

pH or osmolality associated with high EGBE concentrations), they may indicate contribution from BAL which has caused clastogenic changes in Chinese hamster lung (v79) and human lymphocyte cells (Elliot and Ashby, 1997). As we discuss in the full report, available evidence from a published EGBE PBPK model that has been modified to include kinetics for the metabolism of the BAL intermediate (Corley, 2003) suggests that the conditions of these in vitro assays (*e.g.*, no metabolic activation; high, cytotoxic concentrations of BAL) are of little relevance to expected target organ (forestomach) environment (*e.g.*, high metabolic activity; low concentrations of BAL). However, additional research (*e.g.*, verification of these PBPK modeling results and further genotoxicity research using more appropriate assays and currently accepted test protocols) would be beneficial to provide a more definitive determination regarding the role of BAL in the formation of forestomach tumors in female mice.

We conclude that the available data establish a plausible nonlinear, nongenotoxic mode of action for the moderate increase observed by NTP (2000a) in the incidence of forestomach tumors in female mice following chronic inhalation exposure to EGBE. Forestomach tissue irritation caused by constant exposure to EGBE and its metabolites and subsequent cell proliferation appear to be key precursor events in the mode of action for these tumors. While certain dosimetric processes and morphological aspects of the forestomach make rodents particularly susceptible to these events, we judge this mode of action to be of qualitative relevance to humans. However, due to the lack of a comparable organ for storage and the long term retention of EGBE, the exposure concentrations that would be necessary to cause hyperplastic effects and tumors in humans, if attainable, are likely to be much higher than the concentrations necessary to cause forestomach effects in mice. In fact, our analysis indicates that the exposure concentrations necessary to cause hyperplastic effects in humans would be much higher than the existing RfD and RfC for EGBE. Given that humans, including potentially sensitive subpopulations such as children, have no known organ for the retention of a comparable target dose of EGBE or its metabolites, we feel it is reasonable to conclude that the RfC and RfD developed for EGBE (EPA, 1999a) are sufficient for the prevention of

hyperplasia and associate tumors in humans.

With respect to liver tumors in male mice, scientists have placed particular focus on hemangiosarcomas of the liver reported by NTP (2000a) because this was the only tumor type that was increased over both concurrent and historical controls, and because one study proposed a mode of action involving EGBE for this tumor (Sascha *et al.*, 2002).

A metabolite of EGBE, butoxyacetic acid, has long been known to cause hemolysis in rodents (Carpenter *et al.*, 1956). This hemolysis leads to the accumulation of hemosiderin (iron) in phagocytic Kupffer cells of the liver of both rats and mice (NTP, 2000a). Recent research in mice and rats indicates that the increased iron levels associated with EGBE-induced hemolysis can produce oxygen radicals which produce oxidative damage in the liver that is more severe in mice than in other species, and increased DNA synthesis in both cells that line blood vessels and liver cells that is unique to mice (Sascha *et al.*, 2002). This research hypothesizes that these events can contribute to the transformation of the endothelial cells to hemangiosarcomas (and hepatocytes to hepatocellular carcinomas) in male mice. Given the high background rate of these tumors in male mice relative to female mice and rats (NTP, 2000b; Klaunig, 2002), we feel it is reasonable to hypothesize that the endothelial cells and hepatocytes in the livers of male mice are more susceptible to oxidative stress resulting from iron buildup in local Kupffer cells. While additional research would be informative with respect to mechanistic issues such as the relative susceptibility of endothelial cells and hepatocytes to oxidative stress caused by the hemolytic effects of EGBE and the apparent resistance of female mice to the development of hemangiosarcomas despite experiencing similar hemolytic effects, there is enough evidence at this time to support an EPA determination that events associated with hemolysis could have contributed to the increased incidence of these tumors in male mice exposed to EGBE.

Available data establish a plausible nonlinear, nongenotoxic mode of action for the moderate increase observed by NTP (2000a) in the incidence of liver tumors in male mice following chronic inhalation exposure to EGBE. The proposed mode of action suggests that the endothelial cells and hepatocytes of male mice are sensitive to the formation of the subject neoplasms (as evidenced by the relatively high background rate of these tumors in male mice) and that

excess iron from EGBE-induced hemolysis can result in sufficient iron-induced oxidative stress to cause the observed, marginal increase in the incidence of liver hemangiosarcomas and hepatocellular carcinomas in these animals (NTP, 2000a). Given the relatively low sensitivity of humans, including subpopulations such as children, to the hemolytic effects of EGBE, we feel it is reasonable to conclude that the EGBE RfC and RfD (EPA, 1999a) are sufficient for the prevention of hemolysis and associate tumors in humans.

We anticipate additional research may be completed in the near term. We will review those results and peer review our findings at the earliest opportunity.

#### *D. Human Health Risk Characterization and Conclusions*

We used a Hazard Quotient (HQ) approach to characterize the noncancer risk associated with the exposures to EGBE. In this case, the HQ is developed by comparing the level of exposure to the IRIS RfC or RfD for EGBE. If the HQ is less than 1, the reference level is not exceeded, and the adverse health effects are unlikely.

Based on our assessment of the information provided in the petition, it is possible to derive a quantitative evaluation of an inhalation HQ for EGBE. Based on our evaluation of the modeling data, we judge that maximum ambient annual average exposures to EGBE are not likely to exceed 0.3 mg/m<sup>3</sup> for a single major source, or 0.5 mg/m<sup>3</sup> for a group of closely located area sources. The reference level to be used in the determination of EGBE's HQ is the RfC of 13 mg/m<sup>3</sup>. This criterion addresses the health effect of concern due to chronic inhalation exposures to EGBE. In addition, the criterion includes the margins of safety built into the IRIS RfC (*i.e.*, any needed uncertainty factors to address sensitive subpopulations and other factors) and is, therefore, protective of sensitive subpopulations.

Using this approach, we calculate an HQ for the maximum annual ambient concentration of EGBE from a single major source to be 0.02. In other words, the EGBE air concentration is 2 percent of the RfC. For closely located area sources, the HQ is 0.04, or 4 percent of the RfC. To be extremely conservative, we might assume that the single major source is located among the group of area sources. In this case, the maximum annual ambient average concentration would be 0.8 mg/m<sup>3</sup> and the HQ would be 0.06, or 6 percent of the RfC. All HQ are well below the health criterion of an HQ of 1. Further, we judge that the