EXECUTIVE SUMMARY

4-CHLORO-1,2-BENZENEDIAMINE – Oral Risk Assessment CAS # 95-83-0			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMDL_{10}$ (95% confidence limit at 10% response level)	45	mg/kg-day	From a chronic feeding study in rats
10^{-5} Cancer Risk Level	0.005	mg/kg-day	From the $BMDL_{10}$
Oral Slope Factor	0.0022	$mg/kg\text{-}day^{-1}$	From the $BMDL_{10}$
Drinking Water Unit Risk (at the 1×10^{-6} cancer risk level)	0.063×10^{-6}	$\mu g/L^{-1}$	From the oral slope factor
TAC (total allowable concentration)	0.2	mg/L	For a 70 kg adult drinking 2 L/day
SPAC (single product allowable concentration)	0.02	mg/L	From the TAC, assuming 10 potential sources of 4-chloro-1,2-benzenediamine in drinking water
STEL (short term exposure level)	Not applicable	Not applicable	The STEL is not derived for a genotoxic carcinogen

KEY STUDY	National Toxicology Program (NTP)/National Cancer Institute (NCI). 1978. Bioassay of 4-Chloro-o-phenylenediamine For Possible Carcinogenicity. DHEW Publication No. (NIH) 78-1313, U.S. Department of Health Education and Welfare, National Cancer Institute, Bethesda, MD 20014.
CRITICAL EFFECT	Combined urinary bladder tumors and precursor effects, including urinary bladder transitional cell carcinomas, papillary carcinomas, transitional cell papillomas, papillomas not otherwise specified, and urinary bladder papillomatosis in male and female rats.
UNCERTAINTY FACTORS	No uncertainty factors were applied in this risk assessment, since an oral RfD was not determined. The carcinogenic effects observed in chronic animal studies were analyzed using linear extrapolation.
TOXICITY SUMMARY	No human data were located. Hepatic focal hyperplasia and renal pyelonephritis were among the non-neoplastic effects observed in rats at dose-related increased incidences compared to controls after dietary administration of 4-chloro-1,2-benzenediamine for 78 weeks. Urinary bladder tumors and precursor effects were among the neoplastic effects observed in male and female rats. Uterine/endometrial hyperplasia was observed in female mice at an increased incidence compared to controls after chronic dietary administration of 4-chloro-1,2-benzenediamine for 78 weeks, and combined hepatocellular adenomas and carcinomas were observed in male or female mice at a statistically increased incidence compared to controls. No kinetic or metabolism studies in humans or laboratory animals were identified for 4-chloro-1,2-benzenediamine. The weight of evidence suggests that 4-chloro-1,2-benzenediamine is genotoxic *in vivo* and *in vitro*. 4-Chloro-1,2-benzenediamine caused mutations in *Salmonella typhimurium* with metabolic activation and in hepatocytes isolated from Big Blue™ mice exposed *in vivo*. 4-Chloro-1,2-benzenediamine also caused chromosomal aberrations *in vivo* in mouse bone marrow cells and produced dose-related increases in micronucleated polychromatic erythrocytes in the *in vivo* mouse bone marrow micronucleus assay. Sister chromatid exchanges were also observed *in vivo*, but the effect was not dose-related. Positive results in an *in vivo* alkaline single cell (Comet) assay were observed in the liver, but not in other organs. Unscheduled DNA synthesis was detected in an *in vitro* DNA repair assay in primary rat hepatocytes. 4-Chloro-1,2-benzenediamine was positive in an *in vitro* microscreen prophage-induction assay with metabolic activation in *Escherichia coli* for the ability to induce DNA damage. A 10^{-5} cancer risk level for 4-chloro-1,2-benzenediamine was extrapolated from the chronic feeding $BMDL_{10}$ of 45 mg/kg-day, which was based on the combined incidence of urinary bladder tumors and precursors in rats, since these tumors represented the most sensitive endpoint in laboratory animals.
CONCLUSIONS	Based on the statistically increased tumor incidences in rats and mice chronically administered 4-chloro-1,2-benzenediamine, and its positive *in vitro* and *in vivo* genotoxicity data, the weight of evidence supports that 4-chloro-1,2-benzenediamine is *likely to be carcinogenic to humans*. The drinking water action levels derived in this risk assessment are protective of public health since they were based on chronic oral data for 4-chloro-1,2-benzenediamine from the most sensitive endpoint and laboratory animal species.