EXECUTIVE SUMMARY

2-CHLORO-1,4-BENZENEDIAMINE – Oral Risk Assessment CAS # 615-66-7			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (95% confidence limit at 10% response level)	15	mg/kg-day	From a chronic feeding study in rats
Oral RfD (oral reference dose)	0.05	mg/kg-day	From the $BMDL_{10}$ with a 300x total uncertainty factor
TAC (total allowable concentration)	0.3	mg/L	For a 70 kg adult drinking 2 L/day, with a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.03	mg/L	From the TAC, assuming 10 potential sources of 2-chloro-1,4-benzenediamine in drinking water
STEL (short term exposure level)	0.5	mg/L	From a chronic rat feeding study and based on a 10 kg child drinking 1 L/day.

KEY STUDY	NTP/NCI (National Toxicology Program/National Cancer Institute). 1978a. Bioassay of 2-Chlorophenylenediamine Sulfate for Possible Carcinogenicity. Technical Report Series No. 113 DHEW Publication No. (NIH) 78-1368, U.S. Department of Health Education and Welfare, National Cancer Institute, Bethesda, MD 20014.
CRITICAL EFFECT	Transitional cell hyperplasia of the kidney and renal pelvis in male rats.
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for extrapolation from a less-than-lifetime study to lifetime duration • 1x for extrapolation from a LOAEL to a NOAEL • 3x for database deficiencies. The total uncertainty factor is, therefore, 300x.
TOXICITY SUMMARY	No oral data in humans were available. 2-Chloro-1,4-benzenediamine sulfate did not cause a statistical increase in any tumor type in rats or mice after chronic dietary administration. However, transitional cell hyperplasia of the kidney and renal pelvis was observed in male and female rats at increased incidence compared to controls. The incidence of renal epithelial hyperplasia was dose related in males, but a NOAEL could not be identified. Hepatic focal necrosis was observed in male mice at an increased incidence compared to controls, but the incidence was not dose-related. No kinetic and limited metabolism studies in humans and laboratory animals were identified for 2-chloro-1,4-benzenediamine. In the *Salmonella typhimurium* reverse mutation assay, 2-chloro-1,4-benzenediamine sulfate produced dose-related increases in revertant colonies of more than twice the background level at higher doses but in the absence of cytotoxicity. 2-Chloro-1,4-benzenediamine was negative in the *in vivo* alkaline single cell assay (Comet assay) and in the alkaline elution assay for the detection of hepatic DNA damage. The limited genotoxicity data identified for 2-chloro-1,4-benzenediamine or its sulfate salt precluded definitive conclusions regarding its genotoxic potential. However, structure-activity relationship studies suggest that the genotoxic or carcinogenic potential of 2-chloro-1,4-benzenediamine is less than that of 4-chloro-1,2-benzenediamine or 4-chloro-1,3-benzenediamine. Further, no statistical increases in tumors were observed after chronic feeding. The *data are inadequate for an assessment of human carcinogenic potential* of 2-chloro-1,4-benzenediamine or its sulfate salt. For the purposes of this risk assessment, 2-chloro-1,4-benzenediamine was considered a non-carcinogen. A NOAEL could not be identified for the critical effect of transitional cell hyperplasia of the kidney and renal pelvis in male rats. A $BMDL_{10}$ of 15 mg/kg-day was determined, since the incidence was dose-related. This effect was considered non-neoplastic, since the rats were treated for at least 24 months, as recommended by current U.S. EPA health effects testing guidelines, and the effect did not progress into renal tumors.
CONCLUSIONS	The drinking water action levels developed in this risk assessment are protective of public health since they were developed based on chronic oral data for 2-chloro-1,4-benzenediamine sulfate from the most sensitive endpoint and laboratory animal species.