ETHYLENE GLYCOL: EVALUATING THE POTENTIAL FOR ADVERSE EFFECTS FROM OVEREXPOSURE

BACKGROUND

When ethylene glycol is used in accordance with product safety information, including the recommended exposure limits, it can be used safely. Drinking ethylene glycol, for example, is a misuse, and reports of adverse effects from ingestion of ethylene glycol are well documented. Important research is underway to evaluate the potential, if any, of adverse human effects in circumstances of conceivable overexposure scenarios -- outside of oral ingestion.

Earlier research studies in laboratory animals have shown that toxic effects, including kidney toxicity and birth defects, can occur from overexposure to ethylene glycol. The potential for toxic effects depends upon the type of exposure and the amount and rate of ethylene glycol entering the body. These factors largely determine how the body absorbs, distributes, breaks down and eliminates ethylene glycol and other compounds produced by organs exposed to ethylene glycol.

The ongoing research will help to refine further the potential for toxic effects of ethylene glycol in humans in various overexposure scenarios.

RESEARCH PROGRAM

When administered to experimental animals at low doses, ethylene glycol is partly excreted unchanged in urine, and partly broken down through a series of intermediates (metabolites) to carbon dioxide, which is exhaled. At high oral doses, however, the metabolic pathway is overwhelmed and the amount the body can break down is limited. As a result, an intermediate (glycolic acid) accumulates in the blood and tissues. This metabolite is believed to be a factor in producing the toxic effects of ethylene glycol seen in experimental animals at high doses, including kidney toxicity and birth defects.

The amount of glycolic acid formed depends on many factors, including the dose of ethylene glycol administered and the rate at which it is absorbed into the body. Oral ingestion of high doses of ethylene glycol results in rapid absorption and conversion to glycolic acid and subsequent metabolites. Absorption of ethylene glycol is slower when exposure occurs through vapor inhalation and dermal routes. In these situations, the metabolic pathway is not overwhelmed, the conversion to glycolic acid and subsequent metabolites is not limited, and toxic amounts of the metabolites do not accumulate.

Although no adverse effects have been associated with inhalation or dermal exposures from normal use, ethylene glycol is clearly toxic and lethal to humans when large amounts are ingested orally. The objective of the ongoing research is to integrate information from past animal studies in a way that will enable scientists to more accurately predict the likelihood of toxic effects in humans from various situations in which human overexposure could occur. Results from experimental animal studies will be extended to humans.This is being achieved using computer models.

Physiologically based pharmacokinetics (PBPK) is a recently developed computer modeling technique. PBPK allows animal and human physiological characteristics (such as breathing rates, blood circulation and organ perfusion) and chemical-specific parameters (such as rates of oral, dermal and inhalation absorption, and metabolism) to be used to model the formation of metabolites in each species. Currently, data is

being generated to model how ethylene glycol is metabolized in humans after exposure to different doses under different exposure conditions. The hypothesis is that, although ethylene glycol administered orally to humans at high doses may be metabolized to toxic amounts of a metabolite, rates of absorption and metabolism after any conceivable inhalation or dermal exposure will not result in toxic amounts of this metabolite.

As results are finalized, they will be published in the scientific literature, and the general public will be made aware in future communications from the Ethylene Glycol Panel at the Chemical Manufacturers Association.