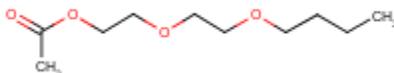


Diethylene Glycol n-Butyl Ether Acetate

(CAS# 124-17-4)

(Synonyms: Butyl carbitol acetate; Butyl diglycol acetate; 2-(2-Butoxyethoxy)ethanol acetate; 2-(2-Butoxyethoxy)ethyl acetate; Acetic acid 2-(2-butoxyethoxy)ethyl ester; Butoxyethoxyethyl acetate; Butyl carbitol acetate; Butyl diethylene glycol acetate; Diethyleneglycol monobutyl ether acetate; Diglycol monobutyl ether acetate; Ektasolve DB acetate; Glycol ether DB acetate; Ethanol, 2-(2-butoxyethoxy)-, 1-acetate; Ethanol, 2-(2-butoxyethoxy)-, acetate; DGBA)



Diethylene Glycol n-Butyl Ether Acetate Acute REL

<i>Reference Exposure Level</i>	44.8 mg/m³ (5.4 ppm) [Inhalation]
<i>Critical effects</i>	Hyperemia, grooming inactivity
<i>Hazard Index target</i>	Circulatory system

Diethylene Glycol n-Butyl Ether Acetate 8-hour REL

<i>Reference Exposure Level</i>	2.82 mg/m³ (0.34 ppm) [based on oral study]
<i>Critical effects</i>	Increased liver weight
<i>Hazard Index target</i>	Liver

1 Physical and Chemical Properties

<i>Physical form</i>	clear, colorless liquid
<i>Structural formula</i>	C ₄ H ₉ -(O-CH ₂ -CH ₂) ₂ -O-CO-CH ₃
<i>Molecular weight</i>	204.3 g/mole
<i>Density</i>	0.985 g/cm ³ @ 20 °C
<i>Boiling point</i>	245 °C
<i>Melting point</i>	-32 °C
<i>Vapor pressure</i>	0.04 mm Hg @ 20 °C
<i>Flash point</i>	116 °C (open cup)
<i>Log K_{ow}</i>	1.30
<i>Water solubility</i>	65,000 mg/L
<i>Atmospheric half-life</i>	11 hours
<i>Conversion factor</i>	1 ppm = 8.34 mg/m ³ ; 1 mg/L = 120 ppm

2 Production, Use, and Exposure

Diethylene glycol n-butyl ether acetate (DGBA) is manufactured by reacting diethylene glycol monobutyl ether (DGBE) with acetic anhydride. DGBE is manufactured by reacting n-butyl alcohol with ethylene oxide. Both chemicals are produced in enclosed processes with all waste streams recycled, therefore emissions to wastewater and air are minimal although small amounts

may be released from spills and cleaning operations (Federal Register, 1984). DGBA can also enter the atmospheric, aqueous or terrestrial environment from its various end uses.

DGBA is used as a solvent and carrier in inks and industrial coatings, as a coalescing agent in consumer latex paint at concentrations of 0.5 to 3 percent by weight, and also as a solvent in the manufacture of microelectronics. Although DGBA has low vapor pressure, releases of glycol ethers from painted walls in consumers' homes are estimated to result in concentrations in indoor air in the range of 1 to 5 parts per million. The doses received from consumers exposed to these levels are estimated to be 1 to 10 mg/kg-d (Federal Register, 1984). In a study of 29 samples of printer's inks from different European manufacturers, one sample used for printing on paper and paper boards was found to contain 9.9% w/w DGBA (Rastogi, 1991).

Gingell et al. (1993) determined the exposure levels to DGBA by inhalation of DGBA-containing paints. A time-weighted average concentration of between 0.03 ppm and 0.05 ppm was seen from personal monitors and a maximal room air DGBA concentration of 0.15 ppm was seen 8-20 hours after the start of painting. The calculated dose of DGBA received during painting was 0.011 mg/kg-d for household consumers and 0.19 mg/kg-d for professionals.

3 Pharmacokinetics and Metabolism

Deisinger and Guest (1989) studied the in vitro hydrolysis of DGBA in rat blood and the in vivo metabolism and disposition of DGBA in male Sprague-Dawley rats. DGBA was hydrolyzed in rat blood to DGBE with a half-life of < 3 minutes. When ¹⁴C-DGBA was orally administered to rats at doses of 200 or 2000 mg/kg, it was rapidly absorbed from the gastrointestinal tract and was eliminated predominantly in the urine after 24 hours. The major urinary metabolite was 2-(2-butoxyethoxy)acetic acid (BEA), while unchanged DGBA and DGBE were not detected in the urine at either dose level. Furthermore, there was no evidence of the excretion of 2-butoxyacetic acid, which has been shown to exert hematological effects in rats.

Boatman et al. (1993, abstract only) exposed Sprague-Dawley rats to radiolabeled DGBA for 24 hours using dermal absorption cells. The total recovered radioactivity from exposed animals ranged from 79.90% to 88.41%, with the primary metabolite identified as BEA, which accounted for 61% and 80% of the total urinary radioactivity. Significantly higher levels of BEA were found in urine from females than from males and trace levels of 2-butoxyacetic acid were found in all samples. In some samples, up to 1.5% of the total radioactivity was contained in a component identified as DGBE.

U.S. EPA (2006) reported a pharmacokinetic study in which rats (strain not specified, 4/sex) underwent a 24-hr dermal exposure to 200 or 2000 mg/kg radiolabeled neat DGBA or to 200 mg/kg DGBA as a 10% w/v aqueous solution. Low dose applications of neat or 10% aqueous solutions were more completely absorbed than the high dose. The high-dose absorption rates were 0.73 mg/cm²/hour in males and 1.46 mg/cm²/hour in females. The primary route of elimination was via urine; the urinary metabolite 2-(2-butoxyethoxy)acetic acid accounted for more than half of the radioactivity. In a study cited by HSDB, the mean permeability constant for DGBA in male Sprague-Dawley rats was 1.38 x 10⁻³ cm/h and the mean absorption rate was 1.36 mg/cm/hr. The authors of the cited study extrapolated the data to human exposure and

concluded that immersion of both hands (740 cm² surface area) of a 70 kg human in DGBA would result in the absorption of 14.4 mg/kg.

4 Acute Toxicity

Toxicity data for DGBA are summarized in the table below, adapted from Draize, et al. (1948).

	Acute Oral	Dermal Toxicity			
Species	Est. LD₅₀	Acute Est. LD₅₀	90-Day LD₅₀	Local Skin Rxn	Pathology
Rabbit	2.8 ml/kg	5.5 ml/kg	2.0 ml/kg	No gross skin irritation	Hematuria; hemolysis in kidneys; renal tubular degenerative changes; inanition. In survivors, slight residual kidney lesions; inconsistently other changes. Dermatitis ±; +.
Guinea pig	2.7 ml/kg				
Rat	7.1 ml/kg				
Mouse	6.6 ml/kg				
Chicken	5.0 ml/kg				

Non-human toxicity values reported by HSDB are as follows:

Species and Route	LD₅₀ or LC₅₀	Species and Route	LD₅₀ or LC₅₀
Rabbit – dermal	14.8 ml/kg	Guinea pig – oral	2340 mg/kg
Rabbit – dermal	5500 mg/kg	Rat – oral	6500 mg/kg
Rabbit – dermal	14,500 mg/kg	Rat – oral	11920 mg/kg
Rabbit – oral	2800 mg/kg	Rat – inhalation	8692.75 ppm
Rabbit – oral	2260 mg/kg	Mouse – oral	6500 mg/kg
Rabbit – oral	2600 mg/kg	Mouse – oral	6600 mg/kg

Cannon Laboratories, Inc. (1976) evaluated acute inhalation toxicity in Sprague-Dawley rats. Groups of 10 male rats were exposed to DGBA at average analytical concentrations of 6780.35, 8233.53, 8666.37, or 9420.54 ppm for 4 hours. Mortality was observed in 3 animals in the 8233.53 ppm dose group, 5 in the 8666.37 ppm dose group, and all 10 animals in the highest dose group. The LC₅₀ was calculated to be 8692.75 ppm. While this study was designed to be a mortality study, a number of clinical observations indicate respiratory toxicity and possibly neurotoxicity associated with the exposures. Clinical observations included face-pawing, grooming inactivity, mild hyperemia, shallow respiration, wet fur, and closed eyes. Red foci and congestion in the lungs were observed at necropsy (Cannon Laboratories, 1976).

Draize et al. (1948) determined that DGBA and an insect repellent (Sta-Way) containing 50% DGBA, 15% diethylene glycol monoethyl ether, 28% ethanol, and 7% corn oil were unsafe for human use. In a case report cited by HSDB, a 3-year-old child developed nephrosis from use of the Sta-Way insect repellent.

5.1 Derivation of Acute REL (1-hour exposure)

<i>Study</i>	Cannon Laboratories, Inc. (1976)
<i>Study population</i>	Sprague-Dawley rats
<i>Exposure method</i>	Whole-body inhalation
<i>Exposure continuity</i>	Once
<i>Exposure duration</i>	4 hours
<i>Critical effects</i>	Hyperemia, grooming inactivity
<i>LOAEL</i>	56,545 mg/m ³ (6780 ppm)
<i>NOAEL</i>	Not observed
<i>Time-adjusted exposure</i>	$C^n * T = K$, $n = 3$ (ten Berge et al., 1986)
<i>Extrapolated concentration</i>	89,718 mg/m ³ (56545 ³ * 4/1) ^{1/3}
<i>Human concentration adjustment</i>	89718 mg/m ³ (RGDR = 1, systemic)
<i>LOAEL uncertainty factor (UF_L)</i>	10
<i>Subchronic uncertainty factor</i>	1 (not applicable for an acute REL)
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	2
<i>Toxicodynamic (UF_{A-d})</i>	√10
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	10
<i>Toxicodynamic (UF_{H-d})</i>	√10
<i>Cumulative uncertainty factor</i>	2000
<i>Acute Reference Exposure Level</i>	44.8 mg/m³ (5.4 ppm)
RGDR: regional gas dose ratio	

An acute REL is derived from the study by Cannon Laboratories, Inc. (1976) in which groups of 10 male Sprague-Dawley rats were exposed to DGBA at average analytical concentrations of 6780.35, 8233.53, 8666.37, or 9420.54 ppm for 4 hours. Mortality was observed in 3 animals in the 8233.53 ppm dose group, 5 in the 8666.37 ppm dose group, and all 10 animals in the highest dose group. The LC₅₀ was calculated to be 8692.75 ppm. Clinical observations included face-pawing, grooming inactivity, and mild hyperemia at the lowest dose, with the addition of shallow respiration, wet fur, and closed eyes at the higher doses. While the observed behavioral changes (nose pawing and grooming cessation) are not definitive indications of neurotoxicity, they are suggestive of extra-respiratory effects. Red foci and congestion in the lungs were observed in animals from the highest dose at necropsy (Cannon Laboratories, 1976). Based on the clinical signs of toxicity, the LOAEL is determined to be 6780 ppm and the NOAEL is not observed. A value of $n = 3$ is used in extrapolating from an experimental exposure duration of greater than one hour to one hour. A LOAEL uncertainty factor of 10 is applied to extrapolate from the LOAEL to the NOAEL. The interspecies uncertainty factor is adjusted to 6 ($2 * \sqrt{10}$) because the U.S. EPA Human Equivalent Concentration procedure is used as a partial adjustment for interspecies toxicokinetic differences. A regional gas dose ratio (RGDR) of 1 is used for gases with systemic effects, following U.S. EPA's recommendation that an RGDR of 1 be used when the relevant blood:air coefficients are unknown. For the intraspecies toxicokinetic uncertainty sub-factor, a value of 10 is used in consideration of the protection of children's health and

sensitive subgroups. Default values of $\sqrt{10}$ are used for the interspecies and intraspecies toxicodynamic uncertainty sub-factors in the absence of data to indicate otherwise.

5.2 Derivation of 8-Hour REL (NOAEL Method)

An 8-hour REL is developed for diethylene glycol monobutyl ether (DGBE) based on a thirteen-week oral toxicity study by Johnson et al. (2005). DGBE is serving as a surrogate for DGBA, assuming that the effects of DGBA will be similar to those of DGBE due to the rapid hydrolysis of DGBA to DGBE (Deisinger and Guest 1989). Groups of 10 male and 10 female Fischer 344 rats were given doses of 0, 50, 250, or 1000 mg DGBE/kg-d in drinking water for 13 weeks. All rats survived the respective exposures. Rats receiving 1000 mg/kg-d had statistically significant increased relative liver weight (7-10%) compared to controls and increased activity of hepatic cytochrome P450s (24-39%) relative to controls. Only female rats receiving 1000 mg/kg-d displayed very slight hepatocyte hypertrophy and increased individual hepatocyte degeneration. There were slight, but statistically significant decrements in red blood cell parameters at the 250 mg/kg-d dose ($\alpha = 0.05$), which the authors considered to be a NOAEL since all the values were within the historical control range. However, the data were amenable to a benchmark dose analysis (BMD). Therefore, the data from Johnson et al. (2005) is modeled with the Benchmark Dose Software, using a continuous linear model, to derive an 8-hour REL (below) based on the BMDL rather than the NOAEL.

Derivation of 8-Hour REL (BMC Method)

<i>Study</i>	Johnson et al. (2005)
<i>Study population</i>	Fischer 344 rats
<i>Exposure method</i>	Oral – drinking water
<i>Exposure continuity</i>	Daily, continuous
<i>Exposure duration</i>	13 weeks
<i>Critical effects</i>	Increased liver weight
<i>LOAEL</i>	1000 mg/kg-d
<i>NOAEL</i>	250 mg/kg-d
<i>Benchmark Dose(BMDL₀₅)</i>	403 mg/kg-d
<i>LOAEL uncertainty factor (UF_L)</i>	1 (NOAEL observed)
<i>Subchronic uncertainty factor</i>	$\sqrt{10}$
<i>Interspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	$\sqrt{10}$
<i>Toxicodynamic (UF_{A-d})</i>	$\sqrt{10}$
<i>Intraspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	10
<i>Toxicodynamic (UF_{H-d})</i>	$\sqrt{10}$
<i>Cumulative uncertainty factor</i>	1000
<i>Oral dose</i>	0.403 mg/kg-d (403 mg/kg-d/1000)
<i>Route-to-route extrapolation factor</i>	70 kg/20 m ³ /d
<i>Chronic to 8-hour adjustment</i>	(20 m ³ /d)/(10 m ³ /d)
<i>8-hour Reference Exposure Level</i>	2.82 mg/m³ (0.403 mg/kg-d*3.5 kg/m ³ d*2)

A subchronic uncertainty factor of $\sqrt{10}$ is used by default when the study duration is 8-12% of the animal's estimated lifetime. Default values of $\sqrt{10}$ are used for interspecies toxicokinetic and toxicodynamic variability and for intraspecies toxicodynamic variability. For the intraspecies toxicokinetic uncertainty sub-factor, a value of 10 is used in consideration of the protection of children's health and sensitive subgroups. In converting the oral dose to an air concentration, it is assumed that the efficiency of DGBE absorption is the same between an oral dose and inhalation. The route-to-route conversion factor assumes that a 70 kg adult male breathes 20 m³ air/d. The chronic to 8-hour adjustment applied here is based on the assumption that half of the 20 m³ of air breathed in any 24-hour period is breathed while active at work. The resultant REL is therefore the oral dose multiplied by the route-to-route extrapolation factor and by the chronic to 8-hour adjustment.

6 Other Toxicity

Due to the rapid conversion of DGBA to DGBE, other toxicity endpoints, such as reproductive and developmental toxicity of DGBA, are likely to be similar to DGBE. One case of acute diffuse erythematous dermatitis was reported as a result of contact with DGBA, which was resolved when the patient was advised to avoid contact with DGBA (Dawson et al. 1989).

7 Environmental Fate

If released into the air, vapor-phase DGBA will be degraded in the atmosphere by photodegradation (reaction with hydroxyl radicals). The estimated half-life is 11 hours. In the soil, DGBA is expected to have very high mobility based on an estimated K_{OC} of 10. The Henry's Law constant of 3.5×10^{-7} atm-m³/mole suggests that volatilization from moist soil surfaces is not expected to be an important fate process. Based on biodegradation studies, DGBA is expected to biodegrade quickly in soil and water. An estimated bioconcentration factor of 2 suggests the potential for bioconcentration in aquatic organisms is low. DGBA will hydrolyze with estimated half-lives of 30 days at pH 8 and 305 days at pH 7 (HSDB).

8 References

Boatman RJ, Schum DB, Guest D and Stack CR (1993). Toxicology of diethylene glycol butyl ether. 2. Disposition studies with ¹⁴C-diethylene glycol butyl ether and ¹⁴C-diethylene glycol butyl ether acetate after dermal application to rats. J Am Coll Toxicol 12: 145-154. Abstract only.

Cannon Laboratories, Inc. (1976). Acute inhalation toxicity of 2-(2-butoxyethoxy)-ethyl acetate (butyl 'carbitol' acetate). EPA/OTS Doc # 878221476.

Dawson TAJ, Black RJ, Strang WC, Millership JS and Davies, IA (1989). Delayed and immediate hypersensitivity to carbitols. Contact Dermatitis 21: 52.

Deisinger PJ and Guest D. (1989). Metabolic studies with diethylene glycol monobutyl ether acetate (DGBA) in the rat. Xenobiotica 19: 981-989.

Draft Interim REL March 2010

Draize JH, Alvarez E, Whitesell MF, Woodard G, Hagan EC and Nelson AA (1948). Toxicological investigations of compounds proposed for use as insect repellents. *J Pharmacol Exp Ther* 93: 26-39.

Federal Register (1984). 2-(2-Butoxyethoxy) ethyl acetate: response to the interagency testing committee. 49(224): 45606-45610.

Gingell R, Krasavage WJ, Wise RC, Knaak JB, Bus J, Gibson WB and Stack CR (1993). Toxicology of diethylene glycol butyl ether. 1. Exposure and risk assessment. *J Am Coll Toxicol* 12: 139-144.

Hazardous Substances Data Bank (HSDB). HSDB number 334. Diethylene glycol monobutyl ether acetate. National Library of Medicine (NLM), Washington, DC. Last updated 10/11/2007.

Johnson KA, Baker PC, Kan HL, Maurissen JP, Spencer PJ and Marty MS (2005). Diethylene glycol monobutyl ether (DGBE): two- and thirteen-week oral toxicity studies in Fischer 344 rats. *Food Chem Toxicol* 43: 467-481.

Rastogi SC (1991). Levels of organic solvents in printer's inks. *Arch Environ Contam Toxicol* 20: 543-547.

ten Berge WF, Zwart A and Appelman LM (1986). Concentration-time mortality response relationship of irritant and systematically acting vapours and gases. *J Hazard Mater* 13: 301-309.

U.S. EPA (2006). Table G039. Diethylene Glycol Butyl Ether/Acetate. Results of Testing. EPA/OTS Doc # 0533107.

Benchmark Dose Model Run Output



Linear Model Males
Liver Wt.pdf