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Provisional Peer-Reviewed Toxicity Values for

4-Methyl-2-pentanol
(CASRN 108-11-2)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 4-METHYL-2-PENTANOL (CASRN 108-11-2)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two National Center for Environment Assessment (NCEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

4-Methyl-2-pentanol, CASRN 108-11-2, also known as methyl isobutyl carbinol (MIBC), belongs to the class of compounds known as secondary aliphatic alcohols. MIBC is used as a solvent in the paint industry, a brake fluid, a cleaning agent for semiconductors, a flotation aid, a fungicide, and an intermediate in the production of plasticizers (Falbe et al., 2013). It is listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2016) and registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2017). MIBC is formed as a byproduct in the production of methyl isobutyl ketone (MIBK) (Falbe et al., 2013).

The empirical formula for MIBC is $C_6H_{14}O$, and the chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of MIBC. MIBC is a colorless liquid at room temperature (HSDB, 2015). Its high vapor pressure and moderate Henry's law constant indicate that it is likely to exist solely as a vapor in the atmosphere and volatilize from either dry or moist surfaces. The estimated half-life of MIBC in the atmosphere is 0.8 days. The high water solubility and low estimated soil adsorption coefficient indicate that any MIBC in the environment that has not volatilized may leach to groundwater or undergo runoff after a rain event. MIBC was found to be readily biodegradable in screening tests, and it is not expected to persist in the environment (ECHA, 2016; HSDB, 2015).

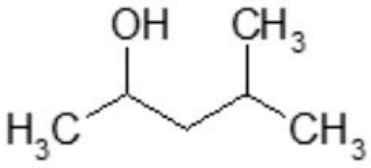


Figure 1. 4-Methyl-2-pentanol (MIBC) Structure

Table 1. Physicochemical Properties of 4-Methyl-2-pentanol (CASRN 108-11-2)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	132[a]
Melting point (°C)	−90[a]
Density (g/cm^3)	0.8[b]
Vapor pressure (mm Hg at 25°C)	5.3[a]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	1.64×10^4 [a]
Octanol-water partition coefficient (log K_{ow})	1.43[c]
Henry's law constant (atm-m^3/mol at 25°C)	4.45×10^{-5} [a]
Soil adsorption coefficient K_{oc} (L/kg)	8 (estimated)[a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.3×10^{-11} (estimated)[a]
Atmospheric half-life (d)	0.8 (estimated)[a]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	102[a]
Flash point (closed cup in °C)	NV

[a]U.S. EPA (2012b).
[b]Falbe et al. (2013).
[c]HSDB (2015).

NA = not applicable; NV = not available.

A summary of available toxicity values for MIBC from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 4-Methyl-2-pentanol (CASRN 108-11-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
IPCS	NV	NA	IPCS (2017); WHO (2017)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA (PEL)	25 ppm (100 mg/m^3)	The PEL is an 8-hr TWA; based on skin and eye irritation and CNS depression (skin designation)	OSHA (2006a); OSHA (2006b); OSHA (2011)
NIOSH (REL)	25 ppm (100 mg/m^3)	Based on skin and eye irritation and CNS depression; skin designation indicates the potential for dermal absorption	NIOSH (2016)
NIOSH (STEL)	40 ppm (165 mg/m^3)	Based on skin and eye irritation and CNS depression; skin designation indicates the potential for dermal absorption	NIOSH (2015)
NIOSH (IDLH)	400 ppm (1,650 mg/m^3)	Based on acute inhalation lethality studies in animals; this may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations >50 ppm	NIOSH (1994)
ACGIH (TLV-TWA)	25 ppm (104 mg/m^3)	Based on irritation of skin and mucous membranes; skin notation assigned based on systemic toxicity in rabbits following dermal application	ACGIH (2016)
ACGIH (TLV-STEL)	40 ppm (167 mg/m^3)	Based on irritation of skin and mucous membranes; skin notation assigned based on systemic toxicity in rabbits following topical application	ACGIH (2016)
Cancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)

Table 2. Summary of Available Toxicity Values for 4-Methyl-2-pentanol (CASRN 108-11-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	Sufficient data not available	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: IDLH = immediately dangerous to life or health; PEL = permissible exposure level; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.

CNS = central nervous system; NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in June 2015 for studies relevant to the derivation of provisional toxicity values for MIBC (CASRN 108-11-2). Searches were updated in August 2017 for MIBC and all identified potential surrogate chemicals (see Table A-1.). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessments and Related Activities (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume Information System (HPVIS), International Agency for Research on Cancer (IARC), International Programme on Chemical Safety (IPCS/INCHEM), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS), International Uniform Chemical Information Database (IUCLID), and HPV, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the noncancer and cancer data, respectively, for MIBC and include all potentially relevant short-term-, subchronic-, and chronic-duration studies. The phrase "statistical significance" and term "significant(ly)," used throughout the document, indicate a *p*-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for 4-Methyl-2-pentanol (CASRN 108-11-2)

Category	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[a]	Critical Effects	NOAEL	LOAEL	Reference (comments)	Notes[b]
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
Subchronic	12 M/12 F, Wistar rat, whole-body chamber; 0, 211, 825, 3,700 mg/m^3; 6 hr/d, 5 d/wk, 6 wk	0, 37.8, 147, 660.7	No toxicologically relevant changes in survival, clinical signs, body weight, hematology, clinical chemistry, urinalysis, or organ weight or histology	660.7	NDr	Blair et al. (1982) as cited in OECD (2005) (primary report not available; data cannot be independently reviewed)	NPR

[a]Dosimetry: HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of blood-gas partition coefficients (animal:human). For MIBC, the values for the human, rat, and mouse blood-air partition coefficients are unknown, so the default ratio of 1 was applied (U.S. EPA, 1994).
[b]Notes: NPR = not peer reviewed.

EXRESP = extrarespiratory; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; MW = molecular weight; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for 4-Methyl-2-pentanol (CASRN 108-11-2)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

No repeated-exposure human studies have been identified.

ANIMAL STUDIES

The repeated-exposure toxicity data for MIBC are limited to an unpublished 6-week inhalation study in rats available only from secondary sources [Blair et al. (1982) as cited in OECD (2005)].

Oral Exposures

No repeated-dose oral exposure studies in laboratory animals have been identified.

Inhalation Exposures

Blair et al. (1982) as cited in OECD (2005)

In an unpublished study available only from secondary sources, groups of Wistar rats were exposed whole-body to MIBC at concentrations of 0, 211, 825, or 3,700 mg/m^3 for 6 hours/day, 5 days/week for 6 weeks. Rats were examined twice daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. Blood and urine were collected at sacrifice for hematology, clinical chemistry, and urinalysis (the endpoints examined were not available). The brain, heart, kidney, liver, spleen, and testes were weighed at sacrifice and histology was conducted on a complete set of 31 tissues.

No deaths, clinical signs of toxicity, or body-weight effects were reported. No exposure-related changes were observed in hematological parameters. Serum alkaline phosphatase (ALP) was significantly increased in females from the high-exposure group by 18%, compared with controls; no other clinical chemistry changes were reported. Exposure-related changes in urinalysis parameters included increased levels of ketone bodies in the urine of all exposed females and males at ≥825 mg/m^3 and proteinuria in males at 3,700 mg/m^3 (magnitude and statistics not reported). Kidney weights were significantly elevated in males from the high-exposure group by 9%, compared with controls; it is unclear from the secondary report whether these data are for absolute and/or relative kidney weights. No other organ-weight changes were attributable to exposure. No histopathological lesions were associated with exposure to MIBC. The clinical chemistry, urinalysis, and kidney-weight findings were not considered toxicologically significant by the study authors.

For this study, the reported concentrations 0, 211, 825, and 3,700 mg/m^3 have been converted to human equivalent concentrations (HECs) of 0, 37.8, 147, and 660.7 mg/m^3, respectively, for extrarespiratory effects from a Category 3 gas, based on the following equation: Concentration (HEC) = Concentration × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio (U.S. EPA, 1994). The values for the human and rat blood-air partition coefficients for MIBC are unknown, so the default ratio of 1 has been applied. The highest exposure of 660.7 mg/m^3 is a no-observed-adverse-effect level (NOAEL) (HEC) based on a lack of toxicologically relevant findings associated with MIBC exposure; however, these findings cannot be independently reviewed due to unavailability of the primary report.

Chronic-Duration/Carcinogenicity Studies

No chronic-duration inhalation studies have been identified in laboratory animals.

Reproductive/Developmental Studies

No reproductive/developmental inhalation studies have been identified in laboratory animals.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity

Genotoxicity data for MIBC are limited to a single study, which found the chemical to be nonmutagenic in *Salmonella typhimurium* and *Escherichia coli* bacteria with metabolic activation (Shimizu et al., 1985).

Absorption, Distribution, Metabolism, and Elimination Studies

Information regarding the pharmacokinetics of MIBC is meager. The compound is metabolized to MIBK and then to 4-hydroxy-4-methyl-2-pentanone (HMP) following exposure.

Gingell et al. (2003) evaluated the extent of metabolism of MIBC to MIBK after administering a single dose of either compound (approximately 500 mg/kg) to male rats by gavage in corn oil. Plasma levels of MIBK, MIBC, and HMP were determined up to 8 hours after dosing. There were no deaths or clinical signs of toxicity in the study. HMP was the predominant metabolite in the plasma following dosing with MIBK or MIBC, with similar areas under the curve (AUCs) and both compounds achieving maximum concentration at 9 hours after dosing. At 9 hours the plasma levels of MIBK and AUC were also comparable after MIBK or MIBC administration. By comparing combined AUCs for MIBK and HMP, the study authors estimated that the extent of metabolism of MIBC to MIBK was at least 73%, and proposed that MIBC is metabolized to MIBK via alcohol dehydrogenase and further oxidized to HMP via mixed function oxidase (OECD, 2005).

Granvil et al. (1994) examined the metabolism of MIBC in mice. Groups of eight male Charles River CD-1 mice were administered a single intraperitoneal (i.p.) injection of 2.5 mmol/kg (255.5 mg/kg) of MIBC, and the concentrations of metabolites were measured in the blood and brain 15, 30, 60, and 90 minutes after dosing. Parent compound, MIBK, and HMP were detected in the blood and brain. Levels of MIBC were highest (≈82 µg/mL and ≈73 µg/g, respectively) at 15 minutes; levels of MIBK were also highest (≈28 µg/mL and ≈23 µg/g, respectively) at 15 minutes and subsequently rapidly decreased at similar rates. In contrast, HMP peaked at ≈34 µg/mL and ≈30 µg/g, respectively after 30−60 minutes and only gradually decreased.

A study in rabbits indicated that MIBC metabolites may undergo glucuronic acid conjugation prior to excretion (Kamil et al., 1953). Following a single gavage exposure of 25 mmol MIBC/rabbit (850 mg/kg), 33.7% of the administered dose was recovered as glucuronic acid in the urine. Urinary glucuronide levels returned to baseline within 48 hours. The study authors also reported a "small amount" of methyl ketone (which they presumed to be MIBK) in the urine.

Divincenzo et al. (1976) identified metabolites from serum of guinea pigs treated with MIBK via i.p. administration. The study authors noted that the concentration of MIBC was too

low to quantify. The study authors determined that the half-life for MIBK is 66 minutes with a clearance time of 6 hours. The major metabolite (HMP) had a clearance time of 16 hours.

Acute Irritation Study in Humans

Human studies are limited to a single acute controlled-exposure irritation-threshold study by Silverman et al. (1946). In this study, a group of 12 subjects (both sexes, number per sex not reported) were exposed to various concentrations of MIBC for 15 minutes. A majority of subjects reported eye irritation at 50 ppm (200 mg/m^3), with nose and throat irritation at >50 ppm. The highest concentration that the majority of subjects estimated to be acceptable for an 8-hour exposure was 25 ppm (100 mg/m^3).

Acute Exposure Studies in Animals

Oral Exposure

Groups of mice (five/group; sex and strain not reported) were exposed to MIBC at doses of 1.0, 1.5, or 2.0 mL/kg via gavage as temporary emulsion (10−40%) in 1% aqueous Tergitol (McOmie and Anderson, 1949). The authors indicate that the chemicals in the study are "closely approximate to, but not necessarily the equivalent of, the pure compounds." Mice were observed for 7 days. Anesthesia (observed as loss of righting reflex) was observed in 2/5, 5/5, and 5/5 mice from the 1.0-, 1.5-, and 2.0-mL/kg dose groups, respectively. Mortality was observed in 1/5, 4/5, and 5/5 mice from the 1.0-, 1.5-, and 2.0-mL/kg dose groups, respectively. Based on the mortality data, a median lethal dose (LD_{50}) value of 1.5 mL/kg (1,200 mg/kg) was estimated for MIBC (McOmie and Anderson, 1949). Hyperemia of the stomach wall and duodenum was a common gross pathology finding in the mice that died from treatment with the chemical. In another acute lethality study, an LD_{50} value of 2.50 g/kg (95% confidence interval [CI]: 2.26−2.97 g/kg) was reported for male Wistar rats exposed to MIBC via gavage in water. The rats were observed for 14 days after dosing (Smyth et al., 1951). No gross pathology data for the rats were presented.

The effect of oral administration of MIBC on the cholestasis induced by manganese-bilirubin or manganese alone was studied in rats (Vézina and Plaa, 1988). The experimental design involved single and repeated (once daily for 3 days) gavage treatment prior to administration of the cholestatic agent. Significant increases in manganese-bilirubin-induced cholestasis were observed following a single exposure to ≥3.75 mmol/kg MIBC or repeated exposures to ≥1.88 mmol/kg MIBC, compared with exposure to the cholestatic agent alone. MIBC pretreatment also caused small, but significant, increases in manganese-induced cholestasis at a dose of 7.5 mmol/kg. The study authors proposed that MIBC potentiated cholestasis via metabolic transformation to MIBK because many ketogenic substances have been shown to potentiate cholestatic liver injury. MIBC did not induce cholestasis when administered without the cholestasis inducers. Similarly, a single gavage exposure of MIBC prior to the administration of chloroform potentiated chloroform-induced liver injury in rats at doses ≥5 mmol/kg (Vézina et al., 1990). None of the animal groups received MIBC alone in the chloroform study.

Inhalation Exposure

Groups of mice (10/group, strain and sex not reported) were exposed to air saturated with commercial-grade MIBC for 4, 8.5, 10, or 15 hours. The mice were observed during exposure and for 7 days thereafter. The study authors estimated air concentrations of 20 mg/L at 20°C (20,000 mg/m^3) (McOmie and Anderson, 1949). Irritation, somnolence, and anesthesia were

observed as early as 5 minutes, 1 hour, and 4 hours after exposure, respectively. Anesthesia (observed as loss of righting reflex) was observed in 7/10 animals in the 4-hour exposure group and 10/10 animals in each of the longer duration exposure groups. Deaths occurred in the 10-hour (6/10) and 15-hour (8/10) exposure groups only. Repeated 4-hour exposures to air saturated with MIBC vapor also caused deep anesthesia in mice, with full recovery after exposure cessation; no cumulative effects or deaths were noted (12 total exposures, and the time between exposures was not reported) (McOmie and Anderson, 1949).

Carpenter et al. (1949) exposed a total of six Sherman albino rats (mixed male and female, number/sex not given) to MIBC for 4 hours at a concentration of 2,000 ppm (8,300 mg/m^3). The study authors reported MIBC within a group of other compounds that killed between two and four rats at this concentration; no further details were provided. Smyth et al. (1951) exposed six male albino rats (strain not given) for 8 hours to 2,000 ppm (8,300 mg/m^3) with a 2-week observation period. Death occurred in 5/6 animals.

Dermal Exposure

Dermal application of undiluted MIBC to three rabbits (sex and strain not reported) caused slight erythema within 15 minutes, with moderate erythema and drying developing postexposure (McOmie and Anderson, 1949). Severe drying of the skin, with some cracking and sloughing, was reported in three rabbits (sex and strain not reported) following five dermal applications of MIBC at a concentration of 3 mL/kg (2,400 mg/kg); no systemic effects were noted (McOmie and Anderson, 1949). Smyth et al. (1951) reported an acute dermal LD_{50} in rabbits of 3.56 mL/kg (2,850 mg/kg).

Subchronic-Duration Animal Studies with Principal Metabolite

Nephropathy was observed in male and female Sprague-Dawley (S-D) rats following oral exposure to HMP for 45 days (premating, mating, gestation, and 3 days lactation) at gavage doses of ≥100 and ≥300 mg/kg-day, respectively [Ministry of Health and Welfare: Japan (1997) as cited in OECD (2005)]. In males, but not females, nephropathy was associated with hyaline droplets. Additional adverse effects at ≥300 mg/kg-day included decreased locomotor activity in both sexes. At 1,000 mg/kg-day, additional effects included decreased body-weight gain in females, altered blood parameters in males (increased platelet count, aspartate aminotransferase [AST], total protein, total cholesterol, total bilirubin, blood urea nitrogen [BUN], creatinine, calcium, and decreased glucose; magnitudes not reported), hepatocellular hypertrophy in both sexes, and vacuolization in zona fasciculate of adrenals in males. No adverse reproductive or developmental effects were reported.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer reference values, respectively.

Table 4. Summary of Noncancer Reference Values for 4-Methyl-2-pentanol (CASRN 108-11-2)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Screening subchronic p-RfC (mg/m^3)[a]	Rat and mouse/both	Reduced fetal body weight, skeletal variations, and increased fetal death in mice; and skeletal variations in rats	3×10^0	NOAEL (HEC)	1,026 (based on surrogate POD)	300	Tyl et al. (1987) as cited in U.S. EPA (2003c)
Screening chronic p-RfC (mg/m^3)[a]	Rat and mouse/both	Reduced fetal body weight, skeletal variations, and increased fetal death in mice; and skeletal variations in rats.	3×10^0	NOAEL (HEC)	1,026 (based on surrogate POD)	300	Tyl et al. (1987) as cited in U.S. EPA (2003c)

[a]Based on MIBK as a surrogate.

HEC = human equivalent concentration; MIBK = 4-methyl-2-pentanone or methyl isobutyl ketone; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 5. Summary of Cancer Reference Values for 4-Methyl-2-pentanol (CASRN 108-11-2)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

No studies have been located regarding the toxicity of MIBC to humans by oral exposure. Animal studies of oral exposure to MIBC are limited to acute lethality studies, which are of inadequate duration and scope to support derivation of a subchronic or chronic provisional reference dose (p-RfD). As a result of the limitations of the available oral toxicity data for MIBC, subchronic and chronic p-RfDs are not derived. Lack of a satisfactory surrogate with an independent peer-reviewed published toxicity assessment for oral exposure precludes development of a screening subchronic or chronic p-RfD. See discussion in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Human studies of inhalation exposure to MIBC are limited to a single, acute irritation study (Silverman et al., 1946). Available repeated-dose animal studies of MIBC are inadequate to support derivation of a subchronic or chronic provisional reference concentration (p-RfC) due to limited reporting or unavailability of the primary report (Blair, 1982). Available acute lethality studies are of inadequate duration and scope to support derivation of a subchronic or chronic p-RfC. As a result of the limitations of the available inhalation toxicity data for MIBC, subchronic and chronic p-RfCs are not derived directly. Instead, screening p-RfCs are derived in Appendix A using an alternative surrogate approach.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No relevant data are available for MIBC. Under the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *"Inadequate Information to Assess Carcinogenic Potential"* of MIBC following both oral and inhalation exposure as shown in Table 6.

Table 6. Cancer WOE Descriptor for 4-Methyl-2-pentanol (CASRN 108-11-2)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no suitable animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No adequate studies evaluating carcinogenicity effects in humans or animals exposed to MIBC are available.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; NA = not applicable; NS = not selected; WOE = weight of evidence.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The absence of suitable data precludes development of cancer potency values for MIBC.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity value (PPRTV) document, it is inappropriate to directly derive provisional toxicity values for 4-methyl-2-pentanol (methyl isobutyl carbinol [MIBC]). However, information is available for a surrogate chemical which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information for potential surrogate chemicals in an appendix and develops a "screening value" based on dose-response data (e.g., point of departure [POD]) from the single best surrogate. Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH

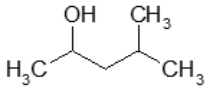
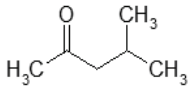
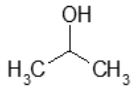
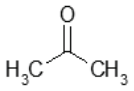
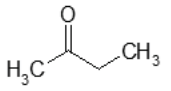
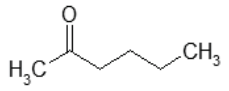
The surrogate approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity-like) are identified to facilitate the final surrogate selection. The surrogate approach may or may not be applicable to multiple routes of exposure. All information is considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable surrogate.

Structural Surrogates (Structural Analogs)

An initial surrogate search focused on identifying structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. Under Wang et al. (2012), structural similarity for analogs is typically evaluated using U.S. EPA's DSSTox database (DSSTox, 2016) and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2017). However, at the time of preparation of this document, DSSTox was not available. In lieu of DSSTox scores, the Organisation for Economic Co-operation and Development (OECD) Toolbox was used to calculate structural similarity using the Tanimoto method (the same quantitative method used by ChemIDplus and DSSTox). Five structural analogs to MIBC that have oral and/or inhalation noncancer toxicity values were identified: 4-methyl-2-pentanone (methyl isobutyl ketone [MIBK]) (U.S. EPA, 2003c), 2-propanol (isopropanol) (U.S. EPA, 2014), 2-propanone (acetone) (U.S. EPA, 2003a; ATSDR, 1994), 2-butanone (methyl ethyl ketone [MEK]) (U.S. EPA, 2003b), and 2-hexanone (methyl butyl ketone [MBK]) (U.S. EPA, 2009). MIBC and isopropanol are secondary alcohols (i.e., aliphatic C2 alcohols). The other identified potential surrogates are aliphatic C2 ketones. Table A-1 summarizes the analogs' physicochemical properties and similarity scores. The ChemIDplus similarity score for MIBK was 66%; there was no information on the other potential surrogates in ChemIDplus. The OECD Toolbox similarity scores were 30% for MIBK,

27% for isopropanol, and <5% for the remaining potential surrogates. Under the current tiered surrogate approach (Wang et al., 2012), similarity scores ≥50% are preferential in identification of structural analogs. The low similarity scores for potential structural analogs of MIBC in OECD's toolbox are likely related to the limited number of structural descriptors available for this target compound. Structural similarity metrics use a variety of structural descriptors to calculate similarity (although the nature of the descriptors may vary across different tools). Similarity scores calculated for compounds with few structural descriptors will be disproportionately influenced by changes in, or absence of, a single descriptor, while these same changes have relatively lower impact on similarity scores for compounds with many descriptors. Thus, similarity scores may be of limited use when comparing surrogates with relatively simple structures such as those evaluated in this assessment. Physicochemical properties of the potential surrogates suggest that MIBC, MIBK, and MBK are less hydrophilic and less volatile than isopropanol, acetone, and MEK; however, all compounds are expected to be bioavailable following oral and inhalation exposure. Based primarily on the highest similarity score across two separate structural platforms (i.e., OECD Toolbox and ChemIDplus), MIBK is identified as a candidate surrogate chemical for MIBC.

Table A-1. Physicochemical Properties of 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates[a]

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Structure						
CASRN	108-11-2	108-10-1	67-63-0	67-64-1	78-93-3	591-78-6
Molecular weight	102	100	60	58	72	100
ChemIDplus similarity score (%)[b]	100	66	NV	NV	NV	NV
OECD Toolbox similarity score (%)[c]	100	30	27	3	2	4
Melting point (°C)	−90	−84	−90	−94.8	−87	−56
Boiling point (°C)	132	117	82	56	80	128
Vapor pressure (mm Hg at 25°C)	5.3	19.9	45.4	232	90.6	11.6
Henry's law constant (atm−m^3/mole at 25°C)	4.45×10^{-5}	1.4×10^{-4} (estimated)[a]	8.1×10^{-6}	3.5×10^{-5}	5.69×10^{-5}	9.3×10^{-5}
Water solubility (mg/L)	1.64×10^{4}	1.9×10^{4}	1×10^{6}	1×10^{6}	2.23×10^{5}	1.72×10^{4}
Log K_{ow}	1.43[d]	1.31	0.05	−0.24	0.29	1.38
pKa	NA	NA	17.1	20	14.7	NA

[a]Data were gathered from PHYSPROP database for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]ChemIDplus Advanced, similarity scores (ChemIDplus, 2017).
[c]OECD (2017).

MBK = methyl butyl ketone; MEK = methyl ethyl ketone; MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; MIBK = 4-methyl-2-pentanone or methyl isobutyl ketone; NA = not applicable; NV = not available; OECD = Organisation for Economic Co-operation and Development.

Metabolic Surrogates

Table A-2 summarizes available toxicokinetic data for MIBC and the structurally similar compounds identified as potential surrogates.

MIBK is considered a metabolic surrogate for MIBC based on bidirectional metabolism between MIBC and MIBK and common downstream metabolites (OECD, 2005; Gingell et al., 2003; U.S. EPA, 2003c; Duguay and Plaa, 1995; Granvil et al., 1994). Figure A-1 shows the metabolic bidirectional metabolism of MIBC and MIBK, modified from Divincenzo et al. (1976). Following oral exposure, MIBK and MIBC can be metabolized into each other, and ultimately produce a common downstream oxidation metabolite, 4-methyl-4-hydroxy-2-pentanone (HMP), with similar kinetics. Available data indicate that both compounds are rapidly absorbed, distributed, and metabolized, but data are inadequate to characterize excretion patterns following exposure. Similar bidirectional metabolism has been described for other C2 alcohol/C2 ketone pairs including potential surrogates for MIBC (MBK, MEK, isopropanol, and acetone) (U.S. EPA, 2014, 2009; Clark et al., 2004; U.S. EPA, 2003a, b; Clewell et al., 2001; ATSDR, 1994). Additionally, bidirectional metabolism between isopropanol and acetone has been used to develop connected physiologically based pharmacokinetic (PBPK) models (Clark et al., 2004; Clewell et al., 2001). These precedents support that C2 alcohol/C2 ketone pairs, including MIBC and MIBK, are metabolic surrogates for one another.

Isopropanol, acetone, and MEK, along with MIBK and MIBC, are all metabolized via common oxidative metabolic pathways leading to carbon dioxide (CO_2) (U.S. EPA, 2014; Clark et al., 2004; U.S. EPA, 2003a, b; Clewell et al., 2001; ATSDR, 1994); however, oxidation to CO_2 is too general a pathway to use in selecting a surrogate because many small organic compounds share this ultimate product. In addition, isopropanol, acetone, and MEK do not show the bidirectional metabolic relationship with MIBC as observed between MIBC and MIBK. Further, MBK and MEK are also rejected as applicable metabolic surrogates for MIBC due to the metabolic formation of 2,5-hexanedione as the primary metabolite (U.S. EPA, 2009; Duguay and Plaa, 1995; ATSDR, 1992a), which is a known potent peripheral nerve toxicant. Metabolic production of a similarly arranged dione is not possible for MIBC (Duguay and Plaa, 1995). Therefore, only MIBK is considered an appropriate metabolic surrogate for MIBC.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
CASRN 108-11-2	CASRN 108-10-1	CASRN 67-63-0	CASRN 67-64-1	CASRN 78-93-3	CASRN 591-78-6
Absorption after oral exposure					
Rapid absorption: • In rats, MIBC and metabolites were detected in blood within 8−9 hr after single gavage doses. • Extent of absorption was not measured.	Rapid absorption: • In rats, dose-related increase in MIBK blood levels occurred 1 hr after 3 daily gavage doses. • Extent of absorption was not measured.	Rapid and extensive absorption: • In humans or rats given oral doses of isopropanol, peak blood levels were attained for isopropanol within 1−2 hr and for acetone within 4−10 hr.	Rapid and extensive absorption based on elimination in urine and expired air (see below).	Rapid absorption: • In rats given single oral doses, MEK was rapidly detected in blood; peak levels at 1−4 hr, depending on dose. • Extent of absorption was not measured.	Extensive absorption: • In humans, 66% of a single oral dose was absorbed. • In rats given single oral doses, 98% of the administered dose was absorbed. • Rate of absorption was not measured.
Distribution after oral exposure					
No data for oral exposure, but similar appearance and clearance of the common metabolite, HMP, occurred in blood and brain after i.p. injection of MIBC or MIBK in mice.	Rapid distribution: • In rats, 1 hr after 3 doses, MIBK and principal metabolite (HMP) were detected in blood, liver, and lung. • Levels in other tissues were not measured.	ND	No data for oral exposure, but wide distribution expected based on mouse inhalation data.	No data for oral exposure, but wide distribution expected based on human inhalation data.	Wide distribution and rapid postexposure clearance: • Radiolabel was detected in most rat tissues at 4 hr with highest counts in liver > kidney > brain. • At 24 hr, radioactivity in tissues was decreased by about 50% of 4-hr values.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Metabolism after oral exposure					
Rapid bidirectional metabolism between MIBC and MIBK and metabolic production of common downstream oxidation products: • In rats after oral dose, MIBK and HMP were detected in blood. • Combined MIBK and HMP AUCs indicated 73% metabolism within 8−9 hr. • 9-hr AUCs for HMP in blood were similar in rats after oral dose of MIBC or MIBK.	Rapid bidirectional metabolism between MIBK and MIBC and metabolic production of common downstream oxidation products: • In rats after oral dose, HMP was detected in blood, liver, and lung; MIBC was a minor component in blood, but was detected after i.p. and inhalation exposure. • 9-hr AUCs for HMP in blood were similar in rats after oral dose of MIBC or MIBK.	Rapid bidirectional metabolism between isopropanol and acetone and entry into intermediary metabolism: • Studies of humans and rodents indicate that absorbed isopropanol, regardless of route, can be metabolically converted to acetone. • Oxidative metabolism to methylglyoxal and 1,2-propanediol, then rapidly converted to CO_2.	Rapid bidirectional metabolism between acetone and isopropanol: • Studies of humans and rodents indicate that absorbed acetone, regardless of route, can be metabolically converted to 2-propanol. • Oxidative metabolism to methylglyoxal and 1,2-propanediol, then rapidly converted to CO_2.	Rapid bidirectional metabolism between MEK and 2-butanol and metabolic production of common downstream oxidation products: • In rats, common metabolites (3-hydroxy-2-butanone and 2,3-butanediol) were formed and eliminated with similar kinetics after oral dose of 2-butanol or MEK. • Metabolic interconversion between MEK and 2-butanol occurs in humans following inhalation exposure.	Rapid bidirectional metabolism between MBK and 2-hexanol and metabolic production of common downstream oxidation products: • In rats after oral dose, 2-hexanol, 5-hydroxy-2-hexanone, and 2,5-hexanedione were detected in blood; 2,5-hexanedione was the predominant metabolite.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Excretion after oral exposure					
Excretion in urine: • In rabbits exposed to MIBC via gavage, 33.7% of the administered dose was recovered as glucuronic acid in the urine. "Small amounts" of MIBK were also detected.	ND	Minor excretion of parent compound in exhaled air and urine; formation of CO_2 through gluconeogenesis: • PBPK model development indicates that pathways of excretion are expected to be the same as acetone.	Minor excretion of parent compound in exhaled air and urine; formation of CO_2 through gluconeogenesis: • In humans, 65−93% of oral dose was metabolized to CO_2 and remainder was eliminated unchanged in urine and expired air. • In rats, 47% of single doses of acetone in water was excreted as CO_2 in exhaled air in 13.5 hr.	ND	Excretion in urine and in exhaled air as CO_2: • In humans, ~40% of ^{14}C-labeled dose was excreted in breath (as CO_2) and 26% in urine (chemical form unidentified) after 8 d. • In rats, 1% of ^{14}C-labeled dose was in feces, 44% in exhaled breath, 38% in urine, and 15% remained in carcass after 48 hr. • In dogs given i.v. ^{14}C-MBK, breath contained ~1% of dose as MBK and ~10% as CO_2; urine contained 6−7% after 8 hr.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Absorption after inhalation exposure					
ND	Rapid and extensive absorption: • In humans breathing MIBK, ~56−62% absorption was measured. • In rats, dose-related elevated MIBK blood levels were noted after the last of 3 daily 4-hr exposures. • Measured human blood-air and oil/air coefficients = 9 and 926.	Rapid and extensive absorption: • In rats breathing isopropanol, blood levels of isopropanol and acetone rose quickly. • Blood-air partition coefficients were 1,290 in rats and 848 in humans.	Rapid and extensive absorption: • In humans breathing acetone, fractional uptakes were 39−52 and 53%. • Blood-air partition coefficients for rats or humans ranged from 210−301.	Rapid and extensive absorption: • In humans breathing MEK, ~70 and ~50% retentions were measured. • Blood-air partition coefficients were ~140 for rats and 125−202 for humans. Oil/air coefficient was 131.	Rapid and extensive absorption: • In humans breathing MBK, 75−92% absorption was measured. • In dogs, 65−68% absorption was measured. • Blood-air coefficient of 127 was measured with human blood.
Distribution after inhalation exposure					
No data for inhalation exposure, but similar appearance and clearance of the common metabolite, HMP, occurred in blood and brain after i.p. injection of MIBC or MIBK in mice.	Wide distribution: • In rats, dose-related increases in MIBK and metabolites were found in plasma, liver, and lungs after inhalation exposure; no other tissues examined.	ND	Rapid and wide distribution with some preference for water-enriched tissues: • In mice breathing acetone, highest levels were in water-enriched tissues. • Acetone levels in all tissues returned to background levels within 24 hr postexposure.	Wide tissue distribution, but fat preference not expected: • In two cases of MEK-exposed workers, postmortem MEK tissue/air solubility ratios for kidney, liver, muscle, lung, heart, fat, and brain were similar. • Air partition coefficients (in vitro) were equivalent in various rat tissues and blood.	Wide distribution: • In rats, dose-related increases in MBK and metabolites (2-hexanol and 2,5-hexanedione) were found in plasma, liver, and lungs after inhalation exposure; no other tissues were examined.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Metabolism after inhalation exposure					
ND	Rapid bidirectional metabolism between MIBK and MIBC, and metabolic production of common downstream oxidation products.	Rapid bidirectional metabolism between isopropanol and acetone and entry into intermediary metabolism, regardless of exposure route (see "Oral Section" above).	Rapid bidirectional metabolism between acetone and isopropanol and entry into intermediary metabolism, regardless of exposure route (see "Oral Section" above).	Rapid bidirectional metabolism between MEK and 2-butanol and metabolic production of common downstream oxidation products: • In humans breathing MEK, 2-butanol and 2,3-butanediol were detected in serum and 3-hydroxy-2-butanone and 2,3-butanediol were detected in urine.	Rapid bidirectional metabolism between MBK and 2-hexanol and metabolic production of common downstream oxidation products: • In humans breathing MBK, 2,5-hexandione was detected in serum postexposure. • In rats after oral or inhalation exposure, 2-hexanol, 5-hydroxy-2-hexanone, and 2,5-hexanedione were identified as metabolites in serum, liver, and lungs.

Table A-2. Comparison of Available ADME Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Excretion after inhalation exposure					
ND	No data characterizing excretion pathways after inhalation: • In humans after breathing MIBK, 2-phase elimination of MIBK in blood was seen, but body-excretion pathways were not characterized. • MIBK, HMP, and MIBC were not detected in 3-hr postexposure urine.	Minor excretion of parent compound in exhaled air and urine and primary elimination by intermediary metabolism to CO_2: • PBPK model development indicates that pathways of excretion are expected to be the same as for acetone.	Minor excretion of parent compound in exhaled air and urine and primary elimination by intermediary metabolism to CO_2, regardless of route: • In humans after breathing acetone for 2 hr, 16−27% of absorbed acetone was in 4-hr expired air as nonmetabolized acetone, <1% was in urine, and remainder was assumed to have been metabolized through intermediary metabolism.	Minor excretion in exhaled air and urine and primary elimination by intermediary metabolism to CO_2: • In humans, urinary excretion of MEK and metabolites and exhalation of MEK only accounted for 0.1−3% of the absorbed dose. The remainder was expected to be converted to CO_2 via intermediary metabolism.	Excretion in exhaled air as parent material and CO_2 and as other metabolites in urine: • In humans breathing MBK for 4−7.5 hr, MBK was detected in expired air during and after exposure, but metabolites were not detected. MBK and metabolites were not detected in urine. • In dogs given i.v. ^{14}C-MBK, breath contained ~1% of dose as MBK and ~10% as CO_2; urine contained 6−7% after 8 hr.
OECD (2005); Gingell et al. (2003); Granvil et al. (1994); Kamil et al. (1953)	U.S. EPA (2003c); Duguay and Plaa (1995); Granvil et al. (1994); Duguay and Plaa (1993)	U.S. EPA (2014); Clark et al. (2004); Clewell et al. (2001)	U.S. EPA (2003a); ATSDR (1994)	U.S. EPA (2003b); ATSDR (1992a)	U.S. EPA (2009); Duguay and Plaa (1995); ATSDR (1992b)

ADME = absorption, distribution, metabolism, and excretion; AUC = area under the curve; CO_2 = carbon dioxide; HMP = 4-hydroxy-4-methyl-2-pentanone; i.p. = intraperitoneal; i.v. = intravenous; MBK = methyl butyl ketone; MEK = methyl ethyl ketone; MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; MIBK = 4-methyl-2-pentanone or methyl isobutyl ketone; ND = no data; PBPK = physiologically based pharmacokinetic.

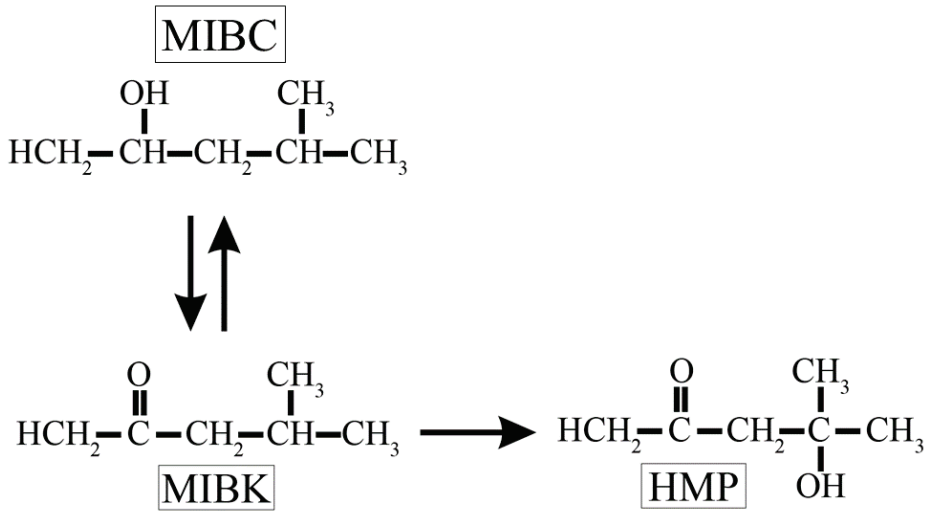


Figure A-1. MIBK Metabolism: 4-Methyl-2-pentanol (MIBC), Methyl Isobutyl Ketone (MIBK), 4-Methyl-4-hydroxy-2-pentanone (HMP) (Divincenzo et al., 1976)

Toxicity-Like Surrogates (Oral)

Table A-3 summarizes available oral and inhalation toxicity values for MIBC and the compounds identified as potential structural surrogates.

MIBC and all potential surrogates exhibit relatively low acute oral toxicity. Although there are no repeated-dose oral toxicity data for MIBC, HMP (the common metabolite for MIBC and MIBK) has been studied in a 45-day gavage study in rats; this study was published in Japanese and was only available from a secondary source [Ministry of Health and Welfare: Japan (1997) as cited in OECD (2005)]. The critical effect was nephropathy in males at 1,000 mg/kg-day and females at ≥300 mg/kg-day (male nephropathy was identified to include hyaline droplets suggesting the potential involvement of an alpha 2u-mediated pathway, bringing into question the biological relevance of the kidney effect in this sex). Additional effects in males and females included general central nervous system (CNS) depression (≥300 mg/kg-day) and liver and adrenal damage (1,000 mg/kg-day). Whereas the oral toxicity database for HMP can provide insight to the potential toxic effects of MIBC, HMP was not identified as a structural surrogate and it is therefore unclear if the oral toxicity data for HMP are directly relevant to MIBC.

There are limited oral toxicity data for MIBK, however increased liver and kidney weights were observed in rats at ≥250 mg/kg-day (U.S. EPA, 2003c). Effects of oral exposure to isopropanol include developmental effects in rabbits (240 mg/kg-day) and rats (≥596-mg/kg-day). Multiple organ weights, including liver and kidney, were increased in rats at ≥711 mg/kg-day isopropanol coupled with decreased body weight at ≥1,605 mg/kg-day (U.S. EPA, 2014). The kidney is a target organ for oral exposure to acetone as nephropathy was observed in rats at ≥500 mg/kg-day. Hematological changes were also observed in rats at ≥1,700 mg/kg-day acetone as well as reproductive effects at 3,400 mg/kg-day. CNS effects (i.e., decreased motor nerve conduction velocity) were observed in rats at 650 mg/kg-day acetone (U.S. EPA, 2003a). There are no oral toxicity data available for MEK; however, oral data are available for 2-butanol which is considered an appropriate surrogate for MEK. Developmental effects were observed after treatment with 2-butanol at ≥1,771 mg/kg-day as well as renal effects (i.e., nephropathy) at ≥3,122 mg/kg-day (U.S. EPA, 2003b). MBK-induced peripheral nerve toxicity was observed in rats at ≥143 mg/kg-day and in chickens and guinea pigs at various doses (U.S. EPA, 2009). As discussed in the "Metabolic Surrogates" section, peripheral nerve toxicity caused by MBK is due to the metabolic formation of 2,5-hexanedione, a product not expected to be produced by the metabolism of MIBC.

In conclusion, MBK and MEK are not considered ideal toxicity-like surrogates for MIBC due to 2,5-hexanedione-dependent peripheral neuropathy. As discussed earlier in the "Metabolic Surrogates" section of this Appendix, it is not possible to form the metabolite responsible for peripheral neuropathy following exposure to MIBC. The remaining surrogates (i.e., MIBK, isopropanol, and acetone) appear to all share the kidneys as a target organ for oral toxicity, but the relevance of these effects to the potential toxicity of MIBC remains uncertain (e.g., hyaline droplet nephropathy following HMP exposure in male rats; complete lack of repeat-dose toxicity information for MIBC). In the complete absence of repeated-dose oral toxicity data for MIBC, there is no basis for identification of a single best toxicity-like surrogate for the oral route of exposure.

Toxicity-Like Surrogates (Inhalation)

As described above, MBK and MEK were not considered as applicable toxicity like surrogates for MIBC due to 2,5-hexanedione dependent peripheral neuropathy. Because this information also pertains to the inhalation route, the potential of MBK and MEK as applicable inhalation toxicity-like surrogates for MIBC is not further discussed.

No acute inhalation toxicity data were available for MIBC; acute inhalation toxicity is low for all surrogates. Repeated-exposure toxicity data available for MIBC are limited to an unpublished 6-week rat inhalation study available only from a secondary source [Blair et al. (1982) as cited in OECD (2005)]. Although the biological relevance of these effects are unknown, Blair et al. (1982) observed renal effects denoted as ketone bodies in the urine in males (≥147 mg/m^3 [HEC]) and females (≥37.8 mg/m^3 [HEC]) and proteinuria in males at 660.7 mg/m^3 (HEC). Additionally, kidney weights were statistically significantly elevated (9%) in males at 660.7 mg/m^3 (HEC), approaching the 10% criteria for biological significance. Similar effects have also been observed after inhalation exposure to MIBK and isopropanol. MIBK inhalation exposure caused the following renal effects: increased kidney weights in mice and rats at ≥367 mg/m^3 (HEC) and increased urine protein was also observed in male rats at 733 mg/m^3 (HEC). In addition, MIBK caused nephropathy in male and female rats at ≥2045 mg/m^3 (HEC) (U.S. EPA, 2003c). For isopropanol, the renal effects were observed following inhalation exposure including increased relative kidney weight and histopathological lesions in male and female rats at ≥1,101 mg/m^3 (HEC) (U.S. EPA, 2014). No kidney effects were observed following inhalation exposure to acetone (ATSDR, 1994). Taken together, these data suggest that the kidneys are a shared site of toxicity between MIBC, MIBK, and isopropanol but not acetone.

In addition to renal effects, developmental effects were also observed in rats following inhalation exposure to MIBK at 3,073 mg/m^3 (HEC). Additional inhalation effects for MIBK include: histopathological changes in the liver, increases in various relative organ weights (liver, testis, cauda epididymis, seminal vesicle, and adrenal weights), and reduced startle reflex at ≥2045 mg/m^3 (HEC) (U.S. EPA, 2003c). Reproductive effects were reported in mice following inhalation exposure to isopropanol at ≥221 mg/m^3 (HEC). Further inhalation effects for isopropanol include neurotoxicity, increased liver weight, adrenal gland congestion, stomach and splenic lesions, clinical signs of toxicity, and mortality. The inhalation toxicity information for acetone was limited to neurological effects in humans.

In summary, inhalation exposure studies of MIBC, MIBK, and isopropanol suggest that the kidneys are a shared site of toxicity. The available data suggest that acetone does not affect the kidneys. Therefore, MIBK and isopropanol are both considered inhalation toxicity-like surrogate compounds for MIBC.

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

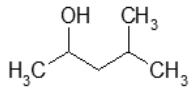
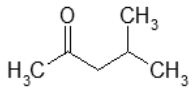
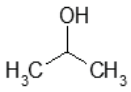
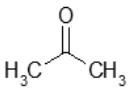
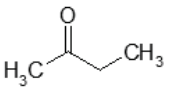
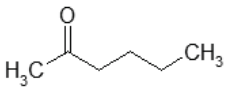
	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Structure						
CASRN	108-11-2	108-10-1	67-63-0	67-64-1	78-93-3	591-78-6
Repeated-dose toxicity—oral, subchronic						
POD (mg/kg-d)	NA	NA	55.2	NA	NA	NA
POD type	NA	NA	$BMDL_{05}$ (HED)	NA	NA	NA
Chronic UF_C	NA	NA	30 (3 UF_A, 10 UF_H)	NA	NA	NA
p-RfD/MRL (mg/kg-d)	NA	NA	2×10^0	NA	NA	NA
Critical effects	NA	NA	Decreased fetal body weight at 240 mg/kg-d	NA	NA	NA
Other effects (in principal study)	NA	NA	Maternal toxicity was observed at 480 mg/kg-d (decreased maternal food consumption and increased mortality).	NA	NA	NA
Species	NA	NA	Rabbit	NA	NA	NA
Duration	NA	NA	GDs 6−18	NA	NA	NA
Route	NA	NA	Gavage	NA	NA	NA

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Additional toxicity data (from other studies)	NA	NA	Preimplantation loss, decreased fetal body weight, and skeletal anomalies were also observed at ≥596 mg/kg-d in developmental rat studies. Several relative organ weights were increased in 12-wk and one- or two-generation reproductive studies in rats (liver, kidney, adrenal, spleen, and/or testes) at doses as low as 711 mg/kg-d. Decreased body weights were reported at ≥1,605 mg/kg-d.	NA	NA	NA
Source	NA	NA	U.S. EPA (2014)	NA	NA	NA
Repeated-dose toxicity—oral, chronic						
POD (mg/kg-d)	NA	NA	55.2	900	639	5
POD type	NA	NA	$BMDL_{05}$ (HED)	NOAEL	$BMDL_{05}$	$BMDL_{10}$
Chronic UF_C	NA	NA	30 (3 UF_A, 10 UF_H)	1,000 (3 UF_A, 10 UF_H, 3 UF_S, 10 UF_D)	1,000 (10 UF_A, 10 UF_H, 10 UF_D)	1,000 (10 UF_A, 10 UF_H, 10 UF_D)
p-RfD/RfD (mg/kg-d)	NA	NA	2×10^{0}	9×10^{-1}	6×10^{-1}	5×10^{-3}

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Critical effects	NA	NA	Decreased fetal body weight at 240 mg/kg-d	Mild nephropathy	Decreased fetal body weight at 1,771 mg/kg-d	Axonal swelling of the peripheral nerve at 143 mg/kg-d
Other effects (in principal study)	NA	NA	Maternal toxicity was observed at 480 mg/kg-d (decreased maternal food consumption and increased mortality).	Increased severity of nephropathy, macrocytic and normochromic anemia in males at 1,700 mg/kg-d Increased relative testes weight, decreased sperm motility, caudal and epididymal weights, and increased incidence of abnormal sperm at 3,400 mg/kg-d	Parental toxicity (decreased male mating index, decreased male and female body weight), decreased pup survival, and nephropathy in F1 males (potentially α2u-g associated) were noted at ≥3,122 mg/kg-d. Note: The principal study evaluated the toxicity of 2-butanol, which was considered an appropriate surrogate for 2-butanone (2-butanol is a metabolic precursor of 2-butanone).	Axonal swelling in the brain and spinal cord, and myofibrillar atrophy of quadriceps and calf muscles at ≥266 mg/kg-d
Species	NA	NA	Rabbit	Rat	Rat	Rat
Duration	NA	NA	GDs 6−18	13 wk	Multigenerational study (~23 wk)	13 mo
Route	NA	NA	Gavage	Drinking water	Drinking water	Drinking water

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Additional toxicity data (from other studies)	NA	A previous IRIS RfD (1991) based on liver and kidney effects was withdrawn in 2003 because the observed effects were not considered clearly biologically relevant.	See "Repeated-dose toxicity—oral, subchronic" section above.	No chronic-duration or multigenerational studies were identified: • Nephropathy was not observed in the companion mouse 13-wk drinking water study at doses up to 4,900 mg/kg-d (M) or 11,000 mg/kg-d (F). • Decreased motor nerve conduction velocity was observed in rats exposed to 650 mg/kg-d for 6 wk in drinking water.	No oral toxicity data were available for 2-butanone, and no additional oral toxicity data were reported for 2-butanol.	Several additional studies also reported neurotoxicity (swelling/ degeneration of peripheral axons, neuropathy, ataxia, hind-limb paralysis), including a 90-d gavage study in hens, 90-d and 40-wk gavage study in rats, 120-d drinking water study in rats, and 24-wk drinking water study in guinea pigs. Peripheral toxicity is attributed to the principal metabolite, 2,5-hexanedione.

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Continued:	Continued:	Continued:	Continued:	Continued: • Increased severity of nephropathy in male and female rats was observed in a 90-d gavage study at ≥500 mg/kg-d; nephropathy in males was associated with hyaline droplet formation. Additional effects noted in rats following subchronic gavage exposure at 2,500 mg/kg-d included excessive salivation, hematological alterations in males (increased Hb, Hct, and mean cell count), increased ALT, and decreased absolute brain weight. No body-weight effects were noted.	Continued:	Continued:
Source	NA	U.S. EPA (2003c)	U.S. EPA (2014)	U.S. EPA (2003a)	U.S. EPA (2003b)	U.S. EPA (2009)

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Repeated-dose toxicity—inhalation, subchronic						
POD (mg/m^3)	NA	NA	661.8	3,000	NA	NA
POD type	NA	NA	NOAEL (HEC)	LOAEL	NA	NA
Subchronic UF_C	NA	NA	100 (3 UF_A, 10 UF_H, 3 UF_D)	100 (10 UF_H, 10 UF_L)	NA	NA
Subchronic p-RfC/ intermediate MRL (mg/m^3)	NA	NA	7×10^0	3×10^1	NA	NA
Critical effects	NA	NA	Increased mean cumulative motor activity at 2,198 mg/m^3 (HEC)	Increased visual evoked responses	NA	NA
Other effects (in principal study)	NA	NA	Clinical signs of neurotoxicity (ataxia, transient narcosis, lack of startle reflex), and transient mild anemia were also observed at 2,198 mg/m^3 (HEC). No toxicologically significant changes in body weight, FOB (performed ~42 hr after most recent exposure at Wk 1, 2, 4, 9, and 13), clinical chemistry, or organ weight or histology.	No changes in respiratory or cardiac function, hematological parameters, serum liver or kidney enzymes, or urinalysis parameters.	NA	NA
Species	NA	NA	Rat	Human	NA	NA
Duration	NA	NA	13 wk	6 wk	NA	NA
Route	NA	NA	Inhalation	Inhalation	NA	NA

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Additional toxicity data (from other studies)	Significantly increased kidney weight and proteinuria were observed in male rats at 660.7 mg/m^3 (HEC). Increased levels of ketone bodies in the urine of all exposed females and males at ≥14.7 mg/m^3 (HEC).	NA	Clinical signs of neurotoxicity and increased relative liver weight (in the absence of histological effects) were observed at ≥661.8 mg/m^3 (HEC) in mice in a 13-wk study. No toxicologically significant changes in body weight, hematology, clinical chemistry, organ weight, or histology. In a developmental rat study, decreased implants, increased resorptions, fetal growth retardation, and malformations were noted at ≥5,048 mg/m^3 (HEC).	Various other neurological effects have been reported in exposed volunteers or workers (weakness, tiredness, headache, dizziness, unsteadiness, confusion, delayed reaction time, tension, narcosis).	NA	NA
Source	OECD (2005)	NA	U.S. EPA (2014)	ATSDR (1994)	NA	NA
Repeated-dose toxicity—inhalation, chronic						
POD (mg/m^3)	NA	1,026	221	3,000	1,517	90
POD type	NA	NOAEL (HEC)	LOAEL (HEC)	LOAEL	$BMCL_{10}$ (HEC)	$BMCL_{05}$ (HEC)
Chronic UF_C	NA	300 (3 UF_A, 10 UF_H, 10 UF_D)	1,000 (3 UF_A, 10 UF_H, 10 UF_L, 3 UF_D)	100 (10 UF_H, 10 UF_L)	300 (3 UF_A, 10 UF_H, 10 UF_D)	3,000 (3 UF_A, 10 UF_H, 10 UF_S, 10 UF_D)
p-RfC/RfC (mg/m^3)	NA	3	2×10^{-1}	3×10^{1}	5	3×10^{-2}

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Critical effects	NA	Decreased fetal body weight, delayed skeletal ossification, increased fetal death at 3,073 mg/m^3 (HEC)	Decreased absolute and relative testes weight at 221 mg/m^3 (HEC)	Increased visual evoked responses at 3,000 mg/m^3 (HEC)	Developmental toxicity (skeletal variations) at 2,980 mg/m^3 (HEC)	Decreased MCV of the sciatic tibial nerve at 73 mg/m^3 (HEC)
Other effects (in principal study)	NA	Maternal toxicity was observed at 3,073 mg/m^3 (HEC), including clinical signs of toxicity, and reduced maternal body weight, and body-weight gain.	Increased relative liver weight, seminal vesicle enlargement, increased incidences of adrenal gland congestion, mucosal cell hyperplasia in the stomach, splenic hematopoiesis, and hemosiderosis at ≥1,101 mg/m^3 (HEC). Body weights remained within 10% of control in all treated groups (up to 2,211 mg/m^3 [HEC]).	No changes in respiratory or cardiac function, hematological parameters, serum liver or kidney enzymes, or urinalysis parameters	Decreased fetal body weight and a slight (7%) increase in maternal relative liver weight were observed at 8,909 mg/m^3 (HEC). No maternal body-weight effects were noted. No treatment-related increases in intrauterine death or number of malformations were observed.	Decreased MCV of the ulnar nerve, hind-limb paralysis
Species	NA	Rat	Mouse	Human	Mouse	Monkey
Duration	NA	GDs 6−15 (6 hr/d)	78 wk	6 wk	GDs 6−15 (7 hr/d)	10 mo (6 hr/d, 5 d/wk)
Route	NA	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Additional toxicity data (from other studies)	NA	Histopathological changes in liver and kidney, increases in various relative organ weights (liver, kidney, testis, cauda epididymis, seminal vesicle, adrenal weights), and reduced startle reflex were observed at higher concentrations in a multigenerational reproductive study. Transient body-weight effects were observed in F0 and F1 parental animals during premating and mating exposure, but not gestation or lactation. Survival was decreased in male rats at the high concentration. The kidney in rats and the liver in mice were the main targets of MIBK toxicity and carcinogenicity. Hepatocellular adenomas, and adenoma of carcinoma (combined) were increased in male and female mice exposed to the high concentration.	In the companion rat study, effects noted at ≥1,101 mg/m^3 (HEC) included increased relative liver weight, kidney lesions, and clinical signs of toxicity (hypoactivity, ataxia, prostration, and narcosis) and mortality (males only). Body weights remained within 10% of control in all treated groups (up to 2,211 mg/m^3 [HEC]).	See "Subchronic p-RfC/intermediate MRL" row in the "Repeated-dose toxicity—inhalation, subchronic" section above.	Limited to equivocal evidence of neurological effects in humans following long-term occupational exposure. Skeletal variations and maternal toxicity were also observed in rats at 2,950 mg/m^3 (HEC).	Altered MCV and hind-limb paralysis were also observed in rats in the same study. Human occupational exposure to *n*-hexane (parent compound for *n*-hexanone) also causes decreased MCV and polyneuropathy. Peripheral toxicity is attributed to the principal metabolite, 2,5-hexanedione.

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Continued:	Continued:	Continued: There were also treatment-related increases in multiple adenomas in both sexes.	Continued:	Continued:	Continued: Transient decreases in body-weight gain, increased absolute and relative liver weight, altered liver enzyme levels, increased relative kidney weight, and decreased absolute and relative brain weight were observed in rats exposed to 14,870 mg/m^3 (HEC = 2,655 mg/m^3) for 90 d. No hematological or histopathological effects were noted. No peripheral neurotoxicity was observed in rats exposed to 3,318 mg/m^3 (HEC) for up to 55 d or 590 mg/m^3 (HEC) for 24 wk.	Continued:
Source	NA	U.S. EPA (2003c); Stout et al. (2008)	U.S. EPA (2014)	ATSDR (1994)	U.S. EPA (2003b)	U.S. EPA (2009)

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Acute toxicity						
Rat oral LD_{50} (mg/kg)	2,590	2,080	5,045	5,800	2,737	2,590
Toxicity at rat oral LD_{50}	NA	NA	Somnolence, altered sleep time, and righting reflex	Tremors, altered sleep time, and righting reflex	NA	NA
Mouse oral LD_{50} (mg/kg)	1,000 (LD_{Lo})	1,900	3,600	3,000	4,050	2,430
Toxicity at mouse oral LD_{50}	GI changes (no further information provided)	NA	Somnolence, altered sleep time, and righting reflex	NA	NA	NA
Rat inhalation LC_{50} (mg/m^3)	NA	100,000	39,000	50,100	23,500	8,000
Toxicity at rat inhalation LC_{50}	NA	NA	NA	NA	NA	NA
Mouse inhalation LC_{50} (mg/m^3)	NA	23,300	31,500 (LC_{Lo})	44,000	32,000	NA

Table A-3. Comparison of Available Assessment Health Values and Acute Toxicity Data for 4-Methyl-2-pentanol (CASRN 108-11-2) and Candidate Surrogates

	4-Methyl-2-pentanol (MIBC)	4-Methyl-2-pentanone (MIBK)	2-Propanol (isopropanol)	2-Propanone (acetone)	2-Butanone (MEK)	2-Hexanone (MBK)
Toxicity at mouse inhalation LC_{50}	NA	NA	NA	NA	NA	NA
Source	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)

α2u-g = alpha 2u-globulin; ALT = alanine aminotransferase; $BMCL_{05}$ = 5% benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; $BMDL_{05}$ = 5% benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; F = female(s); FOB = functional observational battery; GD = gestation day; GI = gastrointestinal; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; LC_{50} = median lethal concentration; LC_{Lo} = lowest lethal concentration; LD_{50} = median lethal dose; LD_{Lo} = lowest lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); MBK = methyl butyl ketone; MCV = motor conduction velocity; MEK = methyl ethyl ketone; MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; MIBK = 4-methyl-2-pentanone or methyl isobutyl ketone; MRL = minimal risk level; NA = not applicable; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = inhalation reference concentration; RfD = oral reference dose; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Weight-of-Evidence Approach

A WOE approach is used to evaluate information from potential candidate surrogates as described by Wang et al. (2012). Commonalities in structural/physicochemical properties, toxicokinetics, metabolism, toxicity, or mode of action (MOA) between potential surrogates and chemical(s) of concern are identified. Emphasis is given to toxicological and/or toxicokinetic similarity over structural similarity. Surrogate candidates are excluded if they do not have commonality or demonstrate significantly different physicochemical properties, and toxicokinetic profiles that set them apart from the pool of potential surrogates and/or chemical(s) of concern. From the remaining potential surrogates, the most appropriate surrogate (most biologically or toxicologically relevant analog chemical) with the highest structural similarity and/or most conservative toxicity value is selected.

Oral Exposure

Based on structural analog analysis, MIBK provided the highest similarity scores to MIBC among potential surrogates. Based primarily on the available metabolism information, only MIBK is identified as a suitable metabolic surrogate compound for MIBC. Specifically, MIBC and MIBK are involved in a rapid bidirectional metabolic relationship that includes the shared production of common downstream metabolites including HMP. MBK and MEK are not considered suitable metabolic surrogates due to the formation of 2,5-hexanedione, a known potent peripheral nerve toxicant that cannot be formed during MIBC metabolism. Whereas MIBC, MIBK, isopropanol, and acetone are all metabolized via a common oxidative metabolic pathway leading to CO_2, isopropanol and acetone do not demonstrate the close bidirectional metabolic relationship with MIBC as observed between MIBC and MIBK. Furthermore, a terminal metabolic product of CO_2 should not be considered a common metabolite because many small organic compounds can be metabolized to CO_2. MIBK, isopropanol, and acetone via the oral route have all been shown to induce kidney effects suggesting the potential for MIBC to share in a common target organ of toxicity. However, kidney effects observed following oral isopropanol or acetone exposure occurred at higher doses than those that induced other systemic toxicity effects. In addition, although HMP, a shared downstream metabolite of MIBC and MIBK, was shown to induce kidney toxicity following oral exposure in rats for 45 days, the study authors identified hyaline droplets in males suggesting the potential involvement of an alpha 2u-globulin-mediated pathway. Lastly, the complete lack of oral repeated-dose toxicity information for the target compound, MIBC, limits toxicity comparisons to the surrogate population.

Based primarily on metabolic considerations, MIBK is selected as the most appropriate surrogate compound for MIBC for the oral route of exposure. Support for MIBK as the chosen surrogate compound is provided by the fact that MIBK displays the highest structural similarity to MIBC. Isopropanol and acetone are not selected as the surrogate compound for MIBC due to the disparities in metabolism (CO_2 is the only shared metabolite) and because neither chemical could be identified as an oral toxicity-like surrogate compound for MIBC.

Inhalation Exposure

As discussed above, MIBK is the only suitable metabolic surrogate for MIBC primarily based on a bidirectional metabolic relationship, and, that they share HMP as a common major metabolite. MIBK and isopropanol are considered toxicity-like surrogate compounds for MIBC based on a demonstrated common target of toxicity (kidneys) following inhalation exposure. In total, MIBK is identified as the most appropriate structural, metabolic, and toxicity-like surrogate

for MIBC and is therefore selected as the surrogate compound for deriving the screening subchronic and chronic p-RfCs.

ORAL TOXICITY VALUES

Derivation of Screening Subchronic and Chronic Provisional Reference Doses

Based on the overall surrogate approach presented in this PPRTV assessment, MIBK was selected as an appropriate surrogate for MIBC for both oral and inhalation exposure. However, because no oral toxicity value exists for MIBK, derivation of a screening subchronic or chronic provisional reference dose (p-RfD) for MIBC is precluded.

INHALATION TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Concentration

Based on the overall surrogate approach presented in this PPRTV assessment, MIBK was selected as the surrogate for MIBC for deriving a screening subchronic provisional reference concentration (p-RfC). While the U.S. EPA's IRIS program does not have a subchronic inhalation reference concentration (RfC) value for MIBK, the chronic RfC value is based on a developmental study in rats and mice [Tyl et al. (1987) as cited in U.S. EPA (2003c)]. While only a chronic RfC is available for MIBK, this value is applicable to the derivation of both a screening subchronic and chronic p-RfC because it is based on a gestational exposure study.

The IRIS summary expresses doses as time adjusted (6 hours of exposure/24 hours in a day). The IRIS summary report for MIBK described this study as follows:

> *Developmental and maternal toxicity were evaluated in groups of 35 pregnant Fischer 344 and 30 pregnant CD-1 mice exposed by inhalation to 0, 300, 1000, or 3000 ppm (0, 307, 1026, 3073 mg/m^3) MIBK for 6 hrs/day on gestation days 6 through 15 (Bushy Run Research Center, 1984; Tyl et al., 1987). Animals were sacrificed on gestation day 21 (rats) or 18 (mice). Dams were evaluated for exposure-related changes in clinical signs, body weight, food consumption, organ weights (kidney, liver, and gravid uterus), and reproductive parameters; fetuses were evaluated for exposure-related changes in body weight and viability and for external, skeletal, and thoracic and peritoneal visceral alterations.*
>
> *Maternal mean body weight, weight gain, and food consumption were significantly decreased in rats exposed to 3073 mg/m^3 (but not to <=1026 mg/m^3) MIBK during the exposure period, but they had recovered to control levels by the day of sacrifice; maternal body weight was not affected in mice. Maternal clinical signs observed in rats or mice included coordination loss, hindlimb weakness, paresis, irregular gait, hypoactivity, ataxia, unkempt fur, negative tail or toe pinch, piloerection, lacrimation, or red perioral encrustation; these clinical signs were observed only during the exposure period and only at 3073 mg/m^3. Three maternal deaths (12% of the animals in the group) occurred in mice exposed to 3073 mg/m^3 after the first exposure on gestation day 6; no further deaths occurred in that group, and no exposure-related deaths occurred in the other mouse or rat exposure groups.*
>
> *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. In mice, there was an increased mean number of dead fetuses per litter at 3073 mg/m^3 (0.6 per litter as compared to 0.1 in controls). Fetal body weights (litter weight, male weight per litter, and female weight per litter) were significantly reduced in rats exposed to 307 (the mean by 3%) and 3073 mg/m^3 (the mean by 6%) (not at 1026 mg/m^3), and in mice at 3073 mg/m^3 (the mean by 13%) (not at <=1026 mg/m^3). The authors indicated that the reduced fetal body weight in rats at 307 mg/m^3 was confounded by litter size and was apparently not treatment-related.

No exposure-related change in the incidence of malformations of any type were observed in rat and mouse fetuses. 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. The numbers of individuals with various manifestations of retarded skeletal ossification were also apparently increased in rats and mice at 3073 mg/m^3 relative to controls, but no results of statistical comparisons were indicated in the study report.

The critical effects for the developmental study included reduced fetal body weight, skeletal variations, and fetal death in mice and skeletal variations in rats at a time adjusted lowest-observed-adverse-effect level (LOAEL) of 3,073 mg/m^3; the no-observed-adverse-effect level (NOAEL) of 1,026 mg/m^3 was used as the POD. Because the current practice is to only adopt existing PODs, benchmark dose (BMD) modeling is not performed when applying the alternative surrogate approach (Wang et al., 2012) in PPRTV assessments. The U.S. EPA (2003c) calculated an HEC according to U.S. EPA (1994) guidance for Category 3 gases by a continuous exposure basis [per U.S. EPA (2002)], and multiplying the result by a ratio of the animal blood-gas partition coefficient for MIBK to the human blood-gas partition coefficient for MIBK. Because blood-air partition coefficients for MIBK are unknown, a default value of 1 was assigned.

$$\begin{aligned} \text{Surrogate POD (NOAEL [HEC])} &= \text{NOAEL}_{\text{ADJ}}\ (\text{mg/m}^3) \times (\text{Hb/g-A}) \div (\text{Hb/g-H}) \\ &= 1{,}026 \times 1 = 1{,}026\ \text{mg/m}^3 \end{aligned}$$

In deriving a screening subchronic p-RfC for MIBC, a composite uncertainty factor (UF_C) of 300 is applied, based on a 3-fold uncertainty factor value for interspecies extrapolation (interspecies uncertainty factor [UF_A], reflecting use of a dosimetric adjustment) and 10-fold uncertainty factor values for both intraspecies variability (UF_H) and database deficiencies (database uncertainty factor [UF_D], reflecting lack of any repeated-exposure toxicity information for MIBC). Using the NOAEL (HEC), the screening subchronic p-RfC for MIBC is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfC} &= \text{Surrogate NOAEL (HEC)} \div UF_C \\ &= 1{,}026\ \text{mg/m}^3 \div 300 \\ &= \mathbf{3 \times 10^0\ mg/m^3} \end{aligned}$$

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfC for MIBC.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfC for 4-Methyl-2-pentanol (CASRN 108-11-2)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following MIBC exposure. The toxicokinetic uncertainty has been accounted for by calculating an HEC.
UF_D	10	A UF_D of 10 is applied to account for the absence of reliable repeated-dose inhalation toxicity data for MIBC.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of MIBC in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the critical effects (i.e., reduced fetal body weight, skeletal variations, and increased fetal death in mice, and skeletal variations in rats) are developmental effects. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than life-time exposure (U.S. EPA, 1991).
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

Based on the overall surrogate approach presented in this PPRTV assessment, MIBK was selected as the surrogate for MIBC for derivation of a screening chronic p-RfC. The IRIS RfC for MIBK was based on the developmental study in rats and mice described in the "Derivation of a Screening Subchronic Provisional Reference Concentration" section [Tyl et al. (1987) as cited in U.S. EPA (2003c)]. The study description, POD, and UF_C are described above.

Using the POD (HEC), the screening chronic p-RfC for MIBC is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{Surrogate NOAEL (HEC)} \div UF_C \\ &= 1{,}026\ mg/m^3 \div 300 \\ &= \mathbf{3 \times 10^0\ mg/m^3} \end{aligned}$$

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfC for MIBC.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfC for 4-Methyl-2-pentanol (CASRN 108-11-2)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following MIBC exposure. The toxicokinetic uncertainty has been accounted for by calculating an HEC.
UF_D	10	A UF_D of 10 is applied to account for the absence of reliable repeated-dose inhalation toxicity data for MIBC.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of MIBC in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the critical effects (i.e., reduced fetal body weight, skeletal variations, and increased fetal death in mice, and skeletal variations in rats) are developmental effects. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than life-time exposure (U.S. EPA, 1991).
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; MIBC = methyl isobutyl carbinol or 4-methyl-2-pentanol; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Consideration of Potential Carcinogenicity

As discussed above, MIBK was selected as the surrogate for 4-methyl-2-pentanol for derivation of a screening subchronic and chronic p-RfC using an alternative surrogate approach (Wang et al., 2012). MIBK was previously identified by the International Agency for Research on Cancer (IARC) as being *"Possibly Carcinogenic to Humans"* (Kegley et al., 2016) and is currently listed as a carcinogen on the Pesticide Action Network (IARC, 2013). Furthermore, MIBK is currently identified on the Cal/EPA's Proposition 65 List as a chemical that causes cancer (Cal/EPA, 2017a). This information suggests that based on similarity to MIBK, 4-methyl-2-pentanol might have carcinogenic potential as well but does not preclude the development of noncancer, surrogate-derived, screening provisional values within this document.

APPENDIX B. REFERENCES

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