EXECUTIVE SUMMARY

t-Butanol – Oral Risk Assessment CAS # 75-65-0			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (benchmark dose level)	133	mg/kg-day	From a chronic rat study
Oral RfD (oral reference dose)	1	mg/kg-day	From a chronic rat study
TAC (total allowable concentration)	9	mg/L	For a 70 kg adult drinking 2 L/day, with a 20% relative source contribution for water
SPAC (single product allowable concentration)	0.9	mg/L	For a 70 kg adult drinking 2 L/day
STEL (short term exposure level)	40	mg/L	From a subchronic study, for a 10 kg child drinking 1 L/day

KEY STUDY	National Toxicology Program (NTP). 1995. Toxicology and Carcingoenesis Studies of t-Butyl Alcohol (CAS No. 75-65-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). Technical Report Series No. 436.
CRITICAL EFFECT	Absolute and relative kidney weight increases in female rats.
UNCERTAINTY FACTORS	• 10x for interspecies extrapolation because there are differences in rate of elimination and identity and quantity of metabolites between rats and humans • 10x for intraspecies extrapolation • 1x for study duration, as a chronic study was used • 1x for LOAEL-to-NOAEL conversion, as benchmark dose modeling was used • 1x for database deficiency, as the required studies are all available, although the two-generation reproduction study on t-butanol is as a metabolite of methyl t-butyl ether The total uncertainty factor is therefore 100x.
TOXICITY SUMMARY	t-Butanol is a relatively nontoxic compound with acute effects similar to ethanol. Subchronic and chronic studies in rats identified the kidney as the target organ in both males and females, based on organ weight increases and pathology. However, male rat kidney effects were discounted as due to α-2μ-globulin accumulation, an effect that is not relevant to human health. Mice showed hypoactivity due to the high dose levels used, and mild kidney effects in a subchronic study, but showed thyroid follicular cell hyperplasia, adenoma, and a single high-dose carcinoma in a chronic study. The kidney effects in rats resulted in a lower oral RfD than the oral RfD in mice, considering the thyroid effects to have a threshold. Relative female rat kidney weights were used for the risk assessment calculations of both the TAC and the STEL. Studies in rats and mice suggest that t-butanol is not a developmental toxicant. A two-generation reproduction study of methyl t-butyl ether, which is metabolized to t-butanol and formaldehyde, showed no effects that could be attributed to t-butanol. Evidence suggests that t-butanol is not a genotoxic chemical, based on a number of *in vitro* genetic toxicity studies. However, based on the chronic studies in rats and mice, the "*data are inadequate for an assessment of human carcinogenic potential*" of t-butanol. No adequate or reliable human epidemiological study exists. Long-term animal studies in rats produced carcinogenic responses in male rats due to an α-2μ-globulin effect that is of no relevance to human health. Relevant kidney weight and histopathology effects were seen in female rats. Long-term animal studies in mice produced hyperplasia, adenoma, and one high-dose carcinoma of the thyroid, of questionable relevance to human health because rodents are significantly more sensitive than humans to thyroid effects.
CONCLUSIONS	The uncertainty factors for interspecies and intraspecies extrapolation, used in conjunction with the female relative kidney weight $BMDL_{10}$ values, should ensure that the drinking water action levels established in this document are adequately protective of public health.