EXECUTIVE SUMMARY

4-CHLORO-1,3-BENZENEDIAMINE – Oral Risk Assessment CAS # 5131-60-2			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no observable adverse effect level)	140	mg/kg-day	From a chronic feeding study in rats
Oral RfD (oral reference dose)	0.5	mg/kg-day	From the chronic feeding study NOAEL in female rats
TAC (total allowable concentration)	0.3	mg/L	For a 70 kg adult drinking 2 L water/day with a 300x uncertainty factor and a 10x safety factor
SPAC (single product allowable concentration)	0.03	mg/L	From the TAC, assuming 10 potential sources of 4-chloro-1,3-benzenediamine in drinking water
STEL (short term exposure level)	0.3	mg/L	Set equal to the TAC due to inadequate information to establish a higher action level.

KEY STUDY	National Toxicology Program (NTP)/National Cancer Institute (NCI). 1978. Bioassay of 4-Chloro-m-phenylenediamine For Possible Carcinogenicity. Technical Report Series No. 85 DHEW Publication No. (NIH) 78-1335, U.S. Department of Health Education and Welfare, National Cancer Institute, Bethesda, MD 20014.
CRITICAL EFFECT	The critical effect was reduced mean body weight in male and female rats administered 4-chloro-1,3-benzenediamine in feed for two years.
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 human epidemiological, kinetic, or metabolic data were available for 4-chloro-1,3-benzenediamine. Reduced mean body weight, renal nephropathy, and hepatic basophilic cytoplasmic changes were observed in male and female F344 rats at an increased incidence compared to concurrent controls after dietary administration of 4-chloro-1,3-benzenediamine for 78 weeks. Renal nephropathy was also observed in control rats. The kidney and liver changes are common findings among control F344 rats from chronic studies, thus were not considered treatment-related. Tumors observed at increased incidences compared to controls included adrenal pheochromocytomas and testicular interstitial-cell tumors in male rats. Both tumor types in rat adrenal glands and testes occurred at incidences within historical control ranges. Thus, those findings were not considered treatment-related. Dose-related reductions in mean body weight in male and female mice and renal glomerulonephritis in male mice were observed compared to concurrent controls after dietary administration of 4-chloro-1,3-benzenediamine for 78 weeks. The combined incidence of hepatocellular carcinomas and adenomas was increased compared to controls in female mice. The biological significance of the hepatocellular tumors in mice is unclear, since the incidence was within some published historical control ranges but outside others. Further, there is a high spontaneous incidence of hepatocellular tumors in B6C3F1 mice. The weight of evidence suggests that 4-chloro-1,3-benzenediamine is genotoxic *in vitro*. In the absence of cytotoxicity, 4-chloro-1,3-benzenediamine was mutagenic in *S. typhimurium* with and without metabolic activation. It also induced chromosomal aberrations and sister chromatid exchanges *in vitro*. No *in vivo* genetic toxicity data were available. Since 4-chloro-1,3-benzenediamine was considered negative for carcinogenicity in the rat but equivocal in the mouse, and due to the positive *in vitro* but lack of *in vivo* genotoxicity data, the weight of evidence supports the conclusion that there is *inadequate information to assess carcinogenic potential* (U.S. EPA, 2005) resulting from oral exposure to 4-chloro-1,3-benzenediamine.
CONCLUSIONS	Reduced mean body weight in rats was considered the critical effect. Rats were considered to be more sensitive than mice since the administered doses were a magnitude lower in rats. The drinking water action levels derived in this risk assessment are protective of public health, since they were based on chronic oral data from the most sensitive laboratory animal species. Further, a safety factor of 10x was applied to the TAC to address the positive *in vitro* genotoxic data and carcinogenic potential demonstrated by 4-chloro-1,3-benzenediamine.