Peer reviewers for the second draft of the Toxicological Profile for Ethylene Glycol were:

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ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in the second draft of the profile, and "L" indicates the line number on that page.

The peer reviewers provided citations and/or copies of papers for some studies they would like to see added to the toxicological profile. Data from some of these studies have been incorporated into the toxicological profile. ATSDR will evaluate the remainder of the references for possible incorporation into future drafts of the toxicological profile.
Review comments provided by Dr. Phillip Goad

PR 14, Section 3.4: Dr. Goad indicated that autopsy/forensic data on ethylene glycol distribution reported by Baselt (2002) should be included in the profile.

Response: The cited reference is in retrieval, but did not arrive in time to incorporate into the revised draft. This comment will be addressed after the public comment period.

All other comments provided by Dr. Goad were addressed as suggested.

Review comments provided by Dr. Jerrold Leiken

PR11, P16-17: Noting that human data should be presented before animal data, Dr. Leiken suggested placing all human studies on page 17 of the acute MRL discussion at the beginning of the section.

Response: Human data are presented before animal data in all sections of the profile. Only one human study (Wills et al. 1974) is presented in the acute inhalation section. This study is briefly discussed before the animal data at the beginning of the section; a detailed summary of the same study is provided later (on page 17) because it is used for MRL derivation.

PR16, Table 4-2: Dr. Leiken suggested adding units to density and molecular weight, adding pH (neutral), and adding that ethylene glycol is soluble in ether.

Response: Density units (g/cm³) are reported in the "Property" column to the left of the value in Table 4-2. Molecular weight values are not reported with units in Chapter 4 tables of ATSDR Toxicological Profiles. Adding the pH to Table 4-2 is not considered relevant for chemicals like ethylene glycol. The language "slightly soluble in ether" is provided in Table 4-2 as reported in HSDB (2007).

All other comments provided by Dr. Leiken were addressed as suggested.

Review comments provided by Dr. Kenneth McMartin

PR21, P6, L2: Referring to the EPA health standards listed in the Public Health Statement, Dr. McMartin asked “How are the drinking water levels set?

Response: It is beyond the scope of the Public Health Statement to include the basis for these standards.

PR 21, P13, L23-24; PR 22, P23, L34; PR 25-26, P77, L21-34; PR 605, P13, L23-24; PR 642, P88, L24-25: Dr. McMartin disagreed with the conclusion of NTP-CERHR (2004) and the
profile authors on the usefulness of the Pottenger study in demonstrating that pregnancy does not alter the kinetics of ethylene glycol and glycolate. Dr. McMartin asserted that 1) the Pottenger study tested rats on GD 10, in the middle of the critical window for developmental effects; 2) physiologic changes during pregnancy would not change the kinetics of ethylene glycol or glycolate, which are controlled by hepatic enzyme activity and renal excretory mechanisms and not hepatic or renal blood flow (implying that pregnancy results in changes in blood flow but not in enzyme activity or renal excretory mechanisms); and 3) that the failure of the Pottenger study to measure embryonic levels of ethylene glycol and its metabolites was not important, since Corley et al. (2002) showed that levels of ethylene glycol and glycolate in the embryo and in embryonic fluid paralleled maternal blood levels, although glycolate levels were consistently higher in the embryos and embryonic fluid than in maternal blood.

Response: The interpretation of the Pottenger study remains consistent with the conclusions of the NTP-CERHR (2004) review, as no new data are available to address the uncertainties raised by that review. NTP-CERHR agreed that GD 10 is a sensitive period for ethylene glycol developmental toxicity in the rat, but noted that this was a narrow window of gestation, and so there was uncertainty as to whether the similarity in kinetics between pregnant and nonpregnant rats observed on GD 10 would also be observed at prior or later time points during pregnancy. No additional data comparing toxicokinetics of ethylene glycol or its metabolites at other gestational time points are available.

NTP-CERHR (2004) also reported that “a literature search has not revealed a reliable assessment of whether ADH or other ethylene glycol metabolizing enzymes might change in the mother during pregnancy”. Thus, NTP-CERHR was not able to identify any reliable data to support the hypothesis that enzyme activity is not affected by pregnancy. Fetal development of ADH and other enzymes involved in ethylene glycol metabolism may differ across species, and as such “rat maternal toxicokinetic data may not extrapolate well for describing dosimetry to the human fetus” (NTP-CERHR 2004). In addition, there are no data at all on the ontogeny of glycolate oxidase in humans or rats (NTP-CERHR, 2004). This data gap is important because glycolate oxidase plays an important role in clearing glycolate. While Corley et al. (2002) showed that embryonic levels of ethylene glycol and glycolate paralleled those of maternal blood, maternal exposure was only on GD 11, also a narrow window of gestation. It is not certain that the relationship between maternal and embryonic levels would hold over the course of developmental changes in embryonic metabolic function. Given these uncertainties, coupled with uncertainty in the specific enzymes involved in human metabolism of ethylene glycol, NTP-CERHR (2004) concluded that “it is difficult to assess how well these data (i.e., the Pottenger data) might extrapolate to the human situation”.

PR22, P15, L16; PR 22, P30, L13-25; PR27, P100, L19-34: Dr. McMartin indicated that kidney toxicity data from the new 12-month study in male Wistar rats (Wilson et al. 2005) should be used to derive a chronic oral MRL.

Response: Basing the chronic oral MRL on this study yields a value that is higher than the acute-duration oral MRL. It is against ATSDR policy to derive a chronic-duration MRL that is higher than the acute-duration MRL. The acute MRL is based on a NOAEL of 150 mg/kg/day
for developmental toxicity in mice (Neeper-Bradley et al. 1995; Tyl 1989), which is the same as the intermediate- and chronic-duration NOAELs for kidney effects in male Wistar rats (Cruzan et al. 2004; Wilson et al. 2005). The available evidence therefore indicates that the acute-duration oral MRL should be protective for chronic kidney effects.

PR23, P27, L11-26; PR 24, P48, L 810; PR27, P100, L1-6: Dr. McMartin indicated that the Cruzan et al. (2004) study should be used as the basis for the intermediate-duration oral MRL because the Gaunt et al. (1974) study is unsuitable for reasons he discussed in other comments.

Response: ATSDR agrees that the kidney toxicity data from the Cruzan et al. (2004) study is a better basis for calculating an intermediate-duration MRL than the kidney toxicity data from the Gaunt et al. (1974) study, but found that the value is higher than the acute-duration oral MRL based on developmental toxicity. Because it is against ATSDR policy to derive an intermediate-duration MRL that is higher than the acute-duration MRL, and available evidence indicates that the acute MRL should be protective for kidney effects following longer-term exposure, the acute-duration value was adopted for intermediate-duration exposure.

PR26, P77, L34: Dr. McMartin disagreed with the statement that the PBPK model is not useful for predicting developmental toxicity in humans.

Response: At this and other locations in the text where the model is described as not useful, this language has either been deleted or modified to indicate that the model was not calibrated to pregnancy, and it is not clear whether physiological and/or biochemical changes that could affect ethylene glycol toxicokinetics might occur during pregnancy.

PR587, P107, L27: Dr. McMartin recommended adding text to note that acute-duration studies of dermal exposure in humans are needed to characterize kinetics for this route.

Response: This data gap was highlighted in the preceding paragraph, which stated that “no data describing the kinetics of in vivo human dermal exposure were found in the literature”. No additional text was added.

PR 633, P73, L6-8: Dr. McMartin recommended deleting the half-life information for hemodialysis because it does not reflect normal elimination.

Response: The half-life data during dialysis were retained because they show the effects of different therapies on half-life, but the paragraph was rearranged to place greater emphasis on the half-life without treatment, and text was added indicate that the rate of elimination is greatly increased by dialysis.

All other comments provided by Dr. McMartin were addressed as suggested.