

Recreational Scenario involving dermal contact with EGBE in surface water, we calculated an average daily intake of 0.0003 mg/kg/day for adults, 0.0002 mg/kg/day for older children, and 0.0006 g/kg/day for younger children.

Combining the Residential and Recreational Scenarios for each of the age groups provided a worst-case exposure scenario. The average daily intake for the combined worst case are: Adults 0.1 mg/kg/day, older children 0.3 mg/kg/day, and younger children 0.3 mg/kg/day. Based on this analysis, we have concluded that exposures to EGBE arising from the ingestion of surface water exposed may not reasonably be anticipated to exceed 0.3 mg/kg/day, and would be significantly less.

C. Human Health Effects of EGBE

The petitioner used the 1997 draft Integrated Risk Information System (IRIS) assessment as the basis for their human health effects evaluation of EGBE. Since then, the IRIS assessment has been completed (in 1999) and more recent toxicological information on EGBE has become available. Therefore, rather than evaluating the information presented in the petition, we focus our evaluation of EGBE's health effects on the more recent data.

We used the IRIS toxicological database to evaluate the human health effects associated with exposures to EGBE, and to identify an appropriate human health criterion for the risk characterization (IRIS, 1999). Specifically, we used the toxicological data presented in support of the IRIS RfC and Inhalation Reference Concentration and reference dose (RfD) which is contained in *The Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE)*. This document is electronically available via EPA's IRIS Page at <http://www.epa.gov/iris>. The IRIS is the Agency's official repository of consensus human health risk information. It was created and is maintained by the Agency to provide assistance to Agency decision makers on the potential adverse human health effects of particular substances. In addition, EPA scientists have investigated and analyzed information on the human carcinogenic potential of EGBE that was published after the IRIS assessment was final. We had our evaluation of the new information peer reviewed by experts external to the agency, and we use this evaluation to help us draw conclusions about the potential for EGBE to cause cancer in humans (see docket for EPA's August, 2003 Interim Final Report, "An evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl

Ether"). Based on these reviews, we have determined that adequate data concerning the potential health effects of EGBE are available and are of sufficient quality to use as the basis for deciding whether or not to delete EGBE.

The IRIS reports that the reproductive toxicity of EGBE has been studied in a variety of well conducted oral and inhalation studies using rats, mice, and rabbits. In addition, several developmental studies have addressed EGBE toxicity from conception to sexual maturity including toxicity to the embryo and fetus, following oral and dermal exposures to rats, mice, and rabbits. Ethylene glycol monobutyl ether was not found to cause adverse effects in any reproductive organs in any study. In a two generational reproductive toxicity study, fertility was reduced in mice only at very high (maternally toxic) doses. Maternal toxicity related to the adverse effects on red blood cells (called hematologic effects) due to exposure to EGBE and relatively minor developmental effects have been reported in developmental studies. We conclude from these studies that EGBE is not significantly toxic to reproductive organs of parents, male or female. In addition, no teratogenic toxicities were noted in any of the studies. Therefore, we also conclude that EGBE is not significantly toxic to developing fetuses of laboratory animals.

Our review of the IRIS assessment confirmed that hematologic effects is the primary response in sensitive species following inhalation, oral, or dermal administration of EGBE. The reported sensitivities range from that of the guinea pig which displays no hemolytic effects from EGBE at exposures levels as high as 1,000 mg/kg (oral) or 2,000 mg/kg (dermally) to the rat which displays increased sensitivity at single-inhalation exposures below 100 parts per million (ppm) (483 mg/m³) and single oral exposures below 100 mg/kg. No hemolysis has been observed in controlled laboratory acute inhalation exposures of human volunteers up to 195 ppm (941.9 mg/m³) and reversible hemolytic effects have been observed in a case where humans consumed single oral doses of 400 to 1,500 mg/kg of EGBE.

Data considered in the IRIS toxicological review, primarily from acute and in vitro studies, indicate that humans are significantly less sensitive to the hemolytic toxicity of EGBE than typical laboratory species such as mice, rats, or rabbits. While studies of chronically exposed humans are lacking, several laboratory animal studies have demonstrated this, as have in vitro studies using either whole blood

or washed red blood cells. In addition, blood from potentially sensitive individuals, including the elderly and those persons with congenital hemolytic disorder such as sickle-cell anemia or hereditary spherocytosis, does not show an increased hemolytic response when incubated with EGBE's active metabolite, 2-butoxyacetic acid (BAA).

The principal study used to determine the EGBE RfC is a 2-year bioassay that involved groups of F344 rats exposed to 0, 31, 125, and 500 ppm EGBE in air for 12 months (6 hours/day, 5 days/week). Female rats exposed to the three highest concentrations at all exposure durations developed clinical signs consistent with hemolytic effects associated with EGBE exposures. A Lowest Observed Adverse Effects Level (LOAEL) of 31 ppm (149.7 mg/m³) was identified in this study for hematologic and histopathologic effects in female rats.

The human equivalent concentration (HEC) was calculated using the standard RfC approach, a physiologically based pharmacokinetic (PBPK) approach, a benchmark concentration (BMC) approach, and a PBPK/BMC approaches combined. The PBPK/BMC approach was determined by the IRIS Peer Review Panel to provide the best estimate of a HEC because it incorporated much of the mechanistic information available for EGBE, best characterized the dose-response relationship for EGBE-induced hematologic effects, and reduced the potential uncertainties to the greatest extent. The HEC as determined by the PBPK/BMC method was then reduced by a series of uncertainty factors to derive the RfC. An overall uncertainty factor (UF) of 30 was applied to account for extrapolation from an adverse effect (UF = 3) and to account for the variation in the sensitivity within the human population (UF = 10).

The principal study for the ingestion RfD involved groups of 10 female F344 rats exposed to 750, 1,500, 3,000, 4,500, and 6,000 ppm of EGBE via drinking water for 13 weeks. Decreases in body weight were observed in female rats exposed to the two highest dose levels. The study results show hematologic changes at all dose levels after 13 weeks that were indicative of mild to moderate anemia. Using this study, EPA calculated human equivalent doses (HED) using all four approaches. We selected the PBPK/BMD approach for the derivation of the RfD because it incorporated much of the mechanistic information available for EGBE, best characterized the dose-response relationships for EGBE-induced hematologic effects, and reduced the potential uncertainties to the greatest extent. Using the HED from the PBPK/