EXECUTIVE SUMMARY

Methyl Isobutyl Ketone– Oral Risk Assessment CAS # 108-10-1			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	1,000	mg/kg-day	From a subchronic gavage study in rats.
Oral RfD (oral reference dose)	1	mg/kg-day	From a subchronic gavage study in rats with a 1,000x uncertainty factor.
TAC (total allowable concentration)	7	mg/L	From the oral RfD, for a 70 kg adult drinking 2 L/day with a default 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	0.7	mg/L	From the TAC, assuming 10 drinking water sources of methyl isobutyl ketone.
STEL (short term exposure level)	100	mg/L	From a subchronic gavage study in rats adjusted for a 10 kg child drinking 1 L/day.

KEY STUDY	MAI (Microbiological Associates, Inc.). 1986. Subchronic toxicity of methyl isobutyl ketone in Sprague Dawley rats. Final Report. Study No. 5221.04. Performed by Microbiological Associates, Inc. for Research Triangle Institute. Unpublished report dated July 15, 1986.
CRITICAL EFFECT	No effects considered adverse were observed after subchronic gavage exposure to methyl isobutyl ketone in rats.
UNCERTAINTY FACTORS	• 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for extrapolation from a less-than-lifetime study to a lifetime exposure duration • 1x for extrapolation from a LOAEL to a NOAEL • 1x for database deficiencies. Therefore, the total uncertainty factor was 1,000x.
TOXICITY SUMMARY	Limited data in humans were identified. Short-term, subchronic, reproduction, and developmental toxicity data via oral or inhalation exposure in laboratory animals were identified, along with a chronic inhalation bioassay in rats and mice. Subchronic gavage exposure in rats caused transient narcosis, liver and kidney weight increases, altered blood parameters, and renal nephropathy. Increased narcosis, liver and kidney weights and altered blood parameters were observed after subchronic inhalation of methyl isobutyl ketone. Maternal and fetotoxicity were observed in developmental inhalation studies. Two subchronic oral studies in rats were available, but a drinking water study evaluated an insufficient number of animals, used only one concentration, and included only females. Increased liver and kidney weights and nephropathy were observed without hepatic histopathology in a standardized subchronic gavage study in rats. The increased liver weight was likely an adaptive response to metabolizing high bolus doses of methyl isobutyl ketone. The renal effects after subchronic gavage were attributed to spontaneous nephropathy and/or alpha-2μ-globulin nephropathy, since they were limited to male rats. The transient narcosis observed after gavage but not after drinking water exposure at the same dose was attributed to bolus dosing. Further, narcosis was inconsistently observed after inhalation exposure and most observations of narcosis after subchronic oral, intraperitoneal or inhalation exposures were present only during the first few to several weeks of exposure, but not at study termination. Gestational inhalation exposure resulted in reduced fetal body weight in rats and mice, reduced ossification in rats, and increased fetal death in mice. The non-neoplastic and neoplastic lesions observed in male and female F344 rats and B6C3F1 mice chronically inhaling methyl isobutyl ketone were attributed to spontaneous nephropathy and/or alpha-2μ-globulin nephropathy, thus not considered relevant to humans and/or were within historical control ranges, thus not considered toxicologically significant. However, interpretation of the effects in male rats chronically inhaling methyl isobutyl ketone was confounded by reduced survival. The subchronic gavage study was selected as the key since it was a standardized study, and the oral route was preferred for derivation of an RfD, since there were no kinetic or metabolism data in humans which could be used to reduce route to route or interspecies extrapolation. The weight of genotoxicity evidence suggests that methyl isobutyl ketone is not genotoxic. Since no epidemiological studies in humans or chronic oral data in animals were identified, the *data are inadequate for an assessment of human carcinogenic potential* of methyl isobutyl ketone after oral exposure.
CONCLUSIONS	Based on the concurrence of oral and inhalation data in laboratory animals, and on the uncertainty factors selected to account for interspecies extrapolation, intraspecies variability, and database deficiencies, the drinking water action levels developed in this risk assessment are protective of public health.