

BMC model, and a total UF of 10 to account for variation in sensitivity within the human population (UF = 10), the EPA determined that the IRIS RfD was 0.5 mg/kg/day.

The IRIS review states that EGBE has been adequately tested in conventional genotoxicity tests for its potential to induce gene mutations in *in vitro* systems and cytogenetic damage in both *in vitro* and *in vivo* systems. The available data do not support a mutagenic or clastogenic potential for EGBE. The EPA's Toxicological Review of EGBE, available at <http://www.epa.gov/iris/toxreviews/0500-tr.pdf#page=68>, states that one laboratory has reported weak genotoxicity responses at toxic doses, though these data are considered to be questionable, may be a result of impurities in the test material.

In addition, the 1999 IRIS describes structure-activity relationship (SAR) analyses that have been conducted to provide insight into EGBE's potential carcinogenicity to humans. These analyses have been found to be useful for agents that are believed to initiate carcinogenesis through Deoxyribonucleic Acid (DNA) reactive mechanisms. Based on chemical structure, EGBE does not resemble any known chemical human carcinogens and is not expected to have electrophilic or DNA reactive activity. The IRIS review states that there are no reliable epidemiologic studies available that address the potential carcinogenicity of EGBE.

The IRIS review utilized a draft report of the results of a 2-year inhalation bioassay performed by the National Toxicology Program (NTP, 1998) using rats and mice that had recently become available. The NTP (1998) report indicates no evidence of carcinogenic activity in male F344/N rats, and equivocal evidence of carcinogenic activity in female F344/N rats based on increased combined incidences of benign and malignant pheochromocytoma (mainly benign) of the adrenal medulla. They also reported some evidence of carcinogenic activity in male B6C3F1 mice based on increased incidences of hemangiosarcoma of the liver, and some evidence of carcinogenic activity in female B6C3F1 mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

The IRIS discusses the relevance of these tumors to humans. For example, the pheochromocytoma in the female rats were indicated as only a marginally significant trend. Further, these types of tumors are difficult to distinguish from

non-neoplastic adrenal medullary hyperplasia, and therefore need to be interpreted with caution. The hemangiosarcoma in livers of male mice appear to be exposure related. However, the increases were slight and, like the forestomach lesions in female mice, were not observed in any other sex or species. There is also evidence to suggest that these cancer lesions in mice are associated with unique aspects of mouse physiology (*i.e.*, the known increased sensitivity of mice to oxidative stress and the existence of a forestomach), and are secondary to noncancer (*i.e.*, hemolysis and forestomach irritation) effects.

The IRIS concludes that because of the uncertain relevance of these tumor increases to humans, the fact that EGBE is generally negative in genotoxic tests, and the lack of human data to support the findings in rodents, the human carcinogenic potential of EGBE, in accordance with the recently proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), cannot be determined at this time, but suggestive evidence exists from rodent studies. Therefore, under existing EPA guidelines, EGBE is judged to be a possible human carcinogen.

Since the publication of NTP's draft report (NTP, 1998) on their 2-year inhalation bioassay of EGBE, and since the IRIS update of December 1999, there has been continued discussion among scientists from government, industry, and academia concerning the human carcinogenic potential of EGBE. The NTP (2000a) finalized their study results without changing their original determination of equivocal evidence of carcinogenic activity in female rats, some evidence of carcinogenic activity in male mice, and some evidence of carcinogenic activity in female mice. These findings by NTP, along with the EPA's conclusion in the 1999 IRIS assessment that the carcinogenic potential of EGBE "cannot be determined at this time, but suggestive evidence exists from rodent studies", prompted scientists from academia and industry to design research projects aimed at determining the mode of action for the formation of the forestomach and liver tumors observed in mice. We report here on recent findings in scientific publications, from scientific meetings and in the EPA (1999b) draft cancer guidelines, to provide an up-to-date evaluation of the mode of action involved in the origin of these tumors in mice and their human relevance.

Establishing the mode of action is critical for determining an effect's relevance to humans and for choosing the approach most appropriate for dose-

response modeling (*i.e.*, whether to use a linear or nonlinear approach). As is extensively discussed in the Agency's interim and draft cancer guidelines (U.S. EPA, 1999b; 2003), in order to determine a chemical's mode of action, one must consider the full range of key influences a chemical or its metabolites might have as an initiator or promoter of the complex carcinogenic process. With this in mind, we evaluated EGBE's role in the formation of female mouse forestomach and male mouse liver tumors that were observed following two-years of inhalation exposure (National Toxicology Program, 2000a). Our August 2003 interim final report provides details of this evaluation.

With regard to forestomach papillomas and carcinoma in female mice, the NTP study (NTP 2000a) shows that at the highest exposure level, 250 ppm, the 10 percent incidence of squamous papilloma and 12 percent combined incidence of squamous cell papillomas or carcinomas were significantly increased over study controls and exceeded the ranges for historical controls of 0–2 percent and 0–3 percent, respectively. This study reports that 8 percent is the highest incidence of forestomach neoplasms that has been observed in contemporary historical controls. NTP (2000a) did not observe significant increases in forestomach papillomas and carcinomas at any other exposure levels in female mice, nor at any exposure level in male mice or either sex of rats.

Recent reviews of available *in vitro* and *in vivo* genotoxicity assays are in agreement that EGBE is not likely to be genotoxic (Commonwealth of Australia, 1996; Elliot and Ashby, 1997; U.S. EPA, 1999a; NTP, 2000a). The NTP (2000a) suggested that EGBE caused chronic irritation leading to forestomach injury including penetrating ulcers and that the observed "neoplasia (papillomas and one carcinoma) was associated with a continuation of the injury/degeneration process."

The Agency believes that EGBE is not genotoxic and that a nonlinear mode of action is principally responsible for the increased forestomach tumor incidence reported by NTP (2000a). However, reports of weak positive effects by EGBE at high concentrations in some *in vitro* assays (see discussion in full report located in the docket under "Other Possible Modes of Action for Forestomach Tumor Development in Female Mice") indicate the potential for contribution from direct interaction of butoxyacetaldehyde (BAL), an EGBE metabolite, with DNA. While these weak positive findings may be due to study design artifacts (*e.g.*, changes in