Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for but-2-yne-1,4-diol

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8 hour TWA:	0.5 mg/m³
STEL (15 min):	not assigned
Notation:	not assigned
BLV:	not assigned

Substance identification: But-2-yne-1,4-diol:

Synonyms: 1,4-Butynediol; 2-Butyne-1,4-diol; 2-Butynediol; 1,4-Dihydroxy-2-butyne; Bis(hydroxymethyl) acetylene

EC No.: 203-788-6

Annex I Index No.: 603-076-00-9

EU Classification:

Skin Corr. 1B	H314	Causes severe skin burns and eye damage
Acute Tox. 3 *	H331	Toxic if inhaled
Acute Tox. 3 *	H301	Toxic if swallowed
Acute Tox. 4 *	H312	Harmful in contact with skin
STOT RE 2 *	H373 **	May cause damage to organs through prolonged or repeated exposure
Skin Sens. 1	H317	May cause an allergic skin reaction

CAS No.: 110-65-6

MWt: 86.089

Conversion factor (20 °C, 101 kPa): 1 ppm = 3.58 mg/m³; 1 mg/m³ = 0.279 ppm

Structural formula:

HO-CH_2-C≡C-CH_2-OH

This evaluation is based on BG-Chemie (2005), ECB (2000), ECB (2005), Greim (2003), Greim (2006) and the references cited in these reviews.

Physico-chemical properties

But-2-yne-1,4-diol (butynediol) is a yellow scaly solid. The melting point of the substance is 50 - 58 °C and the boiling point is 238 °C. Violent decomposition occurs above 200°C. The vapour pressure, water solubility and log Pow are 0.0017 hPa, 750 g/l, and -0.73, respectively, at 20 °C. Butynediol has a density of 1.05 - 1.17 g/cm³ (Greim, 2006; BG-Chemie, 2005; ECB, 2005).

1. Occurrence/Use and occupational exposure

Butynediol is predominantly used as an intermediate in the synthesis of butanediol and butenediol. In minor amounts, it also serves as an intermediate for other chemicals (e.g. polyols, pharmaceuticals, herbicides, insecticides, flame retardants, plasticisers) and as an additive in galvanisation baths, cleaning agents, disinfectants and corrosion inhibitors (BG-Chemie, 2005; ECB, 2005).

2. Health significance

2.1 Toxicokinetics

2.1.1 Human data

No studies on toxicokinetics in humans are available.

2.1.2 Animal data

No quantitative data on the absorption by inhalation exposure are available.

After oral exposure of rats to 50 mg/kg butynediol, the absorption was at least 80%.

The absorption of butynediol (applied as 0.3 or 30% aqueous solutions) was minimal (<10%), regardless of the concentration of the solution (0.3 or 30%). Using a 30% ethanolic solution for the same procedure, an absorption of 7.5% was reported (RTI, 2002, cited by BG Chemie, 2005). Also the relatively low dermal LD50, as compared to the oral, LD50 (see sectiopn 3.2.2) suggest limited dermal absorption.

Experiments with intravenous injection in rats or mice showed that the half-life in blood is < 30 min. About 60% of the injected dose was excreted in bile (within 4 h in F344 rats or within 24 h in Sprague-Dawley rats) and was reabsorbed in the gut. The predominant metabolites in the bile were 4,4-bis(S-glutathionyl)-2-hydroxytetrahydrofurane and 3-(S-glutathionyl)-2(5H)furanone (RTI, 2002). In rats, butynediol is metabolised to toxic metabolites by hepatic alcohol dehydrogenase. Inhibition of this enzyme by Pyrazole reduced the toxicity after oral gavage (Greim, 2006; BG-Chemie, 2005).

After oral exposure of rats to radiolabelled butynediol, 54% of the administered dose was recovered in urine, 20% in faeces and 5 - 9% exhaled as CO_2. Following dermal exposure, approximately 20% of the absorbed activity was recovered in urine, 9% in faeces, 10% as exhaled CO_2 and 1% as exhaled volatile organics substances by 72 h after administration (RTI, 2002, citde by BG Chemie, 2005).

2.1.3. Biological monitoring

There are no data available. The critical effect of inhalation at workplace exposure of butynediol is irritation. This type of effect cannot be tested by biomonitoring.

2.2. Acute toxicity

2.2.1 Human data

Human data on effects of acute exposure are not available.

2.2.2 Animal data

The inhalation LC_{50} (4 h) was 690 mg/m³ in rats (aqueous solution aerosol). Most oral LD_{50} values in rats were about 100 mg/kg, with a range of 50 - 240 mg/kg. In other species the LD_{50} were similar. The dermal LD_{50} in rats was 424 mg/kg in males and 983 - 1240 mg/kg in females (administration as a paste in NaCl solution) (BG-Chemie, 2005; ECB, 2005). Dermal exposure of the pure compound was less toxic than administration of a 40% aqueous solution (Jedrychowski et al., 1992a). Symptoms at high doses were sedation, apathy, disturbances of balance, convulsions, tremor, accelerated respiration, bradycardia and diarrhoea. At necropsy, the animals revealed congestion of the internal organs, pulmonary oedema and haemorrhages as well as fatty infiltration of the liver (BG-Chemie, 2005; ECB, 2005)

2.3. Irritation

2.3.1 Human data

Human data on irritative effects are not available.

2.3.2 Animal data

Skin
Undiluted butynediol is irritating and corrosive to the skin of rabbits. After 4 h of dermal exposure to pure solid or solid moistened with water, the animals showed severe erythema and oedema within 24 h and exhibited crusts and necrosis within 6 days (Hüls AG, 1985a). Aqueous solutions of up to 20% were not irritating to rabbit skin, higher concentrations (> 30%) produced corrosion and irritation in the majority of the studies (Greim, 2006; BG-Chemie, 2005).

Eyes
Mice showed marked signs of eye irritation after repeated inhalation exposure to concentrations ranging from 90 to 120 mg/m³ (Stasenkova and Kochetkova, 1965a,b) (see section "repeated dose toxicity" for more details). Powdered butynediol is moderately irritating to the rabbit eye and may produce irreversible corneal opacity (Hüls AG, 1985b). Studies with solutions of about 30% produced slight irritation (Greim, 2006; BG-Chemie, 2005).

Respiratory tract
Irritation of the upper respiratory tract was observed in a rat study with repeated inhalation exposure to 5 mg/m³ and above (BASF AG, 1997, 1998). The NOAEC was 0.5 mg/m³. In a mouse inhalation study by Stasenkova and Kochetkova (1965a,b), the animals showed marked signs of irritation in the respiratory tract after exposure to concentrations ranging from 90 to 120 mg/m³ (see section "repeated dose toxicity" for more details).

2.4. Sensitization

2.4.1 Human data

There are several case reports describing contact allergies to butynediol. One woman developed dermatitis after use of a cleaning product, which contained 0.7% butynediol. Patch testing with a 0.01% aqueous solution of this substance gave a positive result (Baadsgard and Jörgensen, 1985). Two workers in the galvanic industry developed an itchy dermatitis. They had contact with butynediol during the handling of galvanisation solutions or cleaning products. Butynediol was identified as causative agent in both cases by patch testing (Blaschke et al., 2001; Malten, 1980). Six workers employed in butynediol

production developed allergic contact eczema, suspected to be evoked by butynediol. They were patch tested with a 0.5% solution of the pure material or a 1% solution of technical grade substance (containing formaldehyde). All of them reacted positively to butynediol, but not to formaldehyde (BASF AG, 2001).

2.4.2 Animal data

There are 2 Magnusson-Kligman tests according to OECD guideline 406. RCC (1990) used a 5% solution of butynediol in saline for intradermal induction and a 25% solution for topical induction. The animals were challenged with a 25% solution. Only 1 of 18 treated animals showed a positive response (RCC, 1990). In a study by Hüls AG (1985c), the intradermal induction was performed with a 0.5% solution in paraffin, the challenge with 25% aqueous solution. Five of 20 treated animals, but none of the control animals reacted positively. Another (insufficiently reported) study showed a negative result after intradermal and epicutaneous induction with 2% and 20% solutions, respectively. The challenge was undertaken with 5 or 25% solutions (Jedrychowski et al., 1992a). In a study by Haskell Laboratory (1966), guinea pigs were intradermally injected with a 10% aqueous solution of the substance, followed by two challenges with the same concentration. Five of 11 animals reacted clearly positively after the first challenge and 6 of 11 animals reacted positively after the second challenge (this study was not performed according to OECD guidelines).

In a ranking of a number of chemicals with respect to contact allergenic properties made by a group of thirty experts, butynediol was put in Category B, corresponding to "Solid-based indication for contact allergenic effects…less frequently proven contact allergenic effect in humans taking into account existing positive animal data" (Schlede et al., 2003).

2.5 Repeated dose toxicity

2.5.1 Human data

Human data on effects of repeated exposure are not available.

2.5.2 Animal data

Inhalation

BASF AG (1997) conducted a range-finding study according to OECD guideline 412. Five Wistar rats per sex and group were exposed by inhalation to 0, 25, 100 and 300 mg/m^3 of liquid aerosols of aqueous butynediol solutions (6 h/d, 5 d). All exposed animals showed an increase of urobilinogen in urine (indicative of liver functional disturbance) and irritation in the upper respiratory tract. These consisted of laryngeal inflammation and metaplasia at 25 mg/m^3 and above. Exposure to 100 mg/m^3 and above resulted in hyperplasia of the larynx and lesions of the nose (inflammation, increased mucus formation and epithelial lesions in the olfactory epithelium). At the highest concentration, increased mortality occurred (one animal of each sex), as well as a slightly reduced body weight gain and clinical signs of toxicity (nasal crusts, accelerated respiration, piloerection and tremor). The urine of these animals was discoloured. There were functional and morphologic alterations of the liver (increased gamma GT, bilirubin and cholesterol serum levels, increased urobilinogen levels in urine as well as necrosis and dystrophy of the liver). Inflammation and/or epithelial changes in the nose and/or the larynx were evident in all animals. The animals that died prematurely showed severe damage of the liver, kidney, thymus, spleen and stomach. The LOAEC of this study is 25 mg/m^3 (no NOAEC).

In a study by BASF AG (1998), performed according to OECD guidelines 412/413, Wistar rats (16 per sex and group), were exposed by inhalation to 0, 0.5, 5 and 25 mg/m^3 of liquid aerosols of aqueous butynediol solutions for 6 h/d, 5 d/w (head-nose exposure). Half of the

animals were exposed for 2 weeks (10 exposures, 15 days), the other half for 4 weeks (20 exposures, 30 days). Systemic toxicity (including neurofunctional alterations on days 0, 8 or 18, and neuropathology) was examined after 10 or 20 exposures. Systemic effects were restricted to an increase in urobilinogen in urine in 2/5 males and 2/5 females at the highest concentration. As there were no accompanying signs of liver function disturbances or lesions, the authors regarded the concentration of 25 mg/m^3 as the NOAEC for systemic toxicity. At 5 mg/m^3 and above there were dose-dependent effects in the upper respiratory tract. Except tracheal inflammation in one female, there were no signs of irritation in the control animals. Minimal to slight focal laryngeal irritation (5 mg/m^3: 1/5 of each sex, only after 20 exposures; 25 mg/m^3: 4/5 males and females after 10 exposures, 2/5 males and females after 20 exposures) and squamous metaplasia in the larynx were observed (5 mg/m^3: 4/5 males and 5/5 females after 10 exposures, 2/5 males and 5/5 females after 20 exposures; 25 mg/m^3: 4/5 males and 5/5 females after 10 exposures, 4/5 males and 5/5 females after 20 exposures). Focal inflammation in the trachea occurred only at 25 mg/m^3 after 20 exposures (2/5 animals of each sex). There was no increase in severity of the lesions at the longer exposure duration. The LOAEC for metaplasia and inflammation of this study is 5 mg/m^3. The NOAEC for respiratory effects is 0.5 mg/m^3.

In a mouse inhalation study by Stasenkova and Kochetkova (1965a,b) the animals (n = 20) were exposed for 1 month to air or a butynediol aerosol at concentrations ranging from 90 to 120 mg/m^3 for 2 h/d on 6 d/w. There were marked signs of irritation of eyes and respiratory tract, a retardation of body weight gain and neurofunctional alterations. Two animals died during the study. This study is not appropriate for risk assessment due to insufficient data presentation.

Oral

In a study by BASF AG (1992) according to OECD guideline 407, Wistar rats were gavaged with nominal doses of 0, 5, 10 and 20 mg kg^{-1} d^{-1} butynediol (dissolved in water) on 5 consecutive days. The only effect seen in this study was a significant increase of cholesterol serum levels in high dose males. There were no alterations in neurofunctional tests (NOAEL 10 mg kg^{-1} d^{-1}).

Komsta et al. (1989) exposed Sprague-Dawley rats to 0, 1, 10 and 100 mg kg^{-1} d^{-1} butynediol (aqueous solution, by gavage) for 14 days. The animals of the highest dose showed clinical signs of toxicity, decreased body weight gain, increased liver weights, alterations in the serum concentrations of hepatic enzymes as well as significant increases of serum cholesterol and calcium. Female animals developed anaemia. No effects were seen in the mid and low dose groups (NOAEL 10 mg kg^{-1} d^{-1}).

In a 4-week study by Jedrychowski (1992b) butynediol was gavaged as an aqueous solution to Wistar rats (8 per sex and group) in daily doses of 0, 1, 10 and 50 mg kg^{-1} d^{-1} for 28 days. At 50 mg kg^{-1} d^{-1}, there was an increased mortality and a decreased body weight gain as well as the occurrence of anaemia and leukocytosis. The liver and kidney weights were increased at this dose, the liver weights also in females of the mid dose group. All animals of the 50 mg kg^{-1} d^{-1} group and some of the mid dose group had histopathological liver lesions. These findings were interpreted by the authors as signs of hepatic hyperplasia, but can also reflect cell degeneration (ECB, 2005). Lesions of the red pulp of the spleen were observed in 3/16 animals exposed to 10 mg kg^{-1} d^{-1} and in 5/10 animals examined in the high dose groups. No effects occurred at the low dose (LOAEL 10 mg kg^{-1} d^{-1}, NOAEL 1 mg kg^{-1} d^{-1}).

In a study by Knyshova (1968), male rats were exposed orally to butynediol at doses of 0, 0.04, 0.2 and 2 mg kg^{-1} d^{-1} for 6 months. Animals of the high dose group showed delayed

conditioned reflexes, reductions in cholinesterase activity, sulfhydryl enzyme activity and liver lesions. Other effects noted at this dose were the reduction of Nissl bodies and an increase of neuroglia content in the brain. Other organs showed hyperaemia. This study is not appropriate for risk assessment since the protocol does not conform to current guidelines and the data presentation is insufficient (Greim, 2006).

Dermal
No studies with repeated dermal exposure are available.

2.6. Mutagenicity

2.6.1. In vitro

Two studies (one with a preincubation protocol) investigating the mutagenic activity in bacteria are available. Butynediol was not mutagenic with and without metabolic activation in the Salmonella strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 (BASF, 1981; NTP, 1998). Negative results were also obtained in two in vitro tests on induction of chromosomal aberrations in V79 hamster cells without metabolic activation. In the presence of metabolic activation there was an equivocal result. Two out of three independent trials detected a slight increase in aberrations at toxic concentrations (CRR, 1989; 1991).

2.6.2. In vivo-human data

Human data on genotoxic effects are not available.

2.6.3. In vivo-animal data

A single intraperitoneal injection of 17.5 - 70 mg/kg did not induce micronuclei in the bone marrow of NMRI mice (RCC, 1998).

2.7. Carcinogenicity

2.7.1. Human data

Human data on carcinogenic effects are not available.

2.7.2. Animal data

No adequate studies on the carcinogenic effects in animals are available. In an older tumour initiation/promotion study with dermal exposure of mice, butynediol did not act as a tumour initiator (the promoter was croton oil). The duration of this experiment was short and the exposure to initiator and promoter was overlapping (Greim, 2006; BG-Chemie, 2005)

2.8. Reproductive toxicity

2.8.1. Human data

Human data on reproductive or developmental effects are not available.

2.8.2. Animal data

Fertility

In a one-generation study by BASF AG (1999) according to OECD guideline 415 and extended according to OECD guideline 416, Wistar rats (25 per sex and group) were exposed orally via drinking water at concentrations of 0, 10, 80 and 500 mg/l (about 1, 7.6 and 40 mg kg^{-1} d^{-1}) prior to mating (at least 76 days), during mating, gestation and lactation (until day 21). Then all F_0 animals and most of the pups were examined. One male and one female F_1 animal per litter were selected and a total of 25 animals of each sex were exposed to the same drinking water concentrations as their parents until sexual maturation and examined thereafter. Significant effects in the F_0 generation were seen at 80 mg/l (7.6 mg kg^{-1} d^{-1}) and above. At this dose, the water intake was reduced and the liver weights (only females) and kidney weights (both sexes) were increased. These effects were more marked at 500 mg/l drinking water, which also led to a retarded body weight gain and reduced adrenal and thymus weights in females. No effects on reproduction parameters or histopathological organ changes were evident (a slight, but significant reduction in sperm motility of F_0 males was within the range of historical control data). The only significant effect in the offspring, examined on postnatal day 21, was a reduced body weight gain in pups of the high dose group on postnatal day 7 and later, and corresponding changes in organ weights (brain, thymus, spleen). The offspring which was reared until sexual maturation remained unaffected at drinking water concentrations up to 80 mg/l. In the high dose group, there was a significant reduction of water uptake (both sexes), reduction of food intake and body weight gain (more marked in males). A slight but significant delay of vaginal opening in females and preputial separation in males at the high dose was attributed to the general retardation of development and not regarded as a specific delay of sexual maturation (ECB, 2005). The LOAEL and NOAEL for F_0 animals based on systemic toxicity is 7.6 mg kg^{-1} d^{-1} and 1 mg kg^{-1} d^{-1}, respectively. The LOAEL and NOAEL for developmental toxicity is 40 mg kg^{-1} d^{-1} and 7.6 mg kg^{-1} d^{-1}, respectively.

Developmental toxicity

Hellwig et al. (1997) examined developmental effects in Wistar rats (18 - 22 per group) after oral exposure to doses of 0, 10, 40 and 80 mg kg^{-1} d^{-1} butynediol on gestation days 6 - 15 (according to OECD guideline 414). At the high dose, there was evidence of maternal toxicity (reduced food intake, loss of body weight, one premature death and one animal with clinical signs of toxicity). The only effects seen in the foetuses were significant increases of the ratio of affected foetuses per litter with accessory 14^{th} rib and dilated renal pelvis and/or hydroureter in the 80 mg kg^{-1} d^{-1} group. Evaluation on the basis of foetal incidence or litter incidence revealed no significant differences. The concurrent controls had an uncommonly low incidence for these endpoints, compared to laboratory historical controls, and the observed effects are within the range of normal biological variation. Therefore the findings are not considered to be a substance-related effect (ECB, 2005). The LOAEL and NOAEL for maternal toxicity, is 80 mg kg^{-1} d^{-1} and 40 mg kg^{-1} d^{-1}, respectively. The NOAEL for developmental toxicity is 80 mg kg^{-1} d^{-1}.

2.9. Methods of exposure monitoring and analysis

For the purpose of measuring butynediol concentration in workplace air a method is used which allows the simultaneous determination of the total dust concentration (glass fibre filter) and of the concentration in the gas phase (activated charcoal). The filter and the activated charcoal are subsequently eluted with methylene chloride/methanol and determined by gas chromatography using a flame ionization detector (GC-FID). The detection limit is 0.035 mg/m3. Due to the measurement method and the sampling strategy applied, the measurement results are regarded as valid (ECB, 2005).

Recommendation

No adequate human data for deriving an OEL are available.

Based on animal data, no systemic effects (including neurotoxicity) are expected to occur at non-irritating concentrations, as there were no clear signs of systemic toxicity even at high concentrations (the only effect at 25 mg/m^3 was increased urobilinogen in urine indicative of hepatic effects, but this was not accompanied by other liver effects). Higher exposure levels in a range-finding study produced marked toxicity in the liver, kidney, thymus, spleen and gastrointestinal tract. Subchronic or chronic animal inhalation studies are not available.

Mutagenicity tests in bacteria and one in vivo test (induction of micronuclei in mice) yielded negative results. The outcomes in mammalian cells in vitro concerning chromosomal aberrations are negative, showing positive results only at cytotoxic concentration. Carcinogenicity studies on butynediol are not available.

Animal inhalation and oral studies support that systemic effects occur only at higher exposures than those causing irritation. Thus, the NOAEL of 1 mg kg^{-1} d^{-1} (Jedrychowski et al., 1992b; BASF AG, 1999) corresponds to daily 8-h inhalation exposures at 7 mg/m^3, assuming a daily inhaled volume of 10 m^3, 100% uptake and a body weight of 70 kg. This concentration is above the LOAEC for irritation of 5 mg/m^3 and more than tenfold higher than the NOAEC of 0.5 mg/m^3 in the BASF (1998) study and the proposed OEL of 0.2 mg/m^3.

Based on animal data, the critical effect of inhalation exposure to butynediol is irritation. The NOAEC of 0.5 mg/m^3 established in the BASF (1998) rat inhalation study is used to derive an OEL. No uncertainty factor is considered necessary taking account of the nature of the effect (irritation) and that other effects are only seen at much higher exposure levels. The proposed 8-h OEL is therefore 0.5 mg/m^3. No data are available to derive a short-term exposure level.

No "skin" notation is recommended, since systemic toxicity is expected only at exposure levels far higher than the recommended 8-h OEL. It should be noted, however, that butynediol is a skin sensitizer and that pure and moistened butynediol as well as concentrated aqueous solutions are corrosive or irritating to the skin.

A method based on sampling of dust on a glass fibre filter and vapour on activated charcoal followed by gas chromatography is available. The method measures the particle and vapour phases separately, the detection limit of 0.035 mg/m^3 being well below the proposed OEL.

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