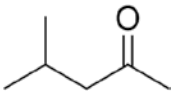
Cal/OSHA Draft Substance Summary for the December 12, 2017 HEAC Meeting

Substance name: Methyl isobutyl ketone

CAS: 108-10-1 **MW:** 100.16

Synonyms: 4-Methylpentan-2-one, Hexone, 4-Methyl-2-pentanone

Molecular formula: $C_6H_{12}O$ Structural formula: 

1 ppm to 4.1 mg/m^3 conversion factors at 25 °C and 760 mm/Hg:

GHS Classification

GHS Hazards

Flammable liquids	Category 2
Acute toxicity (Inhalation)	Category 4
Eye irritation	Category 2A
Skin irritation	Category 3
Specific target organ toxicity - single exposure	Category 3 (Resp. irritation)
Carcinogenicity	Category 2

Signal Word: Danger

GHS Hazard Statements

H225 Highly flammable liquid and vapor.
H319 Causes serious eye irritation.
H332 Harmful if inhaled.
H335 May cause respiratory irritation.
H351 Suspected of causing cancer.

Physical characteristics at room temp: Colorless liquid with sweet odor
Special physical characteristics if any: very low solubility with water but miscible with most organic solvents; can form explosive peroxides upon exposure to air.

Flammability and other hazards: flammable, Vapor pressure 20.2 hPa @ 20 °C

Upper Explosive Limit: 8% Lower Explosive Limit: 1.2%
Major commercial form(s): liquid

Uses/applications: a solvent for nitrocellulose, lacquers, gums, paints, polymers, varnishes, resins and surface coatings. Also used as precursor to N'-phenyl-p-phenylenediamine (6PPD), an anti-oxidant used in rubber and other elastomeric compounds and in manufacturing fungicides, pharmaceuticals, germicides and electroplating solutions. Also found in adhesives, food packaging, denatured alcohol and in synthetic flavorings (it is found naturally in food.)

Occupations with Potential Exposure to MIBK
Occupational exposures to MIBK occur in such industries as tire manufacturing, spray painting and industrial coating applicators.

Occupational Exposure Limits and Other recommendations:

Title 8 PEL (?): 50 ppm STEL 75 ppm
OSHA PEL (1971) 100 ppm
ACGIH TLV (2010): 20 ppm STEL 75 ppm skin notation
NIOSH REL (2000): 50 ppm 75 ppm STEL 500 ppm IDLH
MAK (2006): 20 ppm, 83 mg/m^3

Other recommendations:

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA (2011; 2014)	Cancer; Developmental toxicity.	Cancer based on IARC (2013); developmental toxicity based on US EPA (2003a; 2003b) assessment.	Included under State of California-proposition 65 list as known to the state to cause cancer and reproductive toxicity.
US EPA (2003a; 2003b)	Developmental toxicity - Inhalation reference concentration (RfC) 3.0 mg/m3.	Developmental effects in fetuses (i.e. reduced fetal body weight, skeletal variations, and increased fetal death in mice; and skeletal variations in rats) after repeated inhalation exposure on gestation days 6 to 15 (Tyl et al., 1987).	To derive the inhalation RfC, the $NOAEL_{HEC}$ of 1026 mg/m^3 was divided by the cumulative uncertainty factor (UF) of 300 (i.e. 3 for interspecies following EPA guideline, 10 for intraspecies, and 10 for database deficiency such as developmental neurotoxicity). Inadequate data available for cancer assessment. [NOTE: NTP 2007 chronic study completed].
NTP (2007)	Some evidence of carcinogenic activity in male F344/N rats and in both male and	Increased incidences of renal tubule neoplasms in male rats and increased incidences of liver	While generally exacerbated in all exposed rats, the severity of nephropathy was increased only in the 1,800 ppm group; increased incidences of papillary mineralization were significant in all

	female B6C3F1 mice, and equivocal evidence of carcinogenic activity in female F344/N rats.	neoplasms in both male and female mice (NTP, 2007). Rare renal tumors in female rats.	exposed groups of males. Additional research is needed to characterize the binding of methyl isobutyl ketone to α2u-globulin and to clarify the role of α2u-globulin in the observed tumor outcome in male rats in the current 2-year study.
ATSDR	–	–	–
IARC (2013)	Group 2B - Possibly carcinogenic to humans.	No evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals (NTP, 2007).	While tumor responses corresponded to some extent with a measure of cumulative α2μ-globulin nephropathy, the severity of CNP generally correlated best with the pattern of tumor response. Per IARC, the strength of the evidence that male rat kidney tumors arose through a α2μ-globulin nephropathy mechanism is weak.

Peer-reviewed journal articles used for proposed PEL

Human exposure studies

There are no epidemiological studies available solely of MIBK. Several volunteer studies in ranges between 2.45 and 100 ppm have found CNS and irritancy effects. One study found a non-permanent decrease in olfactory function after exposure to 20 ppm for 7 hours. Human volunteer studies with MIBK are summarized in Table 1.

Table 1: Human exposure studies

Study	Experimental Details	Health Measures	Conclusions
Dick, 1992	68 male/75 adult female volunteers exposed to 100 ppm (410 mg/m^3) Ages 18-32.	Evaluations of performance on five psychomotor tests, one sensorimotor test, and mood test of before exposure, immediately prior to exposure, during each of the two consecutive 2-hour exposure sessions, immediately after exposure, and on day following exposure. Chemical measurements (blood and breath) and reports of sensory and irritant effects were measured.	No effects of MIBK exposure were detected with respect to any of the performance tests or to the percentage of subjects experiencing various neurological or irritation symptoms, but a significant increase in percentage of subjects detecting a strong odor sensation and irritant effects were reported in the MIBK-treated group.
(Hjelm et al., 1990)	8 male volunteers exposed on 3 occasions for 2 hrs under conditions of light exercise to 2.5 ppm (10 mg/m^3), 25 ppm (100 mg/m^3), or 50 ppm (200 mg/m^3) MIBK, followed by 2-hour observation periods. No controls.	Volunteers performed light exercise for two hours during exposure. Simple reaction time (SRT) assessed by test and mood, central nervous system (CNS) and irritation symptoms by 17-point questionnaire at 9 times – once before exposure, 5 times during exposure and 3 times after exposure.	Out of a possible 48 positive responses (6 symptoms rated yes/no by 8 subjects), 4, 11, and 11 responses occurred at 2.5, 25 and 50 ppm, respectively. At 25 or 50 ppm, three of the eight subjects reported nose and throat irritation and two reported headache and vertigo. Local irritation effects differed between exposure groups and appeared to plateau during exposure. No exposure-related effects were observed in mood ratings or performance tests.

Iregren, 1993	6 male and 6 female volunteers exposed to MIBK vapors 2.5 (control) or 50 ppm.	Volunteers performed light exercise during the first 90 minutes and rested during the final 30 minutes of exposure. Performance of heart rate (HR), simple reaction time (SRT) assessed by test and central nervous system (CNS) and irritation symptoms assessed by 17-point questionnaire at 7 times – once before exposure, 4 times during, and twice after exposure ended.	There was no significant effect of exposure on HR or SRT. Sensory irritation ratings were not significantly different between the two exposure levels, plateaued over the course of exposure and declined after exposure. Neurological symptoms increased in occurance and intensity over the 7 tests and were significantly increased in the high dose group compared to the control
Gagnon, 1994	Olfactory function assessed in 4 subjects in two sessions. Subjects exposed to 20 and 40 ppm, for 7 hours, separated by a 25-day interval.	Olfactory perception threshold (OPT) was assessed using standard olfactory kits. An acute symptoms questionnaire was used to survey signs of eye, nose and throat irritation, acute discomfort and perceived odor intensity.	Immediate post exposure OPT was significantly higher than pre-exposure ($t = 9.0$; $p < 0.0001$). OPT was significantly different between individuals and OPT shift was significant for all 4 subjects. OPT remained significantly higher than pre-exposure levels at both 20 and 40 ppm ($p < 0.01$). Although OPT was similar immediately following chamber exit, it was significantly higher at 40 ppm as compared to 20 ppm at 55 and 95 minutes post exposure. Eye and throat irritation was reported once each among the other subjects.

Sub-chronic/chronic studies

MIBK has been evaluated in rodents in numerous sub-chronic studies and one chronic study. The observed effects in rats are almost exclusively in the kidney, liver and CNS. Effects observed in rats are kidney and liver weight gain, total weight loss, kidney hyperplasia and tumors, hyaline droplet lesions and altered serum and urinary chemistries (elevated serum cholesterol and urinary glucose). These metabolic imbalances are believed to be a secondary result associated with kidney and liver toxicity. Effects observed in mice are increased liver and kidney weights and hepatocellular hyperplasia. The CNS effects associated with MIBK were behavioral changes (e.g., hypoactivity, ataxia, and unsteady gait) that were only observed during exposure events in repeated exposure studies and which rapidly dissipated when exposure was terminated. MIBK concentrations causing CNS effects were higher than those causing organ effects. The database of sub-chronic inhalation animal studies includes no reports of MIBK-induced adverse effects in histological examinations of nervous system tissues or in batteries of neurobehavioral task performance tests (IRIS, 2003). Study information and significant effects are summarized in Table 2.

Table 2: **Sub-chronic/chronic inhalation studies**

Study	Duration	Exposure (ppm)	Significant Effects
MacEwen 1971 Rat (NS)	continuous, 90 days	0, 100	Increased mean relative liver and kidney weights, hyaline droplet renal proximal tubule degeneration
Phillips et al., 1987	6 hrs/day, 5 days/week,	0, 50, 250, 1000	50: No significant effects 250: females, 2% increase in body weight over controls; males, 23% increase

Rat (M/F)	14 weeks		in serum cholesterol, 37% increase in urinary glucose, mild hyaline droplet lesions in kidneys 1000: Females, 5% increase in body weights, 26% increase in urinary glucose, 57% decrease in eosinophil number; males, 13% increase in platelet number, 35% increase in serum cholesterol, 28% increase in urinary protein, 55% increase in urinary glucose, increased absolute (13%) and relative (9%) liver weights, increased severity of renal hyaline droplet lesions
Phillips, 1987 Mouse (M/F)	6 hrs/day, 5 days/week, 14 weeks	0, 50, 250, 1000	50: No significant effects 250: Increased absolute liver weight (8%) in males 1000: Increased absolute (11%) and relative (10%) liver weights in males
David,1999 Rat (M)	6 hrs/day, 5 days/week, 13 weeks	0, 250, 750, 1500	750: Reduced activity during first 8 weeks of exposure; increased relative kidney and liver weights; increased terminal body weights 1500: Reduced activity during first 10 weeks of exposure; increased terminal body weights; increased relative kidney and liver weights
WIL Research Labs, 2000 Rat (M/F)	Two-generation study: 6 hrs/day, 70 days prior to mating, through gestation and lactation	F0: 0, 500, 1000, 2000 F1: 0, 500, 1000, 2000	F0: 500: Males, increased relative kidney weight 1000: Males, increased relative kidney weight, centrilobular hepatocellular hypertrophy, reduced startle response. Females, increased relative kidney weight, reduced startle response. Offspring, transient depressed pup weight 2000: Males, increased kidney and liver weights, increased prevalence of centrilobular hepatocellular hypertrophy and nephropathy, reduced startle response. Females, increased adrenal, kidney, ovary, and liver weights, reduced startle response. Offspring, transient depressed pup weight F1: 500: Males, increased relative kidney weight 1000: Males, increased relative liver and kidney weights, increased prevalence of hepatocellular hypertrophy and nephropathy, reduced startle response. Offspring, transient depressed pup weight 2000: Males, increased relative liver, kidney, testis, cauda epididymis, seminal vesicle, and adrenal weights; increased prevalence of hepatocellular hypertrophy and nephropathy; reduced startle response; transient unsteady gait and prostration. Females, increased relative liver and kidney weights, reduced startle response, transient unsteady gait and prostration. Offspring, transient depressed pup weight

Developmental/Reproductive Studies

Few developmental and reproductive studies of MIBK have been conducted. Pregnant rats and mice were exposed by inhalation to MIBK on gestational days 6 through 15 and sacrificed on gestational day 21 (rats) or 18 (mice) (Tyl, 1987). Live fetuses were examined for external, visceral, and skeletal alterations. No exposure-related effects were observed in rats or mice with respect to numbers of corpora lutea, total implants, percent implantation loss, live fetuses per litter, non-viable implants per litter, percent live fetuses, and sex ratio. Fetal body weights (litter weight, male weight per litter, and female weight per litter) were significantly reduced in the low- (by 3%) and high- (by 6%) dose groups in rats and in the high-dose group in mice at 3073 mg/m^3 (by 13%) . In rats, the highest exposure resulted in significantly decreased body weight and body weight gain, increased relative kidney weight, and decreased food consumption in the dams. In mice, the highest exposure resulted in increased maternal death (12.0%, 3/25 dams), clinical signs, and increased absolute and relative liver weight, and in the fetuses, increased incidence of dead fetuses, reduced fetal body weight per litter, and reductions in skeletal ossification. The number of litters with observations indicating retarded skeletal ossification was significantly increased to various degrees in both rats and mice at 3073 mg/m^3 relative to controls for a variety of skeletal endpoints, with scattered increases in litters with retarded ossification at lower exposure levels that were not considered by the authors to be exposure-related.

In a two-generation reproductive study there were no adverse effects on male and female reproductive function or measures of sexual maturation when mating rats were exposed to MIBK before and during gestation (Nemec, 2004). Decreased body weight gain and slight decreased food consumption were observed during the first 2 weeks at the highest exposure in both generations. Increased F0 and F1 liver weights with associated centrilobular hypertrophy occurred at the highest exposure. Increased male kidney weights occurred at all exposure concentrations and were associated with hyaline droplets. Sperm motility and morphology were unaffected in either generation. Skeletal malformations were not analyzed. Specific details of the studies are provide in Table 3.

Table 3: Developmental/Reproductive Studies

Study	Duration	Exposure (ppm)	Significant Effects
Tyl 1987 Rat (F)	6 hrs/day, each gd 6-15	0, 300, 1000, 3000	300 and 1000: No treatment-related effects 3000: Maternal effects, reduced body weight and body weight gain, hypoactivity, ataxia, lacrimation. Reduced fetal body weight, delayed skeletal ossification in pups
Tyl 1987 Mouse (F)	6 hrs/day, each gd 6-15	0, 300, 1000, 3000	300 and 1000: No treatment-related effects 3000: Maternal effects, hypoactivity, ataxia, lacrimation. body weight, delayed skeletal ossification, skeletal fragility
Nemec 2004 Rats (M/F)	Two generation study of 30 M/F per group exposed for 6 h day for 70 days prior to mating. F0 and F1 females exposed from mating through GD 20 and from PND 5; F2 litters maintained through PND 21.	0, 500, 1000, 2000	Males, 500, 1000, 2000: increased kidney weight in F0 and F1; 1000, 2000: decreased body weight in F1 2000: increased seminal vesical weight, F0 and F1. Females, 2000: increased liver weight, F0 and F1; increased ovary weight F0; decreased body weight in F1 Observations: Increased male kidney weights correlated with an increased occurrence of nephropathy. Statistically significant reductions in body weight gain in the 2000-ppm F0 females were observed during weeks 0 to 1 and 1 to 2.

Carcinogenicity Studies

The toxicity and carcinogenicity of MIBK were characterized in a 2-year inhalation study in rats and mice (NTP 2007). The primary targets of MIBK were the kidney in rats and the liver in mice with the male rat exhibiting the broadest array of effects. In male rats, there was significantly increased mineralization of the renal papilla and renal tubule hyperplasia at all exposure concentrations and of chronic progressive nephropathy (CPN) at the highest dose. There was a significant increase in adenoma and adenoma or carcinoma (combined) in male rats at the highest dose. In female rats, there were increases in the incidence of CPN in all exposure concentrations and in the severity at the highest dose. There were renal mesenchymal tumors in two female rats at the highest dose. In mice, hepatocellular adenomas, and adenoma or carcinoma (combined) were increased in males and females at the highest dose. Study details are presented in Table 4 and data on the significant effects observed in the rat and mouse studies presented in Tables 5 and 6.

Table 4: Summary of 2-year Toxicology and Carcinogenesis Studies

Study	Duration/Doses	Measures	Significant Effects
NTP, 2007; Rat (M/F)	50 male/50 female; 0, 450, 900, or 1800 ppm, 6 hours, day, 5 days per week for two years	Survival, Body weight,; Complete necropsies and microscopic examinations;	Male rat: Reduced Survival: 1800 Reduced Body weight: 900 1800 ppm papilla mineralization: all dose groups epithelium hyperplasia: 900,1800

		extended evaluation of the kidney	Renal Tubule Hyperplasia: all dose groups Renal Tubule Adenoma: 1800 Renal Tubule Carcinoma: no dose group Combined: 1800 Female rat: Nephropathy: all dose groups Mesenchymal tumor malignant: elevated, not significant
NTP, 2007; Mouse (M/F)	50 male/50 female; 0, 450, 900, or 1800 ppm, 6 hours, day, 5 days per week for two years		Male and Female mice: Eosinophilic Foci: (female) 450, 1800 Hepatocellular Adenoma: 1800 Multiple Adenoma: male 900, 1800; female 1800 Hepatocellular Carcinoma: no dose group Combined: 1800

Table 5: Incidences (Severity) of Noncancer Lesions in Rat Kidney

2-year		Dose (ppm)			
		0	450	900	1800
Male Rat	Nephropathy	42 (1.0)	45 (2.6)	47(2.4)	50 (3.1)*
	Papilla Mineralization	1 (1.0)	6* (1.2)	22** (1.6)	29** (1.5)
	TEH	1 (1.0)	11** (3.2)	3 (2.0)	18** (2.7)
Female Rat	Nephropathy	19 (1.4)	35** (1.5)	38** (1.5)	44** (1.9)

*Transitional Epithelium, Hyperplasia
* Significantly different ($p \leq 0.05$) from the control group by the logistic regression test for incidences. Severities of nephropathy are significantly different by the Mann-Whitney U test.
** ($p \leq 0.01$)

Table 6: Incidences of Hyperplasia and Neoplasms in Rat Kidney and Mouse Liver in 2-Year Inhalation Study of Methyl Isobutyl Ketone.

	Dose (ppm)			
Male Rat (combined)	0	450	900	1800
Renal Tubule, Hyperplasia	1 (2.0)	14* (2.9)	7* (2.0)	21** (2.5)
Renal Tubule Adenoma	2	3	3	10
Renal Tubule Carcinoma	0	1	0	2
Renal Tubule Adenoma or Carcinoma	2	4	3	11*
Female Rat (Single Sections)				
Renal Tubule, Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	0	0	0
Renal Tubule Adenoma, multiple Tubule	0	0	0	0
Renal Tubule Carcinoma	0	0	0	0
Renal Tubule Adenoma or Carcinoma	0	0	0	0
Mesenchymal Tumor Malignant	0	0	0	2
Male Mice				
Hepatocellular adenoma	17	25	23	34

Hepatocellular carcinoma	12	12	10	9
Female Mice				
Hepatocellular adenoma	13	15	20	23
Hepatocellular carcinoma	6	5	6	11

* Significantly different (P#0.05) from the chamber control group by the Poly-3 test
** P≤ 0.01

Mode of Action Studies

Different modes of actions are proposed for the effects seen in the different organ systems. CNS effects of MIBK are likely due to its easy penetration of tissues leading to the disruption and disorganization of cell membranes. CNS effects observed with MIBK are rapidly reversible once exposure is terminated and are typically only seen at the mid to high exposure in the reviewed studies. Kidney effects in male rats, both in terms of weight gain and histopathology, are attributed to α2u-globulin nephropathy, an effect highly specific to male rats. The proposed sequence of events involved in the induction of α2u nephropathy includes binding of a chemical to the male rat protein α2u-globulin, accumulation of hyaline droplets in renal proximal tubule cells and a cycle of cytotoxicity, apoptotic death and compensatory cell proliferation, that if chronic, may lead to the promotion of neoplasia. Kidney nephropathy in male and female rats is attributed to

Recent studies have attempted to elucidate the mode of action of MIBK in inducing α2u-nephropathy and hepatocellular proliferation (Table 7). A sub-chronic study by Borghoff (2009) confirmed α2u-globulin as the protein found in hyaline droplets formed as a result of MIBK exposure. Borghoff (2015) also confirmed that MIBK bound reversivbly to α2u-globulin, although this finding was in vitro. Neither study was of sufficient duration to detect tumor formation in the kidney however observed histopathology did correlate with cell effects know to occur in nephropathy, a precursor of tumor formation in the rat kidney. The mechanism by which MIBK induces hepatocellular proliferation was examined using a knock out mouse model of the CAR/PXR nuclear receptors (Hughes, 2016). As is the case with MIBK, when a rodent liver carcinogen is not genotoxic, a CAR/PXR nuclear receptor activation MOA is plausible with increases in hepatocellular hypertrophy and hyperplasia constituting key events. Hughes found that acute exposure to 1800 ppm MIBK induced enzyme production associated with the CAP/PXR receptor and associated and hepatocellular proliferation.

Table 7: Mode of Action Studies for MIBK

Objective	Method	Results
Borghoff 2009 Compared measures of *A2G*-nephropathy in male/female F-344 rats treated with MIBK and d-limonene, known inducer of *A2G*-nephropathy	Male F-344 rats were administered corn oil (vehicle control), d-limonene (positive control, 300 mg/kg), or MIBK (1000 mg/kg) for 10 consecutive days by oral gavage. Female F-344 rats corn oil (vehicle control) or MIBK for	Increase in protein droplets, accumulation of α2u globulin and renal cell proliferation in male, but not female rats. MIBK produced identical histopathological changes when compared to d-limonene, except that severity was slightly lower with MIBK. MIBK did not induce any effects in female rats.
Borghoff 2015 Evaluted histological lesions associated with the A2G accumulation over times and sustained renal cell proliferation in the kidneys. Determine MIBK binding to *A2G* protein	Rats exposed 6 h/day for 1 or 4 weeks and kidneys excised approximately 18 h post exposure to evaluate hyaline droplet accumulation (HDA), α2u staining of hyaline droplets, renal cell proliferation, and to quantitate renal a2u concentration.	exposure-related increase in all measures of α2u nephropathy in male but not female kidneys. HDA and α2u concentration were comparable to D-limonene. The dissociation constant (Kd) between MIBK and a2u, estimated to be 1.27 x 10-5 M

Hughes, 2016 Evaluated CAR/PXR nuclear receptor activation MOA for MIBK induced-hepatocellular tumors in mice.	Male/Female B6C3F1, C57BL/6, and CAR/PXR Knockout (KO) mice exposed to either 0 or 1800 ppm MIBK for 6 h/day, 5 days/week for a total of 10 days. Mice were implanted with osmotic mini-pumps containing 5-Bromo-2- deoxyuridine (BrdU).	Significant increases in liver weights compared to controls corresponding with hepatocellular hypertrophy observed in treated but not KO mice. Hepatocellular proliferation indicated induction of S-phase DNA synthesis in normal mice exposed to MIBK but not KO mice. Increases in Cyp2b10 (CAR-associated) and Cyp3a11 (PXR-associated) transcript observed in normal mice but not KO mice.

Discussion: Overall, these studies demonstrate that MIBK produces effects associated with the liver, kidney, CNS and fetal development. The key endpoints occurring at the lowest doses in these studies are the developmental effects observed in Tyl (1987) and the neoplasms in rats and mice in the NTP study (2007). Serum effects were observed at lower doses than developmental effect but the significance of the changes to rat serum and urinary markers (Phillips 1987) markers to humans is unclear. In spite of relatively strong evidence indicating that hypercholesterolemia occurs in rats after subchronic repeated inhalation exposures to MIBK, in the absence of histopathological changes in the liver the effect was not considered to be clearly adverse in the USEPA IRIS assessment. Likewise, increased urinary glucose also occurred in male rats at 185 mg/m3, however hyaline droplet formation appeared at this same dose and may be the cause of the impaired renal function. Neurological impairment (e.g., hypoactivity, ataxia, and unsteady gait) was only observed during exposure events in repeated exposure studies and generally at higher doses than the other effects. The IRIS assessment concluded that until further chronic inhalation data becomes available, the liver, kidney, and CNS effects were not considered to be clearly adverse and therefore were considered to be of uncertain relevance to effects in humans from chronic exposures (ADD IRIS reference). The delayed ossification in rats and mice and reduced fetal body weight and increased fetal death in mice were identified as the critical effects for the development of the RfC in IRIS (USEPA, 2003).

The NTP chronic bioassay (2007) identified the kidney as the primary site of methyl isobutyl ketone-related toxicity but identified other possible effects. The study concluded there was some evidence of carcinogenic activity of MIBK in male F344/N rats based on increased incidences of renal tubule neoplasms. Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure. NTP found equivocal evidence of carcinogenic activity of methyl isobutyl ketone in female F344/N rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group.

The variety of kidney lesions suggests that the tumorigenic effect observed in the kidney in NTP study may be related to "2u-globulin nephropathy. Results from the current 2-year study show exposure-related and significantly increased incidences of minimal to mild linear mineralization of the renal papilla tubule epithelium in all groups of exposed male rats. In addition, there were increased incidences of transitional epithelial hyperplasia in the renal pelvis of male rats exposed to 900 or 1,800 ppm. While the dose-response between MIBK and the kidney lesions (papilla minerlization, TEH, Table 5) is good, the relationship between there markers and neoplasm incidence is marginal - there was no association between hyperplasia severity and neoplasm incidence and the only significant increase in neoplasms was in the high dose group in males; no renal tubule neoplasms occurred in females (table 6). Since completion of the NTP study, others have shown that MIBK binds to α2u-globulin irreversibly (Borghoff, 2009), one of the criteria for the α2u-globulin mechanism.

There was some evidence of carcinogenic activity of methyl isobutyl ketone in male and female B6C3F1 mice based on increased incidences of liver neoplasms. The incidences of hepatocellular adenoma and adenoma or carcinoma (combined) were increased in all exposed groups of males and in 900 and 1,800 ppm females, and the incidences in the 1,800 ppm groups were significantly greater than those in the chamber controls. Although hepatocellular adenoma is the most frequent spontaneous liver neoplasm in B6C3F1 mice, the number of neoplasms detected in mice exposed to 1,800 ppm and the

positive trends in the multiplicity observed in exposed males and females provide some evidence of carcinogenic effect of methyl isobutyl ketone in mice. The histologic appearance of the hepatocellular proliferative lesions was consistent with those commonly observed as spontaneous lesions in mice. The incidences of eosinophilic foci were increased in all exposed groups of female mice, and the differences from the chamber controls were significant in the 450 and 1,800 ppm group.

Two malignant mesenchymal tumors (2/50) occurred in the high dose female rats. Although these neoplasms have not been previously observed in chamber controls, the occurrence of only two neoplasms makes the relationship to methyl isobutyl ketone exposure unclear. These neoplasms are rare and have not been found in male or female controls (all routes) fed the NTP 2000 diet, a low-protein diet intended to minimize background neoplasms. In treated F344/N rats fed NTP 2000 diet, mesenchymal tumors were found in only one male and three female rats in three 2-year studies including the current study

The study by Hughes (2016) provides several lines of evidence that the hepatocellular neoplasms are a result of a mode of action common in mice and not relevant to humans. A constitutive androstane receptor (CAR) MOA has been established for nongenotoxic chemicals whereby activation of CAR leads to the induction of xenobiotic metabolizing enzymes (Cyp2b), enhanced cell proliferation, inhibition of apoptosis, hypertrophy, and development of altered hepatic foci. Evidence shows that MIBK is not genotoxic and hepatocellular tumors in mice form through activation of CAR that induces the Phase 1 enzyme Cyp2B, enhanced cell proliferation, inhibition of apoptosis, hypertrophy, and development of altered hepatic foci. Supporting evidence for this MOA includes increased liver weight, hepatocellular hypertrophy/proliferation, and increased transcription of Cyp2b. Using wild type (CAR+) and knockout (CAR-) mice, Hughes showed statistically elevated BrdU labeling in the treated WT male and female mice compared to controls and knockout mice. Gene expression for two xenobiotic enzymes associated with MIBK were hundreds-fold higher in the WT mice than controls and there was no difference between expression in controls and knockout mice. Finally, body weight gain and hypertrophy were higher WT mice than knockout mice. These responses are similar to other known CAR activators like phenobarbital and are consistent with a CAR-mediated hepatocarcinogenesis MOA.

HEAC Health-based assessment and recommendation

A PEL of 5 ppm and a STEL of 50 ppm is proposed for adoption. That value is based on the selection of the NOAEL from the Tyl 1987 developmental study with the application of occupational duration adjustment and uncertainty factors. There are no human epidemiological studies from which the human health effects of MIBK can be evaluated and human exposures studies are of short duration (< 7 hours).

The Tyl 1987 study is the basis for the current IRIS reference value because the NTP 2007 study was not completed at the time of IRIS assessment (2003). Exposure concentrations in the developmental toxicity study were duration-adjusted to derive HEC exposure levels (U.S.EPA, 1994b). This methodology differs from previous EPA practice where most developmental assessments did not perform duration adjustments based on the premise that developmental effects were more likely to depend on peak exposure concentrations. Further evaluation has indicated that developmental effects for a number of substances may be a function of area under the curve or AUC. To adjust the 6-hour study interval to an occupational interval, the NOAEL was multiplied by 6/8. An interspecies uncertainty factor of 3 was adopted due to the absence of animal and human blood gas partition data. An intra-species uncertainty factor of 10 was applied to address human variability. Finally, the EPA uncertainty factor of 10 for database uncertainty was reduced to 3 as a result of the completion of the NTP 2007 study. A chronic developmental neurologic study in rodents has not been done but there is no evidence for an effect in sub-chronic studies or in the epidemiological literature.

NOAEL 1000 ppm

$NOAEL_{HEC}(occupational) = NOAEL_{ADJ} \times (H_{b/g})_A / (H_{b/g})_H$

= (NOAEL x Occupational duration-adjustment) x $(H_{b/g})_A$ / $(H_{b/g})_H$
[where, $(H_{b/g})_A$ / $(H_{b/g})_H$ is a ratio of the animal blood gas partition coefficient for MIBK to the human blood gas partition coefficient]

= (1000 ppm x 6/8 x 5/5) x 1 (i.e. default as no blood:air partition coefficient data)
= 750 ppm

This $NOAEL_{HEC}$ (occupational) value can be used to derive a PEL by applying default UFs (combined = 100).
This would give a PEL of 7.5 ppm. Propose rounding to 5.

The NTP 2007 was a 2-year chronic inhalation study of MIBK using rats and mice study and looked at multiple endpoints. Renal effects were observed in rats and hepatocellular effects in mice (see Table 6). The key conclusions of the study as stated by NTP are:

"Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male F344/N rats based on increased incidences of renal tubule neoplasms. Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats *may* have been related to methyl isobutyl ketone exposure. There was *equivocal evidence of carcinogenic activity* of methyl isobutyl ketone in female F344/N rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group. There was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms. Exposure to methyl isobutyl ketone resulted in nonneoplastic lesions of the kidney characteristic of α2u globulin accumulation in male rats and nephropathy in female rats."

NTP 2007

The results of this study are difficult to interpret because of the non-neoplastic effects that also occurred. α2u globulin nephropathy and chronic proliferative nephropathy (CPN) were observed in male and female rats at all dose levels, respectively. These two effects occur normally in untreated rats but not humans and may constitute a mode of action through which chemicals can cause kidney tumors in rats that is not relevant to humans. Extensive reviews of NTP studies (Melnick, Hard) have shown that the relationship between these endpoints and renal tumors is complex and needs to be evaluated on a case by case basis. Many studies have shown clear associations between these non-neoplastic effects and tumor incidence while others have shown no association between tumor incidence and nephropathy in rats. OEHHA and IARC have classified MIBK as a carcinogen on the basis of the male rat kidney tumors whereas US EPA IRIS has not undertaken an assessment of the NTP results. No cancer slope factor has been derived for MIBK so a quantitative cancer risk cannot be determined.

In the NTP 2007 study, no tumors were observed in the female rats while CNP was elevated in all dose groups so this endpoint could be examined for deriving a reference value. Using the lowest dose from the NTP 2007 study as a LOAEL, a PEL can be calculated as follows:

LOAEL 450 ppm or 1843 mg/m^3 (lowest dose delivered)
NOAEL 45 ppm or 184 mg/m^3 (applying LOAEL UF = 10)
$NOAEL_{HEC}$ (occupational) = $NOAEL_{ADJ}$ x $(H_{b/g})_A$ / $(H_{b/g})_H$

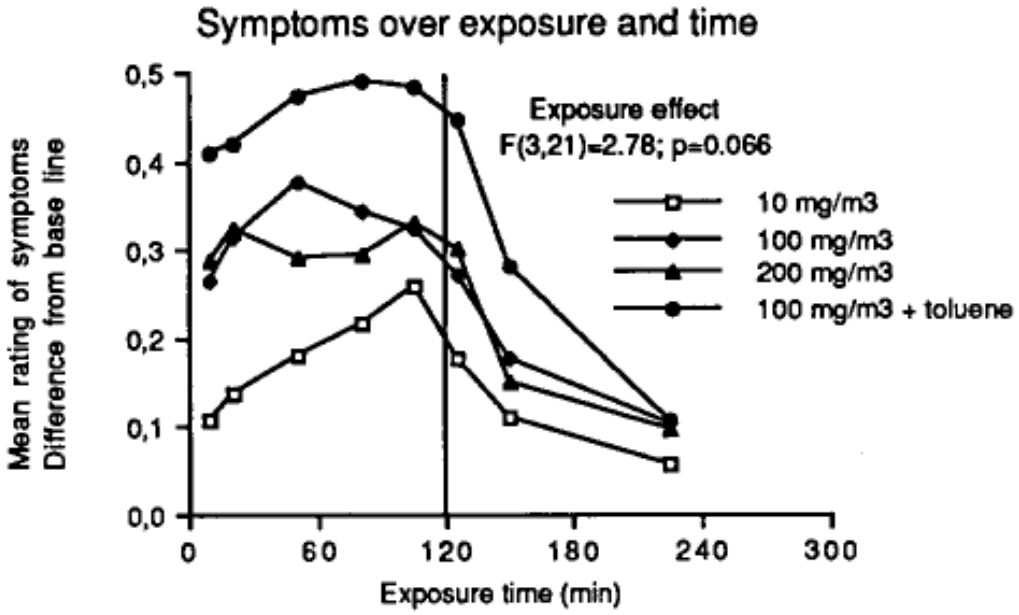
= (NOAEL x Occupational duration-adjustment) x $(H_{b/g})_A$ / $(H_{b/g})_H$
[where, $(H_{b/g})_A$ / $(H_{b/g})_H$ is a ratio of the animal blood gas partition coefficient for MIBK to the human blood gas partition coefficient]

= (45 ppm x 6/8 x 5/5) x 1 (i.e. default as no blood:air partition coefficient data)

= 33.75 ppm or 138 mg/m^3

This $NOAEL_{HEC}$ (occupational) value can be used to derive a PEL by applying default UFs (combined = 100). **This would give a PEL of 0.33 ppm.** Rat CPN has not previously been used as a basis for hazard assessment but is currently proposed as one of several effects used to derive a reference concentration in a draft tert-butyl acetate assessment (USEPA, 2016). The relatively weak dose response between MIBK and CPN increase in the female rat suggests using this approach to determine a NOAEL for MIBK may have considerable uncertainty.

A STEL of 50 ppm is proposed based on increases in symptoms in human volunteer studies. The studies by Dick (100 ppm, 4 hours) and Hjelm (50 ppm, 2 hours) reported no behavioral or motor effects but both reported increases in sensation and irritation in the subjects. Of note, the Hjelm study had the volunteers conduct mild exercise during exposure. Iregren repeated this protocol (2 hours, light exercise) and found significant increases in neurological symptoms in the treated group. Hjelm recorded symptoms during exposure and found similar increases in symptoms within the first 15 minutes of exposure to 25 and 50 ppm. Given this relatively quick response, a STEL of 50 ppm is recommended.



From Hjelm, 1990.

CERS Usage information:

SIC Code	Average Daily Usage
(n = 483)	*(gal)*
10-19 *(14)*	43
20-29 *(88)*	1400
30-39 *(196)*	75
40-49 *(38)*	237
50-59 *(30)*	1027
60-69 *(4)*	5

70-79 *(38)*	1634
80-89 *(63)*	12
90-99 *(12)*	34

Measurement/Implementation Feasibility

	OSHA Method ID 1004 (validated)	NIOSH Method 2555 (validated)
Estimated LOD/LOQ	.009 ppm (12 liters@ 50 ml/min)	0.066 to 6.83 ppm (0.01 to 0.2 L/min to 10 liters)

Measurement issues: use CMS sampler; also passive monitors OK. Labs must refrigerate.

Both NIOSH and OSHA methods use GC/FID analysis. Both methods are feasible for use for proposed PELs of 5 ppm eight hour TWA for a non-cancer developmental effects endpoint or a proposed PEL of 0.34 ppm for a neuropathic effects non-cancer endpoint. Both methods are feasible for adoption of the ACGIH STEL of 40 ppm. A skin notation is also necessary as MIBK is absorbed through the skin; dermatitis from skin exposure also occurs.

Economic Impact Analysis/Assessment

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