EXECUTIVE SUMMARY

Methyl Isoamyl Ketone – Oral Risk Assessment CAS # 110-12-3			
PARAMETER	**LEVEL**	**UNITS**	**CALCULATED:**
NOAEL (no-observed-adverse-effect level)	25	mg/kg-day	From a 13-week rat inhalation study.
Oral RfD (oral reference dose)	0.008	mg/kg-day	From a 13-week rat inhalation study.
TAC (total allowable concentration)	0.06	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)	0.006	mg/L	For a 70 kg adult drinking 2 L/day.
STEL (short term exposure level)	0.8	mg/L	For a 10 kg child drinking 1 L/day.

KEY STUDIES	Katz, G.V., E.R. Renner Jr., and C.J. Terhaar. 1986. Subchronic inhalation toxicity of methyl isoamyl ketone in rats. Fund. Appl. Toxicol. 6:498-505. Katz, G.V. 1983. Two week and 90-day inhalation studies of methyl isoamyl ketone in rats. Health and Environment Laboratories, Eastman Kodak Company.
CRITICAL EFFECT	Hepatocyte hypertrophy in both sexes and minimal necrosis of the liver in males.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for subchronic to chronic extrapolation • 1x for extrapolation from LOAEL to NOAEL • 10x for database deficiencies The total uncertainty factor is therefore 3,000x.
TOXICITY SUMMARY	Toxicology evaluations of methyl isoamyl ketone include acute, subacute, subchronic, and genotoxicity studies. Developmental and neurotoxicity studies are available for structurally related ketones. The gavage studies located for methyl isoamyl ketone contained deficiencies considered to impact the risk assessment. A 13-week study evaluated only one dose level in male rats only, and a three-week study evaluated only male rats and did not include complete clinical chemistry or histological evaluation. The critical study was a 13-week rat inhalation study, which identified a NOAEL of 212 ppm (human equivalent oral dose of 25 mg/kg-day) based on increased mean absolute and relative liver weight and hepatocyte hypertrophy in both sexes. The changes in liver weight and liver pathology were also observed in the subchronic gavage study. Histopathological changes noted in the kidneys of males were associated with alpha-2μ-globulin nephropathy, thus were not relevant to human health. Based on a rat hepatic peroxisome proliferation study, the liver changes are not likely attributable to hepatic peroxisome proliferation, thus were considered relevant for this risk assessment. A human equivalent oral RfD of 0.01 mg/kg-day was derived from the 13-week rat NOAEL, using appropriate dose conversion factors and an inhalation absorption factor of 50%, based on absorption data for methyl ethyl ketone, since oral or inhalation kinetic, dynamic, or metabolic data for methyl isoamyl ketone were unavailable. Methyl isoamyl ketone was not mutagenic in *Salmonella typhimurium* over a range of doses in the presence and absence of metabolic activation, and was negative in a 3T3 cell transformation assay. The evidence of chromosomal aberrations observed at high concentrations was discounted since these concentrations were greater than 10 mM and cytotoxicity was observed.
CONCLUSIONS	Subacute and subchronic toxicity data exist to characterize the magnitude and duration of methyl isoamyl ketone exposure required to induce hepatotoxicity in rats. Although the weight of evidence of genotoxicity data suggests that methyl isoamyl ketone is not genotoxic, no chronic animal or human epidemiological studies were identified for methyl isoamyl ketone. Thus the cancer risk to humans from exposure to methyl isoamyl ketone *cannot be determined*. Taking into account the uncertainty factors used, the drinking water action levels established for methyl isoamyl ketone are considered to be protective of public health.