

The RfD for TCAA of 0.03 mg/kg/day is based on the NOAEL of 32.5 mg/kg/day for liver histopathological changes identified by DeAngelo *et al.* (1997). The RfD includes an uncertainty factor of 1000 (composite uncertainty factor consisting of three factors of 10 chosen to account for extrapolation from a NOAEL in animals, inter-individual variability in humans, and insufficiencies in the database, including the lack of full histopathological data in a second species, the lack of a developmental toxicity study in second species, and the lack of a multi-generation reproductive study).

The MCLG is calculated to be 0.02 mg/L using the following assumptions: an adult tap water consumption of 2 L

of tap water per day for a 70 kg adult, a relative source contribution (RSC) of 20%, and an additional safety factor to account for possible carcinogenicity. EPA has traditionally applied an additional safety factor of 1–10 beyond the uncertainty factors included in the RfD to the MCLG to account for possible carcinogenicity in cases where there is limited evidence of carcinogenicity from drinking water, considering weight of evidence, pharmacokinetics, potency and exposure (USEPA 1994b, p.38678). EPA is proposing this additional safety factor of 10 for TCAA for the following reasons: TCAA causes liver tumors in mice but does not do so in rats. In addition, although peroxisome proliferation (a mode of action of limited relevance to humans) may play

a role in the development of the mouse tumors, rats also exhibit a peroxisomal proliferative response after exposure to TCA, yet do not develop tumors. Other data suggest that promotion of initiated cells and/or disrupted cell signaling may be involved in the mode of action for the mouse tumors. Together these factors argue against quantification of the mouse liver tumors using linear extrapolation from the dose-response curve, but are not sufficient to rule out concern for a tumorigenic response. Accordingly, EPA has employed the ten-fold additional safety factor in determination of the Lifetime Health Advisory for TCAA. EPA requests comment on the use of 10 as the additional safety factor for possible carcinogenicity.

$$\text{MCLG for TCAA} = \frac{(0.03 \text{ mg/kg/day})(70 \text{ kg})(20\%)}{(2 \text{ L/day})(10)} = 0.02 \text{ mg/L (rounded)}$$

An RSC factor of 20% is used to account for exposure to TCAA in sources other than tap water, such as ambient air and food. Although TCAA is nonvolatile and inhalation while showering is not expected to be a major contribution to total dose, rain waters contain 0.01–1.0 µg/L of TCAA (Reimann *et al.* 1996) and it can be assumed to be detected in the atmosphere. Limited data on concentrations of TCAA in air (NATICH 1993) indicate inhalation of TCAA in ambient air may contribute to overall exposure. Concentrations of TCAA that have been measured in a limited selection of foods including vegetables, fruits, grain and bread (Reimann *et al.* 1996) are comparable to that in water. About 3 to 33% of TCAA in cooking water have been reported to be taken up by the food during cooking in a recent research summary (Raymer *et al.* 2001). In addition, there are uses of chlorine in food production and processing, and TCAA may occur in food as a byproduct of chlorination (USEPA 1994a). Therefore, ingestion of TCAA in food may also contribute to the overall exposure. A recent dermal absorption study of DCAA and TCAA from chlorinated water suggested that the dermal contribution to the total doses of DCAA and TCAA from routine household uses of drinking water is less than 1% (Kim and Weisel, 1998).

b. *Monochloroacetic acid*. Subchronic and chronic oral dosing studies suggest that the primary targets for MCAA-induced toxicity include the heart and nasal epithelium. In a 13-week oral gavage study, decreased heart weight

was observed at 30 mg/kg/day and cardiac lesions progressed in severity with increasing dose. Liver and kidney toxicity were only observed at higher doses (NTP 1992). In a two-year study, decreased survival and nasal and forestomach hyperplasia were observed in mice at 50 mg/kg/day (NTP 1992). A more recent study confirms the heart and nasal cavities as target sites for MCAA. DeAngelo *et al.* (1997) noted decreased body weight at 26.1 mg/kg/day and myocardial degeneration and inflammation of the nasal cavities in rats exposed to doses of 59.9 mg/kg/day for up to 104 weeks.

No studies were located on the reproductive toxicity of MCAA and the potential developmental toxicity of MCAA has not been adequately tested. Two developmental toxicity studies were identified. Johnson *et al.* (1998) reported markedly decreased maternal weight gain, but no developmental effects, in rats exposed to 193 mg/kg/day MCAA through gestation days 1–22, only fetal heart was examined. In contrast, in a published abstract, Smith *et al.* (1990) reported an increase in cardiovascular malformations when pregnant rats were exposed to 140 mg/kg/day; this was also the LOAEL for maternal toxicity, based on marked decreases in weight gain. MCAA was noted as a potential developmental toxicant in *in vitro* screening assays using *Hydra* (Fu *et al.* 1990; Ji *et al.* 1998).

MCAA has yielded mixed results in genotoxicity assays (USEPA 1994a; Giller *et al.* 1997), but has not induced a carcinogenic response in chronic

rodent bioassays (NTP 1992; DeAngelo *et al.* 1997). In chronic oral gavage studies, a LOAEL of 15 mg/kg/day (the lowest dose tested) for decreased survival was identified in rats. In mice the NOAEL was 50 mg/kg/day and the LOAEL was 100 mg/kg/day for nasal and forestomach epithelium hyperplasia (NTP 1992). In a more recent chronic study, DeAngelo *et al.* (1997) reported a LOAEL of 3.5 mg/kg/day in rats given MCAA in their drinking water, based on increased absolute and relative spleen weight. Although spleen weight was decreased at the mid and high doses, this might reflect the masking effect of overt toxicity. As evidence for this, decreased body weight (>10%), liver, kidney, and testes weight changes were reported beginning at the next higher dose of 26.1 mg/kg/day. No increased spleen weight was reported in the NTP (1992) bioassays, but the lowest dose in rats caused severe toxicity, and the lowest dose in mice was more than an order of magnitude higher than the LOAEL in the DeAngelo *et al.* (1997) study.

According to the 1999 Draft Guidelines for Carcinogen Risk Assessment (USEPA 1999a), a compound is appropriately classified as “Not Likely to be Carcinogenic to Humans” when it has “been evaluated in at least two well-conducted studies in two appropriate animal species without demonstrating carcinogenic effects.” MCAA can best be described as “Not Likely to be Carcinogenic to Humans” under the 1999 Draft Guidelines for Carcinogen Risk Assessment.