

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: $C_6H_{12}O$



1 ppm to 4.1 mg/m³ 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:

Title 8 PEL (1989): 50 ppm STEL 75 ppm
OSHA PEL (1971): 100 ppm
ACGIH TLV (2010): 20 ppm STEL 40 ppm skin notation
NIOSH REL (2000): 50 ppm 75 ppm STEL 500 ppm IDLH
MAK (2006): 20ppm, 83 mg/m³

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/m ³ . | 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. |
| NTP (2007) | Some evidence of carcinogenic activity in male F344/N rats and in both male and female B6C3F1 mice, and equivocal evidence of carcinogenic activity in female F344/N rats. | Increased incidences of renal tubule neoplasms in male rats and increased incidences of liver neoplasms in both male and female mice (NTP, 2007). Rare renal tumors in female rats. | In the 2-year inhalation study, increased incidence of exposure-related renal tubule hyperplasia and adenomas as well as renal tubule carcinomas were observed (NTP, 2007). An α ₂ μ-globulin synthesis mechanism does not fully account for the tumor pattern seen; other mechanisms are likely involved. MIBK is not listed as a human carcinogen in the current NTP Report on Carcinogens. |
| ATSDR | | | |

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|-------------|---|--|--|
| IARC (2013) | Group 2B - Possibly carcinogenic to humans. | No evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals (NTP, 2007). | Evidence of carcinogenic activity - In a 2-year inhalation study (NTP, 2007), MIBK caused increased incidence of hepatocellular adenoma and hepatocellular adenoma and carcinoma combined in both male and female mice and of renal tubule adenoma and renal tubule adenoma and carcinoma combined in male rats; and caused two rare renal malignant mesenchymal tumors in female rats at high-dose. Per IARC, the strength of the evidence that male rat kidney tumors arose through a $\alpha_2\mu$ -globulin nephropathy mechanism is weak. |
|-------------|---|--|--|

Peer-reviewed journal articles used for proposed PEL

Human exposure studies

MIBK is a widely used industrial and commercial substance and is commonly found in mixture with other solvents. 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 the table below.

| Study | Experimental Details | Health Measures | Conclusions |
|----------------------|--|--|---|
| Dick, 1992 | 13 male/12 adult female volunteers exposed to 100 ppm (410 mg/m ³) MIBK for two consecutive 2-hr exposure periods | 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. | 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 was 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 occurrence 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 | Olfactory perception threshold (OPT) was assessed using standard olfactory | Immediate post exposure OPT was significantly higher than pre-exposure ($t = 9.0$; $p < 0.0001$). OPT |

| | | | |
|--|--|---|--|
| | in two sessions. Subjects exposed to 20 and 40 ppm, for 7 hours, separated by a 25-day interval. | kits. An acute symptoms questionnaire was used to survey signs of eye, nose and throat irritation, acute discomfort and perceived odor intensity. | 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 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). 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 the table below.

| Study | Duration | Exposure | Significant Effects |
|-----------------------------------|---|--|---|
| MacEwen 1971 Rat (NS) | continuous, 90 days | 0, 100 | 410: Increased mean relative liver and kidney weights, hyaline droplet renal proximal tubule degeneration |
| Phillips et al., 1987 Rat (M/F) | 6 hrs/day, 5 days/week, 14 weeks | 0, 50, 250, 1000 | 50: No significant effects 250: females, 2% increase in body weight over controls; males, 23% increase 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. 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 rat fetuses, the highest and lowest exposure resulted in reduced fetal body weight per litter and reductions in skeletal ossification were observed with the highest exposure. In mice, the highest exposure resulted in increased maternal death, 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. 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.

| 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 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 chronic 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 an 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 | 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; extended evaluation of the kidney | Male rat: Reduced Survival: 1800 Reduced Body weight: 900 1800 ppm papilla mineralization: all dose groups epithelium hyperplasia: 900,1800 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 |

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 α 2u-globulin nephropathy, an effect highly specific to male rats. The proposed sequence of events involved in the induction of α 2u nephropathy includes binding of a chemical to the male rat protein α 2u-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 α 2u-nephropathy and hepatocellular proliferation (see table below). A sub-chronic study by Borghoff (2009) confirmed α 2u-globulin as the protein found in hyaline droplets formed as a result of MIBK exposure. Borghoff (2015) also confirmed that MIBK bound reversibly to α 2u-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 known 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. CAR/PXR KO mice exposed to 1800 ppm MIBK showed no evidence of activation of AhR, CAR, PXR or PPAR- α nuclear receptors via their associated transcripts. The authors concluded that MIBK induced hepatic effects are consistent with a phenobarbital-like MOA where

the initiating events are activation of the CAR and PXR nuclear receptors and resultant hepatocellular proliferation leading to rodent liver tumors.

Several of these toxicological effects are considered specific to the male rat (α 2u-globulin nephropathy) or elevated in rodents (CPN in rats, hepatocellular hyperplasia in mice) and

α 2u-globulin in producing kidney tumors in male rats without a similar response in female rats is generally accepted as evidence that the chemical will not cause cancers in human. However, this association is conditional on the nature of the dose response, severity of the α 2u-nephropathy and frequency of tumors induced by the chemical. Cases of weak tumor response with well-defined cumulative α 2u-associated nephropathy suggest that while α 2u-globulin nephropathy may contribute to the renal tumor response, the critical component(s) of the nephropathy most closely associated with the development of tumors cannot clearly be identified (Doi, XXXX). The comparison to D-limonene is not convincing in that D-limonene produced none of elevated CPN in female rats observed in the MIBK study (REF). In addition to α 2u- nephropathy, there are likely other mechanisms of MIBK toxicity that influence kidney nephropathy in rats and potentially in humans. Likewise, levels of CPN and hepatocellular hyperplasia are elevated in rodents compared to humans and their occurrence as a result of chemical exposure must be carefully interpreted.

| Objective | Method | Results | Conclusion |
|---|--|---|---|
| <p>Borghoff 2009</p> <p>Compare ability of MIBK to induce specific measures of α2u-nephropathy in male/female female F-344 rats to d-limonene, known inducer of α2u-nephropathy</p> | <p>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</p> | <p>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.</p> | <p>Renal histopathology, along with the measures of α2u globulin accumulation, provides additional weight of evidence to support the inclusion of MIBK in the category of chemicals exerting renal effects through a α2u-nephropathy-mediated mode-of-action</p> |
| <p>Borghoff 2015</p> <p>evaluate histological lesions associated with the accumulation of α2u, increased renal concentration of α2u, and sustained renal cell proliferation in the kidneys of male but not female rats. Determine MIBK binding to α2u protein</p> | <p>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 α2u concentration.</p> | <p>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 α2u, estimated to be 1.27_10_5 M</p> | <p>Exposure-related increase in measures of α2u nephropathy, sustained increase in renal cell proliferation along with an indication of reversible binding of MIBK to α2u, support the inclusion of MIBK in the category of chemicals exerting renal effects through a protein droplet α2u nephropathy-mediated mode of action (MoA).</p> |
| <p>Hughes 2016</p> <p>evaluate the CAR/PXR nuclear receptor activation MOA for MIBK induced hepatocellular tumors in mice</p> | <p>male and female B6C3F1, C57BL/6, and CAR/PXR Knockout (KO) mice were 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).</p> | <p>Significant increases in liver weights compared to controls corresponding with hepatocellular hypertrophy observed in normal 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.</p> | <p>MIBK induced hepatic effects are consistent with a phenobarbital-like MOA where the initiating events are activation of the CAR and PXR nuclear receptors and resultant hepatocellular proliferation leading to rodent liver tumors.</p> |

HEAC Health-based assessment and recommendation

A PEL of 5 ppm and a STEL of 25 ppm is proposed for discussion. That value is based on the selection of NOAELs from either the Tyl 1987 developmental study or the NTP 2007 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. 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 intraspecies 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.

$$\begin{aligned} \text{NOAEL 1000 ppm} \\ \text{NOAEL}_{\text{HEC(occupational)}} &= \text{NOAEL}_{\text{ADJ}} \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}} \\ &= (\text{NOAEL} \times \text{Occupational duration-adjustment}) \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}} \\ &\quad [\text{where, } (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}} \text{ is a ratio of the animal blood gas partition coefficient for} \\ &\quad \text{MIBK to the human blood gas partition coefficient}] \\ &= (1000 \text{ ppm} \times 6/8 \times 5/5) \times 1 \text{ (i.e. default as no blood:air partition coefficient} \\ &\quad \text{data)} \\ &= 750 \text{ ppm} \end{aligned}$$

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 ppm.

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 x). 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 B6C3F₁ mice based on increased incidences of liver neoplasms. Exposure to methyl isobutyl ketone resulted in nonneoplastic lesions of the kidney characteristic of α 2u globulin accumulation in male rats and nephropathy in female rats.”

The results of this study are difficult to interpret because of the non-neoplastic effects that also occurred. α 2u globulin nephropathy and chronic proliferative nephropathy (CPN) were observed in male and female rats at all dose levels (CONFIRM). 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 male rat kidney tumors whereas US EPA IRIS has not undertaken an assessment of the NTP results. In its current review of tert-butyl alcohol, another chemical known to cause α_2 u globulin nephropathy, EPA appears to reject using tumor data from rats for hazard assessment when it is associated with the non-neoplastic effects:

“Several effects were observed in the kidneys of rats. Based on mechanistic evidence indicating that an α_2 u-globulin-related process is operating in male rats (Hard et al., 2011; Cirvello et al., 1995; NTP, 1995; Lindamood et al., 1992), any kidney effects associated with α_2 u-globulin nephropathy are not considered relevant for human hazard identification. In addition, CPN played a role in the renal tubule nephropathy observed following tert-butanol exposure, and effects associated with such nephropathy are not considered relevant for human hazard identification. Although increases in severity (males and females) or incidence (females) of nephropathy were related to tert-butanol exposure and could have arisen from chemical-specific processes independent from CPN, the association of these effects with CPN makes this measure less suitable for dose-response analysis, and therefore these effects were not considered for the derivation of reference values. Furthermore, some uncertainty exists regarding whether mineralization is also associated with CPN in male rats; due to this uncertainty, and because other kidney effects were identified as being associated with tert-butanol exposure and yet independent from CPN, mineralization in male rats was not considered for dose-response analysis. The remaining effects (suppurative inflammation, transitional epithelial hyperplasia, and increased kidney weights) are considered the result of tert-butanol exposure and relevant to human hazard characterization. These effects therefore are suitable for consideration for dose-response analysis and derivation of reference values.”

US EPA, 2016, DRAFT

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/m³ (lowest dose delivered)

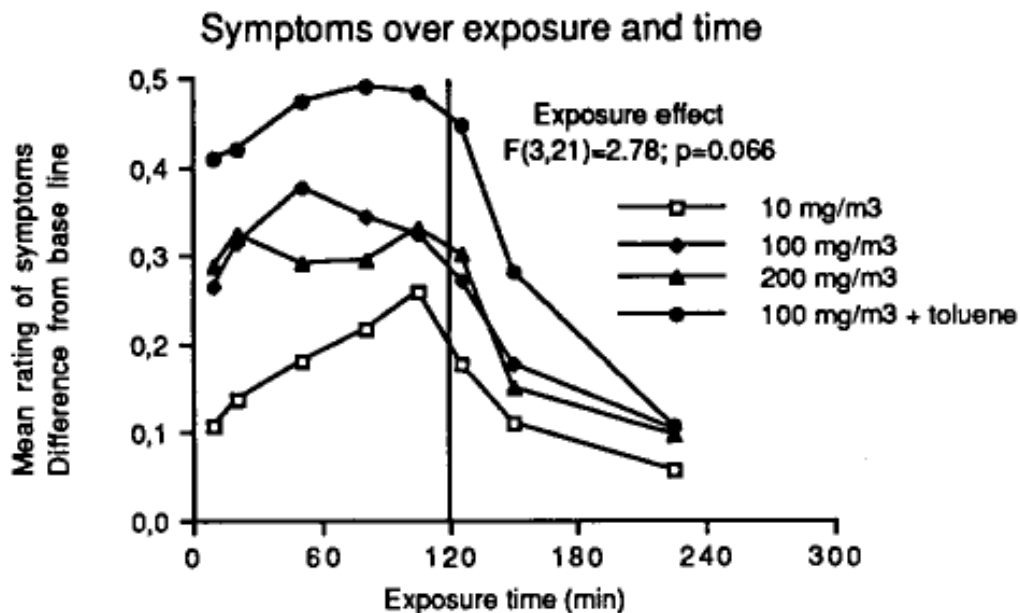
NOAEL 45 ppm or 184 mg/m³ (applying LOAEL UF = 10)

$$\begin{aligned} \text{NOAEL}_{\text{HEC}} (\text{occupational}) &= \text{NOAEL}_{\text{ADJ}} \times (H_{\text{b/g}})_{\text{A}} / (H_{\text{b/g}})_{\text{H}} \\ &= (\text{NOAEL} \times \text{Occupational duration-adjustment}) \times (H_{\text{b/g}})_{\text{A}} / (H_{\text{b/g}})_{\text{H}} \\ &\quad [\text{where, } (H_{\text{b/g}})_{\text{A}} / (H_{\text{b/g}})_{\text{H}} \text{ is a ratio of the animal blood gas partition coefficient for} \\ &\quad \text{MIBK to the human blood gas partition coefficient}] \\ &= (45 \text{ ppm} \times 6/8 \times 5/5) \times 1 \text{ (i.e. default as no blood:air partition coefficient} \\ &\quad \text{data)} \\ &= 33.75 \text{ ppm or } 138 \text{ mg/m}^3 \end{aligned}$$

This NOAEL_{HEC} (occupational) value can be used to derive a PEL by applying default UFs (combined = 100).

This would give a PEL of 0.3 ppm.

Some human studies suggest that 10 ppm may be a NOAEL for odor effects. Gagnon exposed volunteers for 7 hours and saw little differences between the 20 and 40 ppm groups in OPT and perceived odor intensity (see Table). Hjelm exposed volunteers for 2 hours and saw little difference in responses between the 25 and 50 ppm groups (11 for each group). A simple conclusion is that 20 ppm represents a LOAEL for MIBK after 2 hours and effects after that are not discernable between the two concentrations. In addition, the study by Hjelm (1990) suggests that the STEL should be lowered to 25 ppm. Subjective symptom surveys were conducted at 5 time points during the 2-hr exposures in that study and symptoms were significantly different (p = 0.066) from controls (2.5 ppm), especially so at the 5 and 15 minutes times points (estimated, see figure below). No more than 3 of 8 subjects reported symptoms at any concentration tested.



From Hjelm, 1990.

Measurement/Implementation Feasibility

| | OSHA Method | NIOSH Method |
|-------------------|---------------------------------|--|
| | ID 1004 (validated) | 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 0.3 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.

Usage information: EPA TSCA Chemical Data Reporting (CDR), EPA Toxics Release Inventories (TRI), other sources:

There are 974 businesses in the State of California CERS database reporting use of MIBK. The average daily amount of MIBK reported by these businesses is 15, 90 and 13,26 gallons for the 50, 75 and 99 percentiles.

Economic Impact Analysis/Assessment

The Division has made a determination that this proposal is not anticipated to result in a significant, statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. This proposal will not have any effect on the creation or elimination of California jobs nor result in the creation or elimination of existing businesses or affect the expansion of existing California businesses. The Division anticipates that any potential costs will be balanced by avoiding or minimizing the

costs inherent in workers' compensation claims, lost work time, and productivity losses that would have been caused by exposure related illness of employees.

The PEL proposed is consistent with recent scientific findings, of which professional health and safety staff and consultants of these employers and others with significantly exposed employees should be aware. Many of these entities already seek to control employee exposures to substances to levels below existing PELs in the interest of business continuity and minimization of tort and workers compensation liability.

Setting a Permissible Exposure Limit that is up-to-date and consistent with current scientific information and state policies on risk assessment will send appropriate market signals to employers with respect to the costs of illness and injury, which chemicals can impose on workers and their families, the government, and society at large. With appropriate market signals, employers may be better able to protect employees from exposures in the workplace and impose less of a burden on workers and society. There are no anticipated benefits to the state's environment. The economic benefits from the proposed PEL will result primarily from reduced health risk among exposed workers.

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