males, 3/5 females).	
6- to 8-wk-old Wistar Imp:DAK rats	8M, 8F per dose	8M, 8F (distilled water alone)	2-butyne-1,4-diol, ~ 99% pure	1, 10, or 50 mg/kg (12, 120, or 580 _mol/kg), daily by gavage	28 days; rats were killed on day 29 of study	3/8 M and 3/8 F rats died (M: on days 26, 27, 28; F: on days 7, 7, 26)	**Body Weight:** Rats were weighed before the first dosing and twice weekly thereafter. Body weight gain was significantly lower in HD males at all timepoints as compared to controls. Female body weight gain was not significantly lower at any timepoint in any dose group. **Organ Weight**: Mean absolute and mean relative (organ weight to bw ratio) liver weights were significantly increased in HD males and females. Mean relative liver weight was also significantly increased in MD females. Mean relative weight of kidney was significantly increased in HD males and females. Mean absolute weight of kidneys was significantly increased in females, but not males. **Hematology**: Rbc count was significantly lower in MD and HD females. Hematocrit (%) was significantly lower in HD females. Hb (g/dL) was significantly lower In HD females. Reticulocyte and white blood cell counts were significantly higher in HD males and females, due to significantly higher neutrophil and lymphocyte counts. **Chemistry:** Sorbitol dehydrogenase (U/L) was significantly increased in HD males and females. Total protein (g/dL) was significantly increased in HD females. Glucose (mg/dL) was significantly increased in HD males.	Jedrychowski et al. (1992b) continued

Abbreviations: bw = body weight; F= female; M = male; n.g. = not given.

Table 8-3. Chronic Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Survival	Results/Comments	Reference
male rats (strain and age not given)	n.g.	n.g.	2-butyne-1,4-diol, purity not specified	0, 0.04, 0.2, or 2 mg/kg bw (0, 0.5, 2, or 20 _mol/kg bw)	6 mo; observation period not specified	n.g.	None of the doses caused changes in general behavior, body weight, or blood parameters (hemoglobin content, number of erythrocytes, leukocytes, and thrombocytes, and coagulation time). The highest dose, however, caused a delay in conditioned reflexes, with a 40% increase in latency time. Also with the high dose, there was a reduction in the activities of cholinesterase and SH-enzyme and an increase in transaminase activity, as well as an alteration in the serum protein profile. **Brain:** With the highest dose, there was a reduction in the number of Nissl_s bodies and an increase in the neuroglia, as well as a reduction in SH-enzyme activity. **Liver:** The highest dose caused fatty degeneration, sclerotic zones, and reduced glycogen values. **Other Tissues**: The highest dose caused localized hyperemia in organs other than the brain and liver, but the identity of the organs was not specified.	Knyshova (1968; cited by Anonymous, 1990)

Abbreviations: n.g. = not given

Table 8-4. Reproductive Toxicity of 2-Butyne-1,4-diol

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Survival	Comments	Reference
fertile Coturnix quail (*Coturnix coturnix*; age not given)	7M	7M (exposed to 1,2-propanediol alone)	2-butyne-1,4-diol, purity not specified	56.2 mg/kg (653 _mol/kg) by gavage (This dose was selected because it was ~ 50% of the estimated LD_{50})	single dose; female mates were examined 30-35 days after male dosing	1 male died, but it was not specified if this was treatment-related	2-Butyne-1,4-diol was evaluated for use as an avian male chemosterilant. Males were dosed and their testes were extracted and weighed after 30-35 days. Female mates were evaluated for fertility after 30-35 days. Based on the lack of obtaining at least a 50% reduction in fertility and a combined testes weight of 1.1 g or less at sacrifice, 2-butyne-1,4-diol was not classified as a chemosterilant.	Schafer et al. (1982)

Abbreviations: M = male; n.g. = not given.

9.0 STRUCTURE-ACTIVITY RELATIONSHIPS

The lethality of 2-butyne-1,4-diol and two other 4-carbon diols (2-butene-1,4-diol and butane-1,4-diol) was evaluated by Taberner and Pearce (1974). Male and female adult Wistar albino rats (320-360 g) were administered a single dose of one of the compounds in 0.9% (w/v) saline i.p., and mortality was determined after 18 hours. The 95% confidence intervals for the LD_{50} values were as follows: 2-butyne-1,4-diol, 609-635 :mol/kg; 2-butene-1,4-diol, 3710-3740 :mol/kg; butane-1,4-diol, 11,870-11,900 :mol/kg. Thus, lethality increased with increasing unsaturation of the diol. See **Table 8-1** for details of 2-butyne-1,4-diol-induced toxicity, and **Table 9-1** for details of butane-1,4-diol- and 2-butene-1,4-diol-induced toxicity.

Age, Strain, Species	Exposed Animals	Control Animals	Chemical Form, Purity	Dose	Duration of Exposure; Observation Period	Mortality	Results/Comments	Reference
Butane-1,4-diol								
adult Wistar albino rats (320-360 g)	6 rats per dose (not separated by sex)	none	butane-1,4-diol, purity not specified	8900, 10780, 12940, 15530, or 17800 μmol/kg in 0.9% (w/v) saline, i.p.	single dose; mortality determined after 18 h (survivors were observed for an additional 24 h)	dose (μmol/kg) dead/total 8900 0/6 10780 2/6 12940 4/6 15530 5/6 17800 6/6 LD_{50}: 11,870-11,900 μmol/kg (95% confidence interval)	At about 20 min. post-injection, the 8900-μmol/kg dose induced a hypnotic state, with loss of the righting reflex and maintained muscle tone. With an increase in the dose, there was an increase in the depth of hypnosis along with a marked bradycardia (slowing of heart beat), analgesia, and labored breathing. Death appeared to be due to respiratory failure. In rats that received a dose sufficient to cause loss of the righting reflex for 3 h, there was a significant decrease in body temp. ($p < 0.02$), which correlated well with the duration of sleeping time. This decrease in body temp. was much less than that induced by 2-butyne-1,4-diol (see Table 8-1). Rats were not necropsied.	Taberner and Pearce (1974)
2-Butene-1,4-diol								
adult Wistar albino rats (320-360 g)	6 rats per dose (not separated by sex)	none	2-butene-1,4-diol, purity not specified	3200, 3520, 3870, 4260, or 4680 μmol/kg in 9% (w/v) saline, i.p.	single dose; mortality determined after 18 h (survivors were observed for an additional 24 h)	dose (μmol/kg) dead/total 3200 0/6 3520 1/6 3870 5/6 4260 5/6 4680 6/6 LD_{50}: 3710-3740 μmol/kg (95% confidence interval)	The 3200-μmol/kg dose induced few behavioral changes. Higher doses produced sedation and a loss of spontaneous activity 30-40 min. post-injection. These effects lasted 2-3 h, at which time most rats entered into tonic convulsions and died within 40 min. In rats that became sedated, there was no significant decrease in body temperature. Rats were not necropsied.	Taberner and Pearce (1974)

Abbreviations: i.p. = intraperitoneal

10.0 ONLINE DATABASES AND SECONDARY REFERENCES SEARCHED

10.1 Online Databases

Chemical Information System Files

ISHOW (Information System for Hazardous Organics in Water)
SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

285 BioBusiness
50 CAB Abstracts
359 Chemical Economics Handbook

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CBNB (Chemical Business News Base)
CEN (Chemical & Engineering News)
CHEMCATS (Chemical Catalogs)
CIN (Chemical Industry Notes)
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)

HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
NAPRALERT (Natural Products Alert)
PIRA (Pira Int. database on the pulp and paper, imaging, packaging, printing, publishing, and nonwoven industries)
PROMT (Predicasts Overview of Markets and Technology)
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles, often just the toxicology information from the databases named:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA

Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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