

information that would cause EPA to revise its MCLG estimates. New toxicology studies on reproductive and developmental effects and cancer are summarized in sections III.B. and III.D. of today's proposal.

EPA is proposing new MCLGs for TCAA and MCAA. The health effects information and studies described in the following two sections that support the proposed MCLGs are summarized from the Addendum to the Criteria Document for Monochloroacetic Acid and Trichloroacetic Acid (USEPA 2003b). The occurrence of MCAA and TCAA are discussed in the *Stage 2 Occurrence Assessment for Disinfectants and Disinfection Byproducts* (USEPA 2003o). a. Trichloroacetic acid. In the final Stage 1 DBPR, EPA based its health effects assessment of TCAA on developmental toxicity and limited evidence of carcinogenicity (USEPA 1998c). Since then, the Agency has decided that the RfD based on a developmental LOAEL yields a less conservative RfD than that based on liver toxicity derived from the study by DeAngelo *et al.* (1997). Thus, the Agency has reassessed the health effects of TCAA based on liver toxicity and revised the RfD and MCLG.

TCAA induces systemic, noncancer effects in animals and humans that can be grouped into three categories: metabolic alterations, liver toxicity; and developmental toxicity. The primary site of TCAA toxicity is the liver (USEPA 1994a; Dees and Travis, 1994; Acharya *et al.* 1995; Acharya *et al.* 1997; DeAngelo *et al.* 1997).

The liver has consistently been identified as a target organ for TCAA toxicity in short-term (Goldsworthy and Popp, 1987; DeAngelo *et al.* 1989; Sanchez and Bull, 1990) and longer-term (Bull *et al.* 1990; Mather *et al.* 1990; Bhat *et al.* 1991) studies. Peroxisome proliferation has been a primary endpoint evaluated, with mice reported to be more sensitive to this effect than rats. More recent studies have confirmed these earlier findings. TCAA-induced peroxisome proliferation was observed in B6C3F1 mice exposed for 10 weeks to doses as low as 25 mg/kg/day (Parrish *et al.* 1996), while in rats exposed to TCAA for up to 104 weeks (DeAngelo *et al.* 1997), peroxisome proliferation was observed at 364 mg/kg/day, but not at 32.5 mg/kg/day. Increased liver weight and significant increases in hepatocyte proliferation have been observed in short-term studies in mice at doses as low as 100 mg/kg/day (Dees and Travis, 1994), but no increase in hepatocyte proliferation was noted in rats given TCAA at similar doses (DeAngelo *et al.* 1997). More

clearly adverse liver toxicity endpoints, including increased serum levels of liver enzymes (indicating leakage from cells) or histopathological evidence of necrosis, have been reported in rats, but generally only at high doses. For example, in a rat chronic drinking water study, increased hepatocyte necrosis was observed at a dose of 364 mg/kg/day (DeAngelo *et al.* 1997).

In the DeAngelo *et al.* (1997) study, groups of 50 male F344 rats were administered TCAA in drinking water, at 0, 50, 500, or 5000 mg/L, resulting in time-weighted mean daily doses of 0, 3.6, 32.5, or 364 mg/kg for 104 weeks. There were no significant differences in water consumption or survival between the control and treatment groups. Exposure to the high dose of TCAA resulted in a significant decrease in body weight of 11% at the end of the study. The absolute but not relative liver weight was decreased at the high dose. Complete necropsy and histopathology examination showed mild hepatic cytoplasmic vacuolization in the two low-dose groups, but not in the high-dose group. The severity of hepatic necrosis was increased mildly in the high-dose animals. Analyses of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities at the end of exposure showed a significant decrease in AST activity in the mid-dose group and a significant increase in ALT level in the high-dose group. Since increased serum ALT or AST levels reflect hepatocellular necrosis, the increased ALT at the high dose is considered an adverse effect, while a non-dose related decrease of AST is not. Peroxisome proliferation was increased significantly in the high-dose animals. There was no evidence of any exposure-related increase in hepatocyte proliferation. Based on the significant decrease in body weight ($\geq 10\%$), minimal histopathology changes, and increased serum ALT level, the high dose of 364 mg/kg/day is considered the LOAEL and the mid dose of 32.5 mg/kg/day is considered the NOAEL.

There are no reproductive toxicity studies of TCAA. The results of an *in vitro* fertilization assay indicated that TCAA might decrease fertilization (Cosby and Dukelow, 1992). The available data suggest that TCAA is a developmental toxicant. TCAA increased resorptions, decreased implantations, and increased fetal cardiovascular malformations when administered to pregnant rats at 291 mg/kg/day (Johnson *et al.* 1998) on gestation days 1–22. In another study, decreased fetal weight and length, and increased cardiovascular malformations were

observed when pregnant rats were administered 330 mg/kg/day TCAA by gavage during gestation days 6 to 15 (Smith *et al.* 1989). Neither of these studies identified a NOAEL. The results of *in vitro* developmental toxicity assays, including mouse and rat whole-embryo culture (Saillenfait *et al.* 1995; Hunter *et al.* 1996) and frog embryo teratogenesis assay—*Xenopus* (FETAX) (Fort *et al.* 1993) yielded positive results. The *Hydra* test system (Fu *et al.* 1990) produced negative results.

TCAA has been reported to induce liver tumors in mice but not in rats (USEPA 1994a). This observation has also been made in more recent drinking water studies. Pereira (1996) observed an increased incidence of hepatocellular adenomas and carcinomas in female B6C3F1 mice at doses of 262 mg/kg/day and higher after 82 weeks. In contrast, no increase in neoplastic liver lesions were found in F344 rats given doses up to 364 mg/kg/day for 104 weeks (DeAngelo *et al.* 1997). In addition, a variety of recent mechanistic studies have observed that TCAA either induced or promoted liver tumors in mice (Ferreira-Gonzalez *et al.* 1995; Pereira and Phelps, 1996; Tao *et al.* 1996; Latendresse and Pereira, 1997; Stauber and Bull, 1997; Tao *et al.* 1998).

Recent mutagenicity data have provided mixed results (Giller *et al.* 1997; DeMarini *et al.* 1994; Harrington-Brock *et al.* 1998). TCAA did not induce oxidative DNA damage in mice following dosing for either 3 or 10 weeks (Parrish *et al.* 1996). Studies on DNA strand breaks and chromosome damage produced mixed results (Nelson and Bull, 1988; Chang *et al.* 1991; Mackay *et al.* 1995; Harrington-Brock *et al.* 1998).

According to the 1999 Draft Guidelines for Carcinogen Risk Assessment (USEPA 1999a), a compound is appropriately classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" when "the evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects but is judged not sufficient for a conclusion as to human carcinogenic potential". Based on uncertainty surrounding the relevance of the liver tumor data in B6C3F1 mice, TCAA can best be described as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" under the 1999 Draft Guidelines for Carcinogen Risk Assessment. Thus a quantitative estimate of cancer potency is not supported.