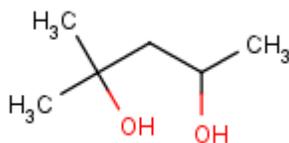


Hexylene Glycol

(CAS# 107-41-5)

(Synonyms: 2,4-Pentanediol, 2-methyl-; 2-Methyl-2,4-pentanediol; (+-)-2-Methyl-2,4-pentanediol; 1,1,3-Trimethyltrimethylenediol; 2,4-Dihydroxy-2-methylpentane; 2-Methylpentane-2,4-diol; 4-Methyl-2,4-pentanediol; 1,1,3-trimethyl trimethylene glycol; 1,1,3-trimethyl trimethylenediol; trimethyltrimethylene glycol; Diolane; Isol; Pinakon; HexG)



Hexylene Glycol Acute REL

<i>Reference Exposure Level</i>	3 mg/m³ (600 ppb) [Inhalation]
<i>Critical effects</i>	Ocular irritation
<i>Hazard Index target</i>	Eyes

Hexylene Glycol 8-hour REL

<i>Reference Exposure Level</i>	0.28 mg/m³ (58 ppb) [Inhalation]
<i>Critical effects</i>	Increased organ weights
<i>Hazard Index target</i>	Liver and kidney

1 Physical and Chemical Properties

<i>Physical form</i>	clear, colorless liquid at room temperature
<i>Structural formula</i>	CH ₃ -CHOH-CH ₂ -C-(OH)(CH ₃) ₂
<i>Molecular weight</i>	118.18 g/mole
<i>Density</i>	0.923 g/cm ³ @ 20 °C
<i>Boiling point</i>	198 °C
<i>Melting point</i>	-50 °C
<i>Vapor pressure</i>	0.013 mm Hg @ 25 °C
<i>Flash point</i>	93 °C
<i>Log K_{ow}</i>	0.580
<i>Water solubility</i>	fully miscible
<i>Atmospheric half-life</i>	9 hrs
<i>Conversion factor</i>	1 ppm = 4.83 mg/m ³

2 Production, Use, and Exposure

Hexylene glycol is formed from the achiral reagents, diacetone alcohol and hydrogen, producing equal amounts of enantiomeric products. Commercial hexylene glycol, as covered by CAS# 107-41-5, contains > 99% 2-methyl-2,4-pentanediol and is described as a racemic mixture containing equal amounts of two enantiomers.

The largest end use for hexylene glycol is in industrial coatings, as a solvent plasticizer in varnishes, lacquers, paints, and also in paint strippers, accounting for about 45% of the total production. Hexylene glycol is also used as a chemical intermediate in chemical syntheses, down hole lubricant for natural gas and oil fields, hydraulic fluid, antifreeze, fuel additive, solvent in dyes and inks, in leather and textile processing, in industrial and household cleaners, and in cosmetics (HSDB; OECD, 2001).

With normal manufacturing practices, emissions to wastewater and air are minimal although small amounts may be released from spills and cleaning operations. Hexylene glycol can also enter the atmospheric, aqueous or terrestrial environment from its various end uses. The primary occupational exposures to hexylene glycol occur via skin contact during manufacturing, or by inhalation or dermal contact during industrial spraying of products containing hexylene glycol. Hexylene glycol is a skin and eye irritant. The American Conference of Governmental Industrial Hygienists (ACGIH) set a Threshold Limit Value (TLV) of 25 ppm for hexylene glycol to avoid eye irritation, which has been reported in volunteer studies at 50 ppm in addition to nasal irritation and respiratory discomfort at 100 and 1000 ppm (OECD 2001). The ceiling concentration set by the National Institute for Occupational Safety and Health is also 25 ppm (RTECS). Consumer exposure occurs mostly from the use of cosmetics, cleaning products, antifreezes, and hydraulic fluids containing hexylene glycol. Exposure of the general population may occur through the ingestion of surface water contaminated with hexylene glycol (OECD, 2001). Hexylene glycol has been detected from apples undergoing the ripening process, thereby providing another source of exposure by ingestion or inhalation (Mattheis et al. 1991).

3 Pharmacokinetics and Metabolism

The predominant mechanism for the metabolism of hexylene glycol appears to be conjugation of the parent compound or its intermediate metabolite with glucuronide, followed by excretion in the urine. Jacobsen et al. (1958, as cited in OECD, 2001) administered single and repeated daily oral doses of 1-5 g hexylene glycol as a 10% aqueous solution to five human male volunteers and found about 20-35% of the ingested dose excreted in urine, half of which was conjugated. Only urinary excretion was investigated and found to continue for 5-10 days after the cessation of exposure.

Gessner et al. (1960) administered 1 mmol/kg hexylene glycol to 3 chinchilla rabbits by stomach tube with water. Urine collected from the animals for 1-2 days after dosing showed 67% (range 49-93%) of the dose excreted as glucuronate conjugates. Larsen et al. (1958, as cited in OECD, 2001) studied the excretion of free and bound hexylene glycol in the 24-hr pooled urine of groups of 6 male rats following acute and repeated exposures. The rats were administered milk containing nominal concentrations of 100 mg/kg-d for 62-98 days or 200 mg/kg-d for 60-131 days. The high dose of 400 mg/kg was administered as a single dose in aqueous solution by stomach tube. At 100 mg/kg-d, 51% was excreted in urine, of which 7% was in the form of free

glycol. At 200 mg/kg-d, 40% of the dose was excreted in urine, of which 4% was in the form of free glycol. Forty-nine percent of the 400 mg/kg dose was excreted in urine, with 14% in the form of free glycol. Furthermore, the urine from rabbits fed ¹⁴C-hexylene glycol contained 7 metabolites, including glucuronide of hexylene glycol (46% of dose), unchanged hexylene glycol (2.5%), diacetone alcohol (1.4%) and an unidentified glucuronide (HSDB). Mice fed 20 mg/day hexylene glycol in 2 ml of whole milk for up to 81 days excreted approximately 40% of the dose in the urine, 4% of which consisted of free glycol while 36% were conjugated with glucuronic acid (HSDB).

4 Acute Toxicity

Acute mammalian toxicity is summarized as follows:

Species/Route	LD ₅₀ or LC ₅₀	Reference
Rat – inhalation	> 310 mg/m ³ /1 hour	RTECS
Rat – oral	> 2.0 g/kg	Gardner (1996a) in OECD (2001)
Rat – oral	4.47 g/kg	Industrial Biotest (1970) et al. in OECD (2001)
Rat – oral	4.70 g/kg	Smyth & Carpenter (1948) in OECD (2001)
Rat – oral	3.70 g/kg	RTECS
Rat – oral	4.76 g/kg	Union Carbide (1949) in OECD (2001)
Rat – oral	4.0 ml/kg (3.68 g/kg)	Woodard et al. (1945) in OECD (2001)
Mouse – oral	4.5 ml/kg (4.14 g/kg)	
Rabbit – oral	3.2 ml/kg (2.94 g/kg)	
Guinea pig – oral	2.8 ml/kg (2.6 g/kg)	
Mouse – oral	3.8 ml/kg (3.5 g/kg)	SCC (1958) and Anderson & McOmie (1946) in OECD (2001)
Mouse – oral	3.097 g/kg	RTECS
Mouse – oral	3.90 g/kg	CIR (1985) in OECD (2001)
Mouse – oral	3.5 g/kg	HSDB
Rat – dermal	> 2 g/kg	Gardner (1996b) in OECD (2001)
Rabbit – dermal	> 5 g/kg	Opdyke (1978) in OECD (2001)
Rabbit – dermal	> 1.84 g/kg	SCC (1958) in OECD (2001)
Rabbit – dermal	13.3 ml/kg (12.3 g/kg)	Smyth & Carpenter (1948) in OECD (2001)
Rabbit – dermal	> 9.4 ml/kg (8.068 g/kg)	Anderson & McOmie (1946) in OECD (2001)
Rabbit – dermal	8.56 ml/kg (7.90 g/kg)	BIBRA (1991) in OECD (2001)

Table adapted from OECD (2001) with additions.

In addition to the animal toxicity data summarized above, there have been documented cases of coma associated with the use of hexylene glycol-impregnated dressings in burn patients. Procter (1966) first reported the occurrence of unexplained coma and subsequent death of children who were being treated for burns. Further investigation found that 15 deaths occurred, all in patients

whose burns covered from 10% to greater than 20% of their bodies and were dressed with hexylene glycol (80%)-impregnated dressings. All the fatal cases of coma had renal failure or obvious renal impairment. In other non-fatal cases of coma, the author observed that patients recovered from the coma after removal of the dressings and coma recurred when the dressings were replaced. Use of the dressings was discontinued and in the following 7 months, there were no cases of coma and only 1 death from 151 burns admissions. Procter (1966) also notes that during 1964 and 1965, 8 cases of unexplained coma were reported in adults whose burns were dressed with the same dressing. All had large burned areas and 3 died, while 3 recovered after removal of the dressing and 2 recovered spontaneously. Fisher et al. (1968) reported a case of an adult male burn patient whose split-skin donor and graft sites were covered with the same dressing, who suffered progressive delirium and ataxia, deepening into coma, associated with bradycardia, hypotension and hypothermia. Deterioration continued for 30 hours and the dressings were removed as a measure of desperation when death appeared imminent. The patient responded to his name within 2 hours and reached full recovery within 12 hours with no recurrence of coma throughout his subsequent stay in the hospital. The calculated potential dose of hexylene glycol that a 15 kg individual with a body surface area of 0.64 m² and 25% burns could receive was 2-7 g/kg, depending on how many layers of dressing were applied. In an investigation to identify the toxic ingredient in the dressings, Fisher et al. (1968) administered intraperitoneal injections of 4 g/kg of each of the 4 ingredients in the dressing (beeswax, iso-propyl myristate, synthawax, and hexylene glycol) to mice. No effects were observed for beeswax, iso-propyl myristate, or synthawax, but hexylene glycol induced coma within 30 seconds and resulted in death within 24 hours. The authors therefore concluded that the outbreak of unexplained coma in burn patients was probably due to hexylene glycol, the main constituent of the dressings applied to the affected patients.

5 Derivation of Acute REL (1-hour exposure)

<i>Study</i>	Toxicodynamic (UF_{H-d})	Silverman et al. (1946)
<i>Study population</i>	Uncertainty factor	Unspecified number of human volunteers
<i>Exposure Reference</i>	Exposure Level	1200 mg/m ³ gas cabinet
<i>Exposure continuity</i>		Not available
<i>Exposure duration</i>		15 minutes
<i>Critical effects</i>		Subjective ocular irritation
<i>LOAEL</i>		241.5 mg/m ³ (50 ppm)
<i>NOAEL</i>		Not observed
<i>Time-adjusted exposure</i>		$C^n * T = K$, $n = 1$ (ten Berge et al., 1986)
<i>Extrapolated concentration</i>		60.4 mg/m ³ (241.5 * 15/60)
<i>Human concentration adjustment</i>		Not applicable
<i>LOAEL uncertainty factor (UF_L)</i>		6
<i>Subchronic uncertainty factor</i>		1 (Not applicable to an acute REL)
<i>Interspecies uncertainty factor</i>		
<i>Toxicokinetic (UF_{A-k})</i>		1 (default: human study)
<i>Toxicodynamic (UF_{A-d})</i>		1 (default: human study)
<i>Intraspecies uncertainty factor</i>		
<i>Toxicokinetic (UF_{H-k})</i>		1 (site of contact; no systemic effects)

An acute REL was calculated as shown above based on a study by Silverman et al. (1946), in which human volunteers were exposed to hexylene glycol vapor for 15 minutes. The age, sex, and health status of the volunteers were not provided in this citation. At a concentration of 50 ppm (the approximated saturation concentration at 25 °C), the majority of the subjects reported slight irritation to the eyes. At unspecified concentrations > 50 ppm, irritation effects included the nose and throat. There was no independent clinical assessment of the reported effects. Since a NOAEL was not determined in this study and the effect of the exposure was mild, a LOAEL uncertainty factor of 6 is applied. A value of $n = 1$ is used in extrapolating from an experimental exposure duration of less than 1 hour to a 1-hour level. A default value of $\sqrt{10}$ is used for the intraspecies toxicodynamic uncertainty sub-factor in the absence of data to indicate otherwise.

6 Derivation of 8-Hour REL

<i>Study</i>	Union Carbide Corporation 1976
<i>Study population</i>	Harlan-Wistar derived rats
<i>Exposure method</i>	Inhalation of 0.7 g/L (140 ppm) aerosol
<i>Exposure continuity</i>	7 hrs/day, 9 days
<i>Exposure duration</i>	2 weeks
<i>Critical effects</i>	Lesions of the respiratory epithelium
<i>LOAEL</i>	676.2 mg/m ³ (140 ppm)
<i>NOAEL</i>	Not observed
<i>Time-adjusted exposure</i>	$C^n * T = K$, $n = 1$ (ten Berge et al., 1986)
<i>Extrapolated concentration</i>	422.6 mg/m ³ (676.2 * 7/8 * 5/7)
<i>Human concentration adjustment</i>	1690 mg/m ³ (422.6 * 4 (RGDR, respiratory))
<i>LOAEL uncertainty factor (UF_L)</i>	10
<i>Subchronic uncertainty factor</i>	10
<i>Interspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	2
<i>Toxicodynamic (UF_{A-d})</i>	$\sqrt{10}$
<i>Intraspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10
<i>Cumulative uncertainty factor</i>	6000
<i>8-hour Reference Exposure Level</i>	0.28 mg/m³

RGDR: regional gas dose ratio

This draft 8-hour REL is derived from a study by Union Carbide Corporation (1976, cited in OECD, 2001), in which a group of 10 male and female Harlan-Wistar rats were exposed to an aerosol atmosphere of 676.2 mg/m³ (140 ppm) hexylene glycol for 7 hrs/day for a total of 9 exposures over a period of 2 weeks. Tissues collected at necropsy included the lung, trachea, heart, liver, kidneys, spleen, adrenals, thyroid, parathyroid, esophagus, bronchi, thymus glands,

and cervical lymph nodes. No overt signs of toxicity, effects on body weight gain, or absolute or relative liver or kidney weights were observed. There were no microscopic lesions in the major organs. Upon histological examination, two rats demonstrated tracheal congestion and 1 had submucosal hemorrhage. In the absence of more detailed inhalation toxicity studies, the single dose at which the respiratory lesions were observed is taken to be the LOAEL, bearing in mind that additional experimentation might find a considerably lower concentration than this value where adverse effects still occur. Since a NOAEL was not determined in this study, a LOAEL uncertainty factor of 10 is applied. A value of $n = 1$ is used in extrapolating from an experimental exposure duration of less than 8 hours to an 8-hour level. A regional gas dose ratio (RGDR) of 4 is used for gases with respiratory effects, accounting for differences between human and rat in minute volume (MV) and tracheobronchial surface area (SA). The RGDR calculation, using the equation $(MV_A/MV_H)/(SA_A/SA_H)$, is as follows: $(0.214/7.5)/(22.5/3200) = 4$. Minute volumes and surface areas are as published by Brown et al. (2005) and U.S. EPA (1994), respectively. To account for the possibility of long-term repeated occupational exposures, a subchronic uncertainty factor of 10 is applied since the experimental exposure was < 8% of the expected lifetime of the species tested. 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 default value of $\sqrt{10}$ is used for the interspecies toxicodynamic uncertainty sub-factor in the absence of data to indicate otherwise while a value of 10 is applied for the intraspecies toxicodynamic uncertainty sub-factor due to the potential for asthma exacerbation.

7 Other Toxicity

Human Repeated Dose Toxicity

Jacobson (1958, cited in OECD, 2001) administered oral doses of 37 g hexylene glycol daily to 5 human volunteers for 24 days (estimated daily dosage 14-28 mg/kg body weight) and found no subjective symptoms that could be attributed to the intake of hexylene glycol. No alterations in urine parameters were detected in this study.

Reproductive and Developmental Toxicity

In a 90-day oral gavage study in Sprague-Dawley rats receiving daily doses of 0, 50, 150, or 450 mg/kg-d hexylene glycol, no microscopic effects were observed on the reproductive organs examined, which included the testes, prostate, seminal vesicles, epididymes, ovaries, vagina, and uterus (Fabreguettes, 1999, unpublished report cited in OECD, 2001).

8 Environmental Fate

The EPIWIN/APO model (U.S. EPA) estimates that the atmospheric photodegradation (reaction with hydroxyl radicals) half-life of hexylene glycol is 9 hours, based on 12 hours of sunlight/day. Glycols have no hydrolysable groups and are generally not susceptible to hydrolysis in water under neutral conditions at ambient temperatures. The estimated Henry's Law Constant of 2.94×10^{-8} atm-m³/mole for hexylene glycol indicates it has limited potential to partition from water to air. The environmental distribution of hexylene glycol, as predicted by Mackay Level I fugacity modeling, is 0.169% in air, 99.5% in water, 0.335% in soil, and 0.0074% in sediment. Although there are insufficient experimental data to determine whether hexylene glycol is readily

biodegradable, it is considered at least inherently biodegradable. With a predicted bioconcentration factor of 3.162 and Log K_{OW} of 0.58, hexylene glycol is not expected to bioaccumulate. Hexylene glycol is therefore unlikely to persist in the environment (OECD, 2001).

9 References

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Benchmark Dose Model Run Output:



Log-Logistic Model
Occipital.pdf