Excerpt: "TOXICOLOGICAL PROFILE FOR ETHYLENE GLYCOL"

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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2.2 SUMMARY OF HEALTH EFFECTS

Ethylene glycol is quickly and extensively absorbed through the gastrointestinal tract of many species, but dermal absorption is slow in rodents and is expected to be slow in humans. Limited information is available on absorption of inhaled ethylene glycol, but the existing toxicity studies suggest absorption via the respiratory tract by both humans and rodents. Following absorption, ethylene glycol is distributed in aqueous compartments throughout the body. Ethylene glycol is initially metabolized to glycolaldehyde by alcohol dehydrogenase (with possible contribution from cytochrome P-450 enzymes). Glycolaldehyde is rapidly converted to glycolate and glyoxal by aldehyde oxidase and aldehyde dehydrogenase. Metabolism of glycolate by glycolate oxidase or lactate dehydrogenase results in the formation of glyoxylate, which may be further metabolized to formate, oxalate, glycine, and carbon dioxide. Elimination of ethylene glycol occurs via exhaled carbon dioxide and urinary elimination of both ethylene glycol and glycolic acid. The half-life for elimination in humans has been estimated to be in the range of 2.5–8.4 hours.

The vast majority of information relating to the toxicity of ethylene glycol is from studies of oral exposure. Information on the health effects of oral exposure in humans is largely limited to case reports of acute accidental or intentional ingestion of ethylene glycol. These case reports have identified three stages of acute oral ethylene glycol toxicity in humans. These stages are well documented and occur within 72 hours after ingestion. The first stage involves central nervous system depression, metabolic changes (hyperosmolality), and gastrointestinal upset, and spans the period from 30 minutes to 12 hours. During the second stage (12–24 hours after ingestion), metabolic acidosis and associated cardio-pulmonary symptoms (tachypnea, hyperpnea, tachycardia, cyanosis, pulmonary edema, and/or cardiac failure) become evident. During stage three, which covers the period 24–72 hours after ethylene glycol ingestion, renal involvement becomes evident. The third stage is characterized by flank pain and oliguria/anuria. Histopathological findings show renal tubular necrosis and deposition of calcium oxalate crystals. Often, the cardiopulmonary effects in the second stage are not evident, so the distinguishing symptoms of ethylene glycol intoxication are central nervous system depression, acidosis, and nephrotoxicity. Limited information suggests that a fourth stage involving cranial nerves may occur 6 or more days after exposure. This stage is characterized by neurological symptoms including deafness, facial paralysis, and other sequelae.

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2. RELEVANCE TO PUBLIC HEALTH

Reports of fatalities following ingestion of ethylene glycol indicate that a volume of 150–1,500 mL consumed at one time may cause death. In humans, the lethal dose of ethylene glycol is estimated to be in the range of 1,400–1,600 mg/kg. Based on these estimates, it appears that humans may be more susceptible to the acute lethality of ingested ethylene glycol than other species. In laboratory animals (rats, mice, monkeys), oral doses of ≥4,000 mg/kg were needed to cause death. However, difficulties in quantifying the amounts consumed by persons who have succumbed to the toxic effects lead to uncertainty in the human lethal dose estimates.

A study with human subjects found that inhalation exposure to ethylene glycol vapor at an average concentration of 30 mg/m3 for 20–22 hours/day for 30 days was well tolerated, with effects that were essentially limited to occasional complaints of mild upper respiratory tract irritation. There were no indications of renal or other systemic effects as shown by urinalysis, hematology and clinical chemistry evaluations, and neurobehavioral tests throughout the exposure period. Short-term, high-exposure sessions found that ethylene glycol was tolerated for only 15 minutes at 188 mg/m3, 2 minutes at 244 mg/m3, and one or two breaths at 308 mg/m3. The study authors stated that respiratory tract irritation became common at an ethylene glycol concentration of approximately 140 mg/m3 (incidence data and exposure duration not specified) and that concentrations ≥200mg/m3 were intolerable due to strong irritation of the upper respiratory tract that included a burning sensation in the trachea and a burning cough. This study was used as the basis for an acute-duration inhalation MRL for ethylene glycol (see Section 2.3).

3.2.2.4 Neurological Effects

Adverse neurological reactions are among the first symptoms to appear in humans after ethylene glycol ingestion. These early neurotoxic effects are also the only symptoms attributed to unmetabolized ethylene glycol. Together with metabolic changes, they occur during the period of 30 minutes to 12 hours after exposure and are considered to be part of the first stage in ethylene glycol intoxication (Davis et al. 1997; Hess et al. 2004; Robinson and McCoy 1989; Vale 1979). In cases of acute intoxication, in which a large amount of ethylene glycol is ingested over a very short time period, there is a progression of neurological manifestations which, if not treated, may lead to generalized seizures and coma (Chung and Tuso 1989; Froberg et al. 2006; Hantson et al. 2002; Jobard et al. 1996; Leth and Gregersen 2005; Olivero 1993; Siew et al. 1975a; Takayesu et al. 2006; Zeiss et al. 1989). Ataxia, slurred speech, confusion, and somnolence are common during the initial phase of ethylene glycol intoxication (Boyer et al. 2001; Buell et al. 1998; CDC 1987; Parry and Wallach 1974; Reddy et al. 2007; Takayesu et al. 2006; Tobe et al. 2002; Zeiss et al. 1989), as are irritation, restlessness, and disorientation (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Rothman et al. 1986; Woolf et al. 1992), and semiconsciousness and unresponsiveness (Blakeley et al. 1993; Chung and Tuso 1989; Heckerling 1987; Spillane et al. 1991; Underwood and Bennett 1973). In an unusual case of ethylene glycol poisoning, initial neurological symptoms of confusion, slurred speech, and somnolence were followed by the

development of deafness, dysphagia, and dysarthria after 7 days and full paralysis after 12 days (Tobe et al. 2002). The patient was completely unresponsive to any stimulus, all brainstem reflexes were absent, clinical neurophysiological examination showed a severe axonal polyneuropathy, and sural nerve biopsy findings showed severe axonal degeneration and oxalate deposits.