EXECUTIVE SUMMARY

p-tert-Butylphenol – Oral Risk Assessment CAS # 98-54-4			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	70	mg/kg-day	From a two-generation reproduction study in rats
Oral RfD (oral reference dose)	0.07	mg/kg-day	From a two-generation reproduction study in rats with a 1000x total uncertainty factor
TAC (total allowable concentration)	0.5	mg/L	For a 70 kg adult drinking 2 L/day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.05	mg/L	From the TAC, using the default 10 sources of *p-tert*-butylphenol in drinking water
STEL (short term exposure level)	7	mg/L	From a rat repeat dose reproductive / developmental screening test, for a 10 kg child drinking 1 L/day

EXPOSURE SUMMARY	Human exposure to *p-tert*-butylphenol may occur through its use as a component of resins, adhesives, and epoxy coatings, including those used in food contact articles and drinking water components.
KEY STUDY	Clubb S and Jardine L. 2006. *p-tert*-Butylphenol two generation reproduction study in rats. Charles River Laboratories Study Number 493595.
CRITICAL EFFECT	Decreased litter size and pup weights in F1 and F2 offspring. In F0 parents, reduced body weight gain in both sexes and reduced relative weight of ovaries and vaginal epithelial atrophy in females, in the two-generation reproduction study in rats.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 3x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 1000x
TOXICITY SUMMARY	*p-tert*-Butylphenol has low acute toxicity in rats, with LD_{50} values of 2,500-4,000 mg/kg. The neat substance is moderately irritating to skin and highly irritating to eyes, and human direct skin exposure results in local depigmentation. *p-tert*-Butylphenol exhibits weak estrogenic activity *in vitro*. In a repeat dose reproductive / developmental screening test in rats, there were no adverse systemic, reproductive, or developmental effects observed at doses up to 200 mg/kg-day. In a two-generation reproduction study in rats using doses of 0, 70, 200, and 600 mg/kg-day, there was a significant decrease in body weight gain and food consumption in male and female parents, and reductions in litter size and pup weights in F1 and F2 offspring at doses of ≥ 200 mg/kg-day. A dose-dependent reduction of relative weights of ovaries and adrenal glands and increased vaginal epithelium atrophy was also seen in females at 200 mg/kg-day. The NOAEL for parental and developmental effects was 70 mg/kg-day. Oral *p-tert*-butylphenol caused forestomach hyperplasia and forestomach papillomas in male hamsters at a dietary dose of ~1,250 mg/kg-day for 20 weeks; a 5% reduction in mean body weight which was not biologically significant, and a 20% increase in liver weight, not associated with any histopathology was considered adaptive. Forestomach hyperplasia developed in rats given *p-tert*-butylphenol alone at ~750 mg/kg-day for 51 weeks, and treatment with *p-tert*-butylphenol promoted the development of forestomach tumors in rats if first initiated by treatment with N-methyl-N'-nitrosoguanidine. A significant 16% decrease in mean body weight was also observed. The effects of *p-tert*-butylphenol were less severe than the effects of butylated hydroxyanisole, and were attributed to cytotoxicity at high doses. *p-tert*-Butylphenol was negative in three bacterial reverse mutation assays and in *in vitro* chromosomal aberration assays with and without activation in rat lymphocytes and without activation in rat liver epithelial-type cells. Another chromosomal aberration assay in Chinese hamster lung cells reported structural chromosomal aberrations in the presence of metabolic activation and polyploidy with and without activation; it was aneugenic when evaluated by the fluorescence *in situ* hybridization technique. The substance was negative when evaluated in an *in vivo* bone marrow micronucleus test in mice. In the absence of chronic studies, the carcinogenicity of *p-tert*-butylphenol *cannot be determined*.
CONCLUSIONS	Based on the available toxicity data, selection of the most sensitive endpoint as the critical effect, and the applied uncertainty factors, the derived drinking water action levels are protective of the public health.