

Addendum to the Toxicological Profile for
Propylene Glycol

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ADDENDUM for PROPYLENE GLYCOL

Supplement to the 1997 Toxicological Profile for Propylene Glycol

BACKGROUND STATEMENT

This addendum for Propylene Glycol supplements the Toxicological Profile for Ethylene Glycol/Propylene Glycol that was released in 1997.

Toxicological profiles are developed in accordance to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepares toxicological profiles on the 100 most common substances detected at National Priorities List Sites, or on the Priority List and the toxicological profiles be revised “no less often than once every three years”. CERCLA further mandates that the Administrator will establish and maintain an inventory of literature, research and studies on the health effects of toxic substances [§116].

The purpose of this addendum is to provide to the public, other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the initial release of the toxicological profile in 1997.

Chapter numbers in this addendum coincide with the [toxicological profile for propylene glycol \(1997\)](#). This document is to be used in conjunction with the toxicological profile, and does not replace it.

SUMMARY

Propylene glycol is a colorless, odorless liquid which is generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) under 21 CFR §184.1666, for use as a direct food additive under the conditions prescribed. It is also approved by the U.S. FDA for use as certain indirect food additives. Propylene glycol is used as a constituent in a large variety of cosmetics, and is approved and used as a vehicle for topical pharmaceutical preparations. It has a wide range of other practical applications, e.g., used as deicers, coolants, antifreeze, heat transfer and hydraulic fluids, plasticizers and other products. Propylene glycol has low toxicity, is not acutely toxic, and does not irritate the skin. However, contact dermatitis has been reported from a wide variety of topical preparations. Inhalation of the vapors of propylene glycol may present no significant hazard in ordinary applications, but limited human experiences indicate that its mists may be irritating to some individuals [Dow Chemical, 2006].

2.0 HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.5 Reproductive Effects

One study using propylene glycol evaluated the reproductive effects of male and female rats over two generations. Groups of male and female Sprague-Dawley rats were exposed via inhalation to 0, 300, 1,000, or 3,000 parts per million (ppm) of propylene glycol for 6 hours/day for 5 weeks prior to mating, and 6 hours/day 7 days/week during mating and gestation. These investigators observed decreased fertility, and decreased ovary weights in maternal rats. In the dams' offspring, they noticed decreased body weights, reduced survival and litter size, slight delays in

puberty onset, and histologic changes in liver and thymus in the F1 and F2 offspring [Carney et al., 1999].

2.2.1.6 Developmental Effects

New Zealand White rabbits and Fischer-344 rats were exposed via inhalation to propylene glycol at 0, 50, 150, or 300 ppm for 6 hours/day from day 7 through 19 (rabbits), or day 6 through day 15 (rats) of gestation. The results indicated that the chemical is not embryo-fetotoxic, or teratogenic in rabbits, or rats when administered at the highest concentration of 300 ppm by inhalation which is the appropriate route of potential human exposure [Breslin, et al., 1996].

Pure ochratoxin A administration to 150 chicken embryos through the air sac route at the rate of 0.02 microgram/egg ($\mu\text{g}/\text{egg}$) and administration of propylene glycol in 50 embryos at the same dose and level through the same route, produced ultra structural changes in the bursa of Fabricius. The bursa of Fabricius in poultry is a blind saclike structure located on the poster dorsal wall of the cloaca which is the chamber into which opens the hindgut, bladder and genital ducts. The bursa of Fabricius performs a thymus like function. The thymus is a primary lymphoid organ located in the lower part of the neck that is necessary in early life for the normal development of immunological function [Farshid, et. al., 1996].

2.2.2 Oral Exposure

2.2.2.1 Death

Human case studies reporting death caused by exposure to propylene glycol (including industrial use exposure) have not been found in the scientific literature [LaKind, et al. 1999], except the report of a decomposed body of a 45 year old woman found, face down, in a mobile home along

with a suicide note and 2 antifreeze containers. Analysis of the body fluid collected from the deceased revealed the presence of 1, 3 propanediol at 445 milligram/deciliter (mg/dl). The decedent's body fluid was analyzed using gas chromatography with flame ionization detector [Frazee et. al. 2008]. No lethal oral dose of propylene glycol has been reported for humans. However, the minimal lethal oral doses calculated for rats, and rabbits, are 20.9 gram/kilogram (g/kg) and 20 g/kg, respectively [LaKind, et al. 1999].

2.2.2.2 Systemic Effects

In humans, propylene glycol has caused skin and mucous membrane irritation when given orally. It has induced skin sensitization reactions in several individuals and when taken orally, can also induce skin rashes. By the oral route, or by injection, propylene glycol has resulted in severe effects on the CNS and metabolic disruptions [BIBRA Working Group, 1996].

Male and female CD-1 rats were exposed orally to various concentrations of propylene glycol i.e., from 0 to 2,100 milligram/kilogram/day (mg/kg/d) and various parameters were investigated i.e., behavioral, body weights, organ weights, and hematological effects. No statistically significant differences were observed in either parameter examined [Gaunt et. al., 1972]. Additionally, propylene glycol and choline have been shown to protect dairy cattle from developing fatty liver. Propylene glycol most likely reduces fatty acid mobilization from adipose tissue [Grummer, 2008].

Hematological Effects

Single oral doses of propylene glycol were administered to adult female albino Wistar rats at 730 mg or 2,940 mg propylene glycol/kg to investigate the various hematological effects. The results

showed that propylene glycol decreased packed cell volume for up to 2 days, mainly due to hyper-osmolality (increased concentration of a solution expressed as osmoles of solute per kilogram of serum water) of the plasma, and altered morphology of erythrocytes. A reversible decline in red blood cell count was also noted and was probably due to either the destruction of cells, or their removal from circulation [Lakinda, et. al. 1999]. Others reported no changes in hemoglobin content, clotting time, and differential leucocyte cell count in a 30-day study of adult male rats fed 0.284 ml propylene glycol/100 g body weight-day (0.09 mg/kg/d) [Ahluwalia, et. al., 1980].

Propylene glycol was administered to two groups of female rats at 73 mg or 294 mg propylene glycol/100 gram body weight and various hematological effects were examined. Hemoglobin content, packed cell volume, and red cell counts were statistically significantly decreased for 2 days, but the changes rebounded to basal levels on the 8th day. Reticulocyte counts, plasma hemoglobin, and osmolality increased after propylene glycol dosing in both groups and the changes were pronounced after 2 days. Electron microscopic morphology revealed rough cell surface, ruptured membranes and increased cell adherence throughout the observation period, but these effects were unremarkable on the 8th day [Saini, M, 1996].

Cardiovascular

At high doses, propylene glycol ingestion may lead to hyperosmotic changes (i.e., effects of components that can alter bulk water movement across cells); irregular heart rate; sinus arrhythmia (abnormal heart rhythm); tachypnea (rapid breathing); and tachycardia (rapid heart rate) [LaKind et al. 1999].

2.2.2.4 Neurological Effects

Primarily, acute clinical effects include consequences of CNS effects e.g., depression; lactic acid acidosis from extreme high doses [LaKind, et al.,1999].

A 2 year old boy developed central nervous system (CNS) depression and metabolic acidosis following accidental ingestion of about 3 ounces of hair gel which contained about 1.75 – 2.25% of propylene glycol. The child experienced a few rounds of emesis, became lethargic, and responsive only to deep pain. For treatment, the child underwent gastric lavage and was administered sodium bicarbonate intravenously. His metabolic acidosis dissipated and clinical status improved and he was released from the hospital [Glover, ML and Reed, MD, 1996].

Symptoms of acute toxicity of oral exposure to high doses of propylene glycol include CNS depression or narcosis. In rats and mice these symptoms include ataxia (inability to coordinate muscle activity during voluntary movement), ptosis (sinking down of an organ, eg. an eye), decreased spontaneous motor activity, body/limb tone, and respiration. Blood pressure was unaffected in dogs and cats. These investigators concluded that propylene glycol can be used safely as a vehicle at concentrations of up to 10% [Lakind et. al., 1999].

2.2.2.5 Reproductive and 2.2.2.6 Development Effects

Chen et al. found no evidence from histopathological data from the repeated dose studies that would indicate that propylene glycol would pose an adverse reproductive, developmental, teratogenic, or genotoxic effect in humans. This is based on the rapid bio-transformation of this chemical. Chen et al. found that propylene glycol enhanced oocyte survival following cryopreservation [Chen et al., 2005].

Propylene glycol was administered via drinking water to post-partum cows to determine the effects on metabolic variables related to ovarian function and on oocyte developmental competence. It was noticed from blood samples collected on post-partum days, 5, 15, 25 and 35 that insulin, and glucose concentrations increased, but beta-hydroxybutyrate and non-esterified fatty acids decreased over 90 minutes in comparison to control animals. Oocyte quality as measured by blastocyst development after IVF was not affected by treatment. These results indicate that administration of propylene glycol has the ability to positively alter the systemic concentrations of a number of metabolic variables related to fertility. By contrast, these investigators did not observe an effect of propylene glycol on follicular dynamics, or the length of the postpartum interval. Therefore, an adverse effect on oocyte development competence remains to be shown [Rizos, et. al., 2008].

2.2.3 Dermal Exposure

2.2.3.3 Systemic Effects

Dermal exposure to propylene glycol may occur during activities such as changing antifreeze, but it is very unlikely that any adverse health effects would occur. Propylene glycol toxicity is low because of bio-transformation, and it is unlikely to cause adverse health effects at these exposure levels. Dermal exposure to creams containing propylene glycol (20%) has been shown to be beneficial under certain circumstances. For example, a fatty cream (Locobase, R and Diprobase R) containing propylene glycol was found to be effective in a dermal disease which is generalized scaling of the skin (Lamellar ichthyosis). While hyperkeratosis (thickening of the horny layer of the epidermis or mucous membrane) and xerosis (dryness of the skin) were reduced, there was slight irritation and an adverse effect on the epidermal barrier function [Gånemo et al. 1999]. Similarly, propylene glycol in an excipient mixture was found to enhance

the permeation of estradiol in-vitro across hairless skin [Irion, G.D. et. al., 1995]. Another study using propylene glycol in a vehicle mixture showed an enhanced lipophilicity and permeation of erythromycin to combat acne vulgaris [Matschiner, S. et. al., 1995]. Moreover, study concerning allogenic skin grafts showed that when skin is immersed in an 85% solution of propylene glycol that water activity was reduced. A reduced skin water activity of 0.3 is known to minimize lipid peroxidation and reduce other degradation reaction rates to very low levels.

Hepatic Effects

Recent advances in the understanding of production of diseases include the emergence of propylene glycol, and rumen protected choline as the supplements of choice for preventing fatty liver, and the absence of any preventive effect of increased energy density in the close-up dry period diet on this condition.

2.2.3.3 Immunological Effects

In a case study, a 39 year-old woman was presented with pruritic eczematous (itching inflammatory condition of the skin) plaques on her face, neck and right hand, which she had for about 2 months, following an abrasive injury caused by the deployment of an airbag during a car accident. The patch test results indicated the presence of propylene glycol. The patient's condition of contact dermatitis cleared after she discontinued using topical products containing propylene glycol. However, she noted flares of this condition whenever she ate foods which contain propylene glycol. Recurrent dermatitis despite complete avoidance of identified topical allergens and a history of recurrent eczema (inflammation of the skin) at the patch-test site are clues to diagnosis of systemic contact dermatitis [Lowther, A. et. al., 2008].

Allergy

Allergy to vehicle ingredients in topical steroids is well known, however, there are no data regarding which vehicle ingredients are in common use, or which vehicle and active molecules are associated with the ingredients. Propylene glycol is a vehicle ingredient that is used in topical corticosteroid and is a well know allergen. Dermatologists should be aware of the possibility of vehicle ingredients that induce contact dermatitis and should avoid prescribing agents which have these potentially allergenic vehicle ingredients [Coloe, J and Zirwas, M J, 2008].

Sensitization

Although propylene glycol is a very weak sensitizer, if it is at all, propylene glycol containing products might be associated with an elevated risk of sensitization. For example, allergic contact dermatitis due to propylene glycol and parabens in an ultrasonic gel has been reported. Patch tests with an expanded European standard series and 20 different wound dressings showed sensitization in 78% (36) of patients, while 8.3% (3) of patients were sensitized to propylene glycol in modern wound dressings [Gallenkemper, G, 1998].

2.2.3.4 Neurological

A premature infant was exposed topically to burn dressing which contained propylene glycol and went into a coma. Cessation of the topical application of the bum dressing resulted in complete recovery. It has been suggested that topical preparations containing propylene glycol should not be used in premature infants [Peleg, O. et. al., 1998].

2.3 TOXICOKINETICS

2.3.1 Absorption

An animal study showed that a mixture of propylene glycol and stearic acid enhanced the in-vitro permeation of nimodipine through rat skin. Nimodipine is a calcium channel blocker with vasodilation properties which may be used as an antihypertensive drug. Also, it has been shown that a mixture containing propylene glycol enhanced the absorption of verapamil which is another calcium channel blocker.

2.4 RELEVANCE TO PUBLIC HEALTH

Minimal Risk Levels

No changes in MRL from the 1997 toxicological profile.

Intermediate-duration inhalation MRL = 0.009 ppm.

3.0 CHEMICAL AND PHYSICAL INFORMATION

No data.

4.0 PRODUCTION, IMPORT/EXPORT, USE, DISPOSAL

No data.

5.0 POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

Fisher et al. conducted a study to characterize the potential impact on aquatic life from acute exposure to propylene glycol from de-icing and anti-icing agent activities. The study showed that flathead minnows and daphnids had lethal concentration values at 1% to 2% effluent

concentrations [Fisher et. al., 1995]. In another study of industrial de-icers in water from a stream that received runoff from a large commercial airport, daphnids, fathead minnows, and photobacterium phosphoreum bioassays showed toxic effects of propylene glycol and other glycol ethers [Hartwell, et. al., 1995].

A bio-degradation experiment was conducted on three propylene glycol ethers. The test compounds were labeled with Carbon-14 at the methoxy, or phenoxy moiety. The time required for degradation of 50% of the compounds from < 1 day at 0.2 ppm to < 7 days at 107 ppm. Degradation rates were slower in sandy soils indicating lower levels of microorganisms present [Gonsior and West, 1995].

Propylene glycol ethers are unlikely to persist in the environment, once in the air, the half life of the category members due to direct reactions with photochemically generated hydroxyl radicals are only a few hours.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In 1995, Laitinen et al. conducted a study of 10 car mechanics that were frequently exposed to glycol based cooling liquids. The workers gave urine samples at the end of the work shift. Indoor air levels of propylene glycol and ethylene glycol were measured. The car workers' urinary propylene glycol levels were compared to an unexposed group of office workers and were found to be the same level as the controls [Laitinen, J., 1995].

6.0 ANALYTICAL METHODS

No data.

7.0 REGULATIONS AND ADVISORIES

No data.

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