EXECUTIVE SUMMARY

DIACETONE ALCOHOL – Oral Risk Assessment CAS # 123-42-2			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
$BMCL_{10}$ (Benchmark Concentration)	25	mg/m^3	From a chronic inhalation study with methyl isobutyl ketone in rats
Adjusted HED_{10} (Human Equivalent Oral Dose at 10% Effect Level)	3.9	mg/kg-day	From the $BMCL_{10}$ after dosimetric adjustment for internal dose of diacetone alcohol
Oral RfD (oral reference dose)	0.1	mg/kg-day	From the adjusted HED_{10} with a 30x uncertainty factor.
TAC (total allowable concentration)	3	mg/L	For a 70 kg adult drinking 2 L/day using ~0.7 relative source contribution for drinking water.
SPAC (single product allowable concentration)	0.3	mg/L	From the TAC, assuming 10 drinking water sources of diacetone alcohol.
STEL (short term exposure level)	10	mg/L	From a 44-54 day gavage study with diacetone alcohol in rats, adjusted for a 10 kg child drinking 1 L/day.

EXPOSURE SUMMARY	General population exposure to diacetone alcohol occurs mainly from the intake of methyl isobutyl ketone associated with food and drinking water, followed by absorption and biotransformation to diacetone alcohol.
KEY STUDIES	NTP (National Toxicology Program). 2007. TR-538. Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and $B6C3F_1$ Mice (Inhalation Studies). NIHS, 1997a. OECD 422 Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (44-54-day) oral study with diacetone alcohol in Crj:CD (SD) rats
CRITICAL EFFECT	Exacerbated chronic progressive nephropathy (CPN) incidence and to a lesser extent severity was observed in female rats that inhaled methyl isobutyl ketone, of which diacetone alcohol is the principal metabolite.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 1x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 30x
TOXICITY SUMMARY	Prolonged dermal or inhalation exposure to diacetone alcohol in humans was associated with central nervous system depression, decreased blood pressure, renal and hepatic injury and mucous membrane irritation. Diacetone alcohol is of low acute toxicity by the oral, dermal, and inhalation routes of exposure. The longest-term oral study for diacetone alcohol was a 44/54-day reproductive/developmental toxicity screen by gavage in which the parental NOAELs were 30 mg/kg-day for males rats based on hyaline droplet nephropathy and 100 mg/kg-day for female rats based on renal tubular histopathology (slight dilatation, fatty degeneration, and slight or moderate vacuolar degeneration) and decreased locomotor activity. The reproductive/developmental NOAEL was 300 mg/kg-day based on slight changes in reproductive performance (decreased fertility and implantations) and pup viability at 1,000 mg/kg-day, possibly secondary to maternal toxicity (reduced weight gain, increased relative kidney, liver, and adrenal weights with histopathological lesions). The systemic effects after oral exposure are supported by a 6-week inhalation study for diacetone alcohol in rats with rat-equivalent oral NOAELs of ~61 and 80 mg/kg-day in males and females, respectively. Diacetone alcohol was not mutagenic in bacterial reverse mutation assays or clastogenic in mammalian cells. The data *are inadequate for an assessment of human carcinogenic potential* due to the lack of chronic or epidemiology studies. Diacetone alcohol is the primary metabolite of methyl isobutyl ketone in several species, and the spectrum of toxic effects observed is very similar between the two substances when evaluated in single or repeated-dose oral or inhalation studies and in genotoxicity assays. Toxicokinetic studies confirm rapid metabolism and clearance of methyl isobutyl ketone to the more persistent diacetone alcohol. Consequently, the majority of the internal exposure is to diacetone alcohol in both oral and inhalation studies with methyl isobutyl ketone. Thus the extensive database for methyl isobutyl ketone was used to supplement the evaluation of diacetone alcohol systemic toxicity.
CONCLUSIONS	Based on the toxicokinetic relationship between diacetone alcohol and methyl isobutyl ketone, selection of the most sensitive, relevant endpoint from the available animal studies as the critical effect, and the use of benchmark dose modeling with application of appropriate uncertainty factors, the drinking water action levels derived in this risk assessment are protective of public health.