EXECUTIVE SUMMARY

Hexamethylenediamine – Oral Risk Assessment CAS # 124-09-4			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	150	mg/kg-day	From a 2-generation reproduction study in rats.
Oral RfD (oral reference dose)	2	mg/kg-day	From a 2-generation reproduction study in rats with a 100x uncertainty factor.
TAC (total allowable concentration)	10	mg/L	From the oral RfD, for a 70 kg adult drinking 2L/day with a default 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	1	mg/L	From the TAC, assuming the default 10 sources of hexamethylenediamine in drinking water.
STEL (short term exposure level)	20	mg/L	From a developmental study in rats, for a 10 kg child drinking 1L/day

KEY STUDY	Short, R.D, F.R. Johannsen, and J.L. Scharden. 1991. A two-generation reproduction study in rats receiving diets containing hexamethylenediamine. Fundamental and Applied Toxicology. 16 : 490-494.
CRITICAL EFFECT	Decreased parental body weight, decreased pup weight, decreased absolute testicular weight and decreased litter size.
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies variability • 1x for extrapolation from a less-than-lifetime study to lifetime duration • 1x for extrapolation from a LOAEL to a NOAEL • 1x for database deficiencies. Therefore, the total uncertainty factor is 100x.
TOXICITY SUMMARY	The only human toxicity data were from a metabolism study in which the excretion of hexamethylenediamine was determined to be a rapid process. A possible pathway for the metabolism of hexamethylenediamine to mono-acetylated hexamethylenediamine and 6-aminohexanoic acid was proposed. *In vitro* metabolism data using mouse fibroblasts suggested that hexamethylenediamine inhibited the activity of ornithine decarboxylase, an enzyme involved in the biosynthesis of polyamines. Toxicological data available for hexamethylenediamine in laboratory animals included short-term, subchronic, two-generation reproduction, developmental and genetic toxicity studies. The critical study chosen to derive the oral RfD was a two-generation reproduction study in which rats were administered hexamethylenediamine in the diet at 0, 50, 150, or 500 mg/kg-day. The NOAEL identified was 150 mg/kg-day, based on decreased parental body weight, decreased pup weight, decreased absolute testicular weight and decreased litter size. Hexamethylenediamine administration did not affect reproductive success. *Salmonella typhimurium* reverse mutation and *in vivo* and *in vitro* chromosomal aberration assays showed hexamethylenediamine was not genotoxic. An *in vivo* micronucleus assay showed an increase in polychromatic erythrocytes in the total erythrocyte population with no increase in micronucleated normochromatic or polychromatic erythrocytes.
CONCLUSIONS	Due to the lack of epidemiological data in humans or chronic data in laboratory animals, there is *inadequate information to assess the carcinogenic potential* of hexamethylenediamine. Decreased parental body weight, decreased pup weight, decreased absolute testicular weight and decreased litter size in the two-generation reproduction study were the most sensitive endpoints of toxicity observed in the available studies. Based on the identified critical effects and the uncertainty factors applied, the drinking water action levels derived in this risk assessment are protective of human health.