Fact Sheet Date: June 2004

NEW YORK STATE
HUMAN HEALTH FACT SHEET

Ambient Water Quality Value for
Protection of Human Health and Sources of Potable Water

SUBSTANCE: Propylene Glycol **CAS REGISTRY NUMBER**: 57-55-6

AMBIENT WATER QUALITY VALUE: 1,000 ug/L*

Remark: *A value of 300 ug/L shall apply at the point of intake of a public or private water supply that uses ozonation in its treatment process.

BASIS: Specific MCL (6 NYCRR 702.3(a))

INTRODUCTION

Data on the health effects of exposure to propylene glycol, including data on chronic (oncogenic and non-oncogenic), developmental, and reproductive effects observed in animals and effects observed in humans were reviewed and critically evaluated. The selected ambient water quality value for propylene glycol was derived considering the available toxicological data (see bibliography) and the procedures outlined in 6 NYCRR 702.2 through 702.7.

SPECIFIC MCL AND PRINCIPAL ORGANIC CONTAMINANT CLASS (702.3)

Propylene glycol has a Specific MCL (maximum contaminant level) of 1,000 ug/L as defined in 700.1. This MCL applies to public drinking-water supplies and was promulgated (NYS, 2003) by the New York State Department of Health (DOH) under the State Sanitary Code (10 NYCRR Part 5). It is not based on aesthetic considerations, therefore, a water quality value of 1,000 ug/L (the Specific MCL) can be derived under 702.3(a).

ONCOGENIC EFFECTS (702.4)

Oncogenic effects were not observed in rats exposed for two years to propylene glycol dose levels up to 2,100 milligrams per kilogram body weight per day (mg/kg/day)(Gaunt et al., 1972). Oncogenic effects were not found in dogs exposed for two years to propylene glycol dose levels up to 5,000 mg/kg/day (Weil et al., 1971) nor on the skin of mice exposed to dermal applications of 2 mg propylene glycol twice weekly for 120 weeks (Stenback and Shubik, 1974). Propylene glycol was inactive in short-term tests indicative of potential oncogenic activity, including tests for gene mutations, mitotic recombination and chromosomal aberrations (Ishidate et al., 1984; Kennedy et al., 1975; Litton Bionetics, 1974, 1976; Pfeiffer and Dunkelberg, 1980; Stolzenberg and Hine, 1979). Thus, propylene glycol did not cause an “oncogenic effect” as defined in 700.1.

NON-ONCOGENIC EFFECTS (702.5)

Several subchronic studies in cats (Bauer et al., 1992; Christopher et al., 1989; Dow Chemical as cited in Rowe and Wolf, 1982) report the formation of Heinz bodies at doses as low as 443 mg/kg/day propylene glycol over 94 days. Heinz bodies are visible aggregates of oxidized, denatured hemoglobin within red blood cells, which may lead to hemolysis. Cats are recognized as the species whose hemoglobin is most susceptible to oxidative denaturation due to the presence of eight reactive sulfhydryl groups per hemoglobin molecule. Hemoglobin in most species (including humans) contains four sulfhydryl groups per molecule. In addition, the feline spleen is unique in its inability to cull red blood cells containing Heinz bodies, which accounts for their persistence in circulation. The uncommon physiological sensitivity of cats to propylene glycol suggests that the effects on blood reported in studies involving this species are not relevant to the evaluation of propylene glycol toxicity in humans.

Dogs fed dietary doses of propylene glycol for two years (2,000 or 5,000 mg/kg/day) showed reduced red blood cell counts, hemoglobin and hematocrit values, and slightly increased bilirubin at the highest dose (Weil et al., 1971). These findings are suggestive of increased erythrocyte hemolysis and synthesis. No effects were observed at the lower dose. Rats exposed to dietary doses of up to 2,100 mg/kg/day for two years showed no adverse effects on numerous parameters, including mortality, body weight gain, food consumption, hematology, urinary cell excretion, urine-concentrating ability of kidneys, organ weights, histopathology and tumor incidence (Gaunt et al., 1972). The no-observed-effect level (NOEL) of 2,100 mg/kg/day in rats is consistent with the NOEL of 2,000 mg/kg/day from the two-year study in dogs. Studies in several animal species on the developmental and reproductive toxicity of propylene glycol do not indicate it is a developmental or reproductive toxicant (Driscoll et al., 1993; Food and Drug Research Labs, 1973; Kavloc et al., 1987; NTP, 1985), and are supportive of an animal NOEL of 2,100 mg/kg/day.

Human case reports and clinical studies indicate that propylene glycol can be acutely toxic (Arulanantham and Genel, 1978; Cawley, 2001; Glover and Reed, 1996; Martin and Finberg, 1970; Sawchuk et al., 1982; Yu et al., 1985). Humans quickly metabolize propylene glycol to lactic acid, and elevated blood lactate, resulting in lactic acidosis, is consistently found in humans acutely poisoned by propylene glycol (Cate and Hedrick, 1980; Demy et al., 1984; Glover and Reed, 1996). Symptoms associated with lactic acidosis include mental confusion and disorientation, slurred and incoherent speech, unresponsiveness to pain, lethargy, stupor, and coma. These data suggest that many, if not all, of the observed central nervous system (CNS) effects are likely caused by changes in blood chemistry (i.e., acidosis), primarily by the increases in blood lactate levels.

Metabolic acidosis (associated with lactate and pyruvate, another metabolite of propylene glycol) and CNS effects (lethargy, depressed responsiveness to pain) were observed in a two-year old child who ingested a large amount (estimate single dose = 200 mg/kg/day) of propylene glycol (Glover and Reed, 1996). In a second case study, a hospitalized 11-year old boy treated with an oral vitamin preparation containing propylene glycol (estimated dose 100 - 200 mg/kg/day) began, after 13 months of treatment, to suffer repeated CNS effects, including seizures. The seizures typically occurred soon (2 - 4 hours) after his second daily dose of medicine (Arulanantham and Genel, 1978), and stopped once the vehicle was changed from propylene glycol to triglyceride. Given that the lowest-observed-effect-levels (LOEL) in humans for CNS effects (100-200 mg/kg/day) are significantly lower than the highest NOEL for animals (2,100 mg/kg/day; Gaunt et al., 1972), the human case reports are selected as the basis for a potential water quality value for propylene glycol.

The weight-of-evidence (metabolic, clinical, and toxicity) indicates that two critical effects of propylene glycol in humans (lactic acidosis and CNS effects) are causally linked. The evidence suggests, but does not conclusively show, that preventing acidosis prevents CNS effects. Consequently, an acceptable daily intake based on acute effects (lactic acidosis) should be protective against CNS effects. The lowest confirmed human LOEL for lactic acidosis is 200 mg/kg/day; however, it is likely that the CNS effects observed by Arulanantham and Genel (1978) at doses potentially as low as 100 mg/kg/day were caused, or at least, accompanied, by lactic acidosis. Thus, 100 mg/kg/day is selected as the basis of the acceptable daily intake. The effects (seizures followed by unconsciousness lasting 20 to 30 minutes, followed by a spontaneous recovery) observed at this dose level are considered “acute toxic effects” as defined in 700.1 because they often occurred soon after the child received medication containing propylene glycol. Therefore, a potential ambient water quality value can be derived based on acute non-oncogenic toxic effects.

If an uncertainty factor of 100 is applied to the LOEL (100 mg/kg/day), an acceptable daily intake (based on acute toxic effects) of 1 mg/kg/day can be derived for propylene glycol using procedures consistent with those outlined in paragraphs (a) and (b) of 702.5. Under 702.5(a), an uncertainty factor of 10 was used because the study used to derive the acceptable daily intake identified an effect level rather than a NOEL and because the observed effect was

sufficiently severe to preclude the use of a lower uncertainty factor. Under 702.5(b), an uncertainty factor of 10 was selected because the acceptable daily intake is based on the results from a human study and results from one or more animal studies are available. This uncertainty factor accounts for intraspecies (human) variation. A smaller factor was not selected given that the LOEL estimates were based on two individuals in case studies, and thus, it is uncertain whether the affected individuals were more or less sensitive than the general population. A value of 2 mg/L is derived assuming a 10-kg child drinks 1 liter of water per day and allowing 20% of the acceptable daily intake (1 mg/kg/day, acute toxic effects) to come from drinking water (702.2 (c) and 702.5(d)).

There remains a small probability that the CNS effects observed by Arulanantham and Genel (1978) were not caused by short-term increases in blood lactate levels. Alternatively, the CNS effects could have been caused by some other mechanism over the course of the exposure period (13 - 15 months). If so, the potential for lower doses given over a longer period of time to cause CNS effects should be evaluated. In consideration of this possibility, a potential ambient water quality value based on chronic non-oncogenic effects can be derived.

If an uncertainty factor of 300 is applied to the LOEL (100 mg/kg/day), a potential acceptable daily intake (based on chronic effects) of 0.33 mg/kg/day can be derived for propylene glycol using procedures consistent with those outlined in paragraphs (a) and (b) of 702.5. An uncertainty factor of 100 (as discussed above) was used to account for the use of an effect level rather than a NOEL (10) and for intraspecies (human) variation (10). An additional uncertainty factor of 3 was used to account for the use of a less-than lifetime study to estimate an acceptable daily intake for chronic effects. An uncertainty factor of 3 (rather than 10, which is typically used when a subchronic animal study is used in the derivation of a chronic acceptable daily intake) was selected because the length of exposure (13 - 15 months) was considered longer than subchronic but shorter than chronic exposure. A value of 2.3 mg/L is derived assuming a 70-kg adult drinks 2 liters of water per day and allowing 20% of the acceptable daily intake (0.33 mg/kg/day, chronic effects) to come from drinking water (702.2(c) and 702.5(d)).

Thus, regardless of whether the critical effect in the principal study is evaluated as an acute or a chronic effect, a value of 2 mg/L (one significant figure) is selected as the water value based on non-oncogenic effects.

CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because the toxicity data show that propylene glycol was tested for, but did not cause, an “oncogenic effect” and data are insufficient for deriving a value based on chemical correlation to the oncogenic effects of any other chemical (702.4). In addition, a value based on chemical correlation to the non-oncogenic effects of another chemical (702.5) is not necessary because the toxicity data of

propylene glycol are sufficient to derive a value based on its non-oncogenic effects.

OZONATION BY PRODUCTS

High levels of propylene glycol in ambient water could increase the levels of toxic disinfectant by-products in drinking water treated with ozone (ozonation) to kill disease-causing micro-organisms. Ozonation is known to produce aldehydes from organic matter in water (US EPA, 1994). Krasner et al. (1989) showed that the effluent of some water treatment plants that ozonated water contained higher levels of acetaldehyde and formaldehyde than did the effluent of plants that chlorinated water. A more recent study (Parson, (19980, sponsored by the ARCO Chemical Corporation) of acetaldehyde and formaldehyde production when one of four disinfection treatments (ozonation, chlorine, chlorine dioxide, and potassium permanganate) was applied to water containing propylene glycol gave similar results. The highest levels of acetaldehyde and formaldehyde were found after ozonation and ozonation was the only treatment to show a significant increase in aldehyde production.

In the ARCO study, ozonation was applied to two reactors each containing 2,300 ug/L of propylene glycol in water. Formaldehyde production was 390 and 450 ug/L, respectively, yielding an average propylene glycol to formaldehyde ratio of 5.48 (390 + 450/2 = 420, and 2,300/420 = 5.48). Acetaldehyde production was 180 and 190 ug/L, respectively, yielding an average propylene glycol to acetaldehyde ratio of 12.4. The production of formaldehyde from the ozonation of propylene glycol was substantially greater than the production of acetaldehyde.

A limitation of the ARCO study was the unexpected occurrence of higher levels of total organic carbon in water samples treated with ozone compared to the water samples used in the other treatments. These higher levels of organic matter may have contributed to the formation of aldehydes. Despite this limitation, the ratios from the ARCO study represent the best determination of the production of aldehydes from ozone treatment of water containing propylene glycol.

The DOH MCL for formaldehyde and for acetaldehyde is 50 ug/L; each is an unspecified organic contaminant (10 NYCRR Part 5). Using the propylene glycol to formaldehyde ratio (5.48) determined in the ARCO study, it would require the ozonation of ambient water containing 274 ug/L of propylene glycol to produce a level of 50 ug/L of formaldehyde in drinking water (X ug/L, propylene glycol concentration in ambient water/5.48 = 50 ug/L of formaldehyde in drinking water, X = 50 ug/L x 5.48 = 274 ug/L). Thus, an ambient water quality value for propylene glycol of 300 ug/L (rounded to one significant figure) is calculated to prevent the formation of greater than 50 ug/L of formaldehyde as an ozonation by-product. A propylene glycol ambient water concentration of 300 ug/L will also prevent the formation of acetaldehyde concentrations greater than 50 ug/L in drinking water.

SELECTION OF VALUE

According to 702.2(b), the selected ambient water quality value for protection of human health and sources of potable water shall be the most stringent of the values derived using the procedures found in 702.3 through 702.7. This value is 1,000 ug/L (the Specific MCL). However, a value of 300 ug/L for propylene glycol, however, is needed to prevent adverse effects due to formaldehyde formed during disinfection treatment with ozone. Considering the infrequent use of ozonation, it is appropriate to establish 1,000 ug/L (based on Specific MCL) as a general ambient value and 300 ug/L (based on formation of formaldehyde) as an ambient value that applies at the point-of-intake for water suppliers that use ozone in the treatment process.

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SEARCH STRATEGY

Toxline (1981 - August, 1994) was searched linking the CAS RN for propylene glycol and the keyword "toxicity." Medline (1994 - 1998) was searched using propylene glycol as the keyword. PubMed (1998 - 2003) was search using propylene glycol as the keyword.

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