EXECUTIVE SUMMARY

p-Chloro-m-Cresol – Oral Risk Assessment CAS # 59-50-7			
PARAMETER	**LEVEL**	**UNITS**	**CALCULATED:**
NOAEL (no-observed-adverse-effect level)	103	mg/kg-day	From a 2-year rat feeding study
Oral RfD (oral reference dose)	0.1	mg/kg-day	From a 2-year rat feeding study
TAC (total allowable concentration)	0.7	mg/L	For a 70 kg adult drinking 2 L/day with a 20% Relative Source Contribution from drinking water.
SPAC (single product allowable concentration)	0.07	mg/L	For a 70 kg adult drinking 2 L/day.
STEL (short term exposure level)	1	mg/L	For a 10 kg child drinking 1 L/day.

KEY STUDY	Leser, K.H. 1992. Chronic Toxicity and Carcinogenicity Study in Wistar Rats (Administration in Feed for 104 Weeks). Unpublished study prepared by Bayer AG Toxicological Institute. Wuppertal, Germany. Study Number T9030673.
CRITICAL EFFECTS	In males, increased incidence of unilateral papillary necroses, truncated papillae, and cortical dilations and fibrosis of the kidneys.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic • 1x for LOAEL to NOAEL • 10x for database deficiencies The total uncertainty factor is therefore 1,000x.
TOXICITY SUMMARY	The critical study was a two-year feeding study in which rats were administered p-chloro-m-cresol at 0, 21, 103.1, or 558.9 mg/kg-day in males and 0, 27.7, 134.3, or 743.5 mg/kg-day in females. In mid-dose females and low-dose males, statistically significant pituitary adenomas were observed. In mid- and high-dose males, a statistically significant increasing trend of testicular interstitial cell adenomas was observed. All neoplastic effects were within historical control ranges for the laboratory, thus were not considered biologically significant. The non-neoplastic effects observed in females included a dose-related trend of animals with "poor general condition," a statistically significant reduction in mean body weight, a statistically significant, but not dose related, decrease in mean absolute brain weight, and depression of the brain due to an enlarged pituitary at all doses. The brain effects were considered by the authors of this risk assessment to be related to the pituitary adenomas, which were not considered biologically significant, since they were within the historical control range. In high-dose males, an increased incidence of unilateral papillary necroses, truncated papillae, and cortical dilations and fibrosis of the kidneys were observed. Also, an increase in unilateral reduced spermatozoa in the epididymides and unilateral seminiferous tubule degeneration were observed at the mid dose, and combined (unilateral and bilateral) reduced spermatozoa at the high dose. The reproductive effects were not considered by the authors of this risk assessment to be biologically significant based on the high background incidence of these effects in this rat strain. The NOAEL for the study can be considered 103.1 mg/kg-day, based on the male rat kidney effects. In a developmental study, rats received p-chloro-m-cresol by gavage at 0, 30, 100 or 300 mg/kg-day from days 6-15 of gestation. For dams, the NOAEL can be considered 100 mg/kg-day, based on clinical signs of toxicity and decreased mean body weight gain. In offspring, the NOAEL is also 100 mg/kg-day, based on the statistically significant decrease in mean fetal weight per litter. p-Chloro-m-cresol tested positive in one *Salmonella* reverse mutation assay in Strain TA97 with metabolic activation, despite testing negative in all other tested strains in four other *Salmonella* studies, including Strain TA97 with rat and hamster S9 activation. p-Chloro-m-cresol tested positive for SOS DNA repair, although cytotoxicity was observed at all doses, but was negative in chromosomal aberration and unscheduled DNA synthesis assays.
CONCLUSIONS	Chronic oral exposure to p-chloro-m-cresol results in renal pathology in male rats. Due to the lack of human and second-species animal studies, the carcinogenic potential of p-chloro-m-cresol in humans *cannot be determined*. However, the weight of evidence suggests that p-chloro-m-cresol does not cause cancer in rats and is not genotoxic. Based on the uncertainty factors used to account for the database deficiencies, the drinking water action levels are considered adequately protective of human health.