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Provisional Peer-Reviewed Toxicity Values for

tert-Butyl Formate
(CASRN 762-75-4)

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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 *tert*-BUTYL FORMATE (CASRN 762-75-4)

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

tert-Butyl formate, CASRN 762-75-4, belongs to the class of compounds known as formic acid esters. *tert*-Butyl formate has been used as an oxygenate in gasoline formulations (Drogos and Diaz, 2002). It is not listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2015), nor is it registered with Europe's Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2017).

tert-Butyl formate is produced by the oxidation of methyl *tert*-butyl ether (MTBE). Formic acid is a coproduct of this reaction (Reutemann and Kieczka, 2011). *tert*-Butyl formate is also produced by environmental degradation of MTBE, particularly in the atmosphere (Church et al., 1999).

The empirical formula for *tert*-butyl formate is $C_5H_{10}O_2$ and the structure is shown in Figure 1. Table 1 summarizes the compound's physicochemical properties. *tert*-Butyl formate is a flammable, colorless liquid at room temperature (Sigma-Aldrich, 2014). The main fate pathway of *tert*-butyl formate in the environment is hydrolysis to *tert*-butyl alcohol and formic acid. Half-lives in aqueous solution of 6 hours, 5 days, and 8 minutes have been reported at pH 2 (at 4°C), pH 7 (at 22°C), and pH 11 (at 22°C), respectively (Church et al., 1999). *tert*-Butyl formate's high vapor pressure indicates that it will exist solely as a vapor in the atmosphere. Given its vapor pressure and high estimated Henry's law constant, it is likely to volatilize from either dry or moist soil surfaces and from water surfaces. Once in the atmosphere, it will undergo hydrolysis via reaction with atmospheric moisture. The estimated high water solubility and low soil adsorption coefficient for *tert*-butyl formate indicate that it has the potential to leach to groundwater or undergo runoff after a rain event, where it will undergo hydrolysis.

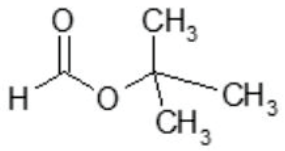


Figure 1. *tert*-Butyl Formate Structure

Table 1. Physicochemical Properties of *tert*-Butyl Formate (CASRN 762-75-4)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	82.5[a]
Melting point (°C)	−94[b]
Density (g/cm^3)	0.886 (at 20°C)[c]
Vapor pressure (mm Hg at 20°C)	81[c]
pH (unitless)	NV
pKa (unitless)	NV
Solubility in water (mg/L at 25°C)	~4.0 × 10^4 [c]
Octanol-water partition coefficient (log K_{ow})	1.19 (estimated)[a]
Henry's law constant (atm-m^3/mol at 25°C)	6.9 × 10^{-4} [a]
Soil adsorption coefficient K_{oc} (L/kg)	13[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	7.37 × 10^{-13} [a]
Atmospheric half-life (d)	22 (estimated)[a]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	102[a]
Flash point (closed cup, °C)	−9[d]

[a]U.S. EPA (2012b).
[b]Yaws (2015).
[c]Drogos and Diaz (2002).
[d]Sigma-Aldrich (2014).

NV = not available.

No toxicity values for *tert*-butyl formate are available from EPA or other agencies/organizations searched, as shown in Table 2.

Table 2. Summary of Available Toxicity Values for *tert*-Butyl Formate (CASRN 762-75-4)

Source[a]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011a)
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	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2016)
Cancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	NA	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.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in November 2015 and updated in July 2017 for studies relevant to the derivation of provisional toxicity values for *tert*-butyl formate (CASRN 762-75-4). 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), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume Information System (HPVIS), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), Japan Existing Chemical Data

Base (JECDB), Organisation for Economic Co-operation and Development Screening Information dataset (OECD SIDS), International Uniform Chemical Information Database (IUCLID), and High Product Volume (HPV).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

No potentially relevant short-term-, subchronic-, or chronic-duration studies or developmental or reproductive toxicity studies of *tert*-butyl formate in humans or animals have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute Animal Studies

The only available animal toxicity study that evaluated *tert*-butyl formate was an acute gavage study that examined the testicular toxicity of MTBE and its environmental breakdown products, *tert*-butyl alcohol and *tert*-butyl formate (Billitti et al., 1998).

Billitti et al. (1998)

Groups of male white mice (five/group; strain not specified) were exposed to MTBE, *tert*-butyl alcohol, or *tert*-butyl formate at doses of 0, 400, 1,000, or 2,000 mg/kg via gavage in canola oil. Mice exposed to MTBE were exposed three times over a 5-day period, and mice exposed to *tert*-butyl alcohol and *tert*-butyl formate were only exposed once. Positive control mice ($n = 3$) were injected with cadmium chloride, a known testicular toxicant (dose not reported). Feces were collected before and after final exposure to determine fecal testosterone levels (biomarker for testicular damage). After fecal samples were collected postexposure, the mice were subcutaneously injected with 2.5 IU/g human chorionic gonadotropin (hCG) in 0.9% sterile saline to stimulate testicular testosterone production. Additional fecal samples were collected 22 and 26 hours postinjection for all groups and 3 days postexposure for mice exposed to *tert*-butyl alcohol and *tert*-butyl formate. After final fecal sample collection, blood samples were taken to determine testosterone levels, and the mice were sacrificed. The testes were removed, weighed, and fixed for histopathological examination (only evaluated in the control and high-dose animals). Body weights were measured (no details provided). No other systemic toxicity endpoints were evaluated.

None of the mice exposed to MTBE, *tert*-butyl alcohol, or *tert*-butyl formate showed dose-related changes in serum or fecal testosterone levels. No body-weight effects were noted. Significantly ($p < 0.05$) increased absolute testes weight was observed at ≥1,000 mg/kg *tert*-butyl alcohol (increased ~10% compared with controls) and significantly ($p < 0.05$) decreased absolute testes weight was observed at ≥400 mg/kg *tert*-butyl formate (decreased ~18, 25, and 9% at 400, 1,000, and 2,000 mg/kg, respectively, compared with controls); no changes in absolute testes weight were noted with MTBE exposure (relative weights were not reported). The only histopathological change noted in the high-dose MTBE group was a significant ($p < 0.05$) increase in the number of tubules having gross disruption (6% compared with 0% in controls); no changes in the percent of tubules with seminiferous epithelial vacuolization, marginated chromatin, or multinucleated giant cells were observed. No treatment-related histopathological lesions were observed in mice exposed to *tert*-butyl alcohol or *tert*-butyl formate. Positive

control mice showed significant ($p < 0.05$) decreases in serum and fecal testosterone levels and testes weight, and evidence of histopathological damage (98.6% of tubules showed gross disruption), compared with control. Taken together, these findings indicate minimal testicular toxicity in mice following acute exposure to MTBE or its breakdown products.

DERIVATION OF PROVISIONAL VALUES

Tables 3 and 4 present summaries of noncancer and cancer references values, respectively.

Table 3. Summary of Noncancer Reference Values for *tert*-Butyl Formate (CASRN 762-75-4)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	S-D rat, M & F	Decreased serum BUN	8×10^{-3}	LOAEL (HED)	23 (based on surrogate POD)	3,000	Robinson et al. (1990) as cited in ATSDR (1996)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BUN = blood urea nitrogen; F = female(s); HED = human equivalent dose;
LOAEL = lowest-observed-adverse-effect level; M = male(s); NDr = not determined; POD = point of departure;
p-RfC = provisional reference concentration; p-RfD = provisional reference dose; S-D = Sprague-Dawley;
UF_C = composite uncertainty factor.

Table 4. Summary of Cancer Reference Values for *tert*-Butyl Formate (CASRN 762-75-4)

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 regarding the toxicity of *tert*-butyl formate to humans by oral exposure have been identified. Animal studies of oral exposure to *tert*-butyl formate are limited to an acute testicular toxicity study, which is of inadequate duration and scope to support derivation of a subchronic or chronic provisional reference dose (p-RfD). Due to limitations in the available oral toxicity data for *tert*-butyl formate, subchronic and chronic p-RfDs were not derived

directly. Instead, a screening subchronic p-RfD is derived in Appendix A using an alternative surrogate approach. A screening chronic p-RfD is not derived due to lack of any relevant data for the target chemical, *tert*-butyl formate and due to the lack of a chronic toxicity value for MTBE (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies regarding the toxicity of *tert*-butyl formate to humans or animals by inhalation have been identified; therefore, subchronic and chronic provisional reference concentrations (p-RfCs) could not be derived directly. An alternative surrogate approach was attempted for the p-RfCs, but screening p-RfCs were not derived due to lack of adequate inhalation toxicity data to identify an appropriate toxicity-like surrogate (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No relevant data are available. Under the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *"Inadequate Information to Assess Carcinogenic Potential"* of *tert*-butyl formate.

Table 5. Cancer WOE Descriptor for *tert*-Butyl Formate

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 animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no 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 *tert*-butyl formate are available.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

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 *tert*-butyl formate.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for *tert*-butyl formate. However, information is available for this 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 in an appendix and develops a "screening value." 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 chemical selection. The surrogate approach may or may not be route-specific or 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, both toxicologically and chemically.

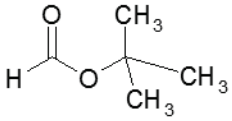
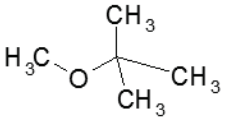
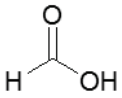
Structural Surrogates (Structural Analogs)

Initial surrogate searches focused on identifying a pool of structurally similar chemicals. Those chemicals that had published oral and/or inhalation 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 were considered further as candidate analogs. Two structural analogs to *tert*-butyl formate with published toxicity values were identified: methyl *tert*-butyl ether (MTBE) (ATSDR, 1996; U.S. EPA, 1993) and formic acid (U.S. EPA, 2010). Coincidentally, these the two candidates had both oral and inhalation toxicity values [i.e., MTBE has oral and inhalation toxicity values published in ATSDR (1996)]; formic acid has oral and inhalation toxicity values published in U.S. EPA (2010)]. The initial surrogate search strategy also identified additional chemicals with structural similarity (e.g., *tert*-butyl alcohol; ChemIDPlus similarity score of 61%, which is the major toxic metabolite of MTBE and a degradation product of *tert*-butyl formate) (see "Metabolic Surrogates" section below). However, there are no published toxicity values for *tert*-butyl alcohol in the IRIS, PPRTV, ATSDR, or Cal/EPA databases, which precludes the identification of *tert*-butyl alcohol as a candidate analog in this PPRTV assessment.

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, DSSTox was not available to the public at the time this PPRTV assessment was developed, and no date is available for the implementation of its replacement dashboard. 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). Table A-1 summarizes the physicochemical properties and similarity scores of MTBE and formic acid. ChemIDplus and OECD toolbox similarity scores for MTBE were 56 and 40%, respectively. The OECD toolbox similarity score for formic acid was only 6%. No similarity score was available for formic acid in ChemIDplus. The low similarity score for formic acid is likely related to the limited number of structural descriptors available for this 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. In total, the similarity results suggest that MTBE is a preferred structural surrogate in contrast to formic acid.

Table A-1. Physicochemical Properties of *tert*-Butyl Formate (CASRN 762-75-4) and Candidate Structural Surrogates[a]

	***tert*-Butyl Formate**	**MTBE**	**Formic Acid**
Structure			
CASRN	762-75-4	1634-04-4	64-18-6
Molecular weight	102	88	46
DSSTox similarity score (%)[b]	100	NV	NV
ChemIDplus similarity score (%)[c]	100	56	NV
OECD toolbox similarity score (%)[d]	100	40	6
Melting point (°C)	−94[e]	−108.6	8.3
Boiling point (°C)	82.5	55.2	101
Vapor pressure (mm Hg at 25°C)	81 (at 20°C)[f]	250	42.6
Henry's law constant (atm-m^3/mole at 25°C)	6.9×10^{-4}	5.87×10^{-4}	1.67×10^{-7}
Water solubility (mg/L)	~4.0×10^4 [f]	5.1×10^4	1×10^6
Log K_{ow}	1.19 (estimated)[a]	0.94	−0.54
pKa	NV	NV	3.75

[a]Data was gathered from PHYSPROP database for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]DSSTox (2016).
[c]ChemIDplus Advanced, similarity scores (ChemIDplus, 2017).
[d]OECD (2016).
[e]Yaws (2015).
[f]Drogos and Diaz (2002).

MTBE = methyl *tert*-butyl ether; NV = not available; OECD = Organisation for Economic Co-operation and Development.

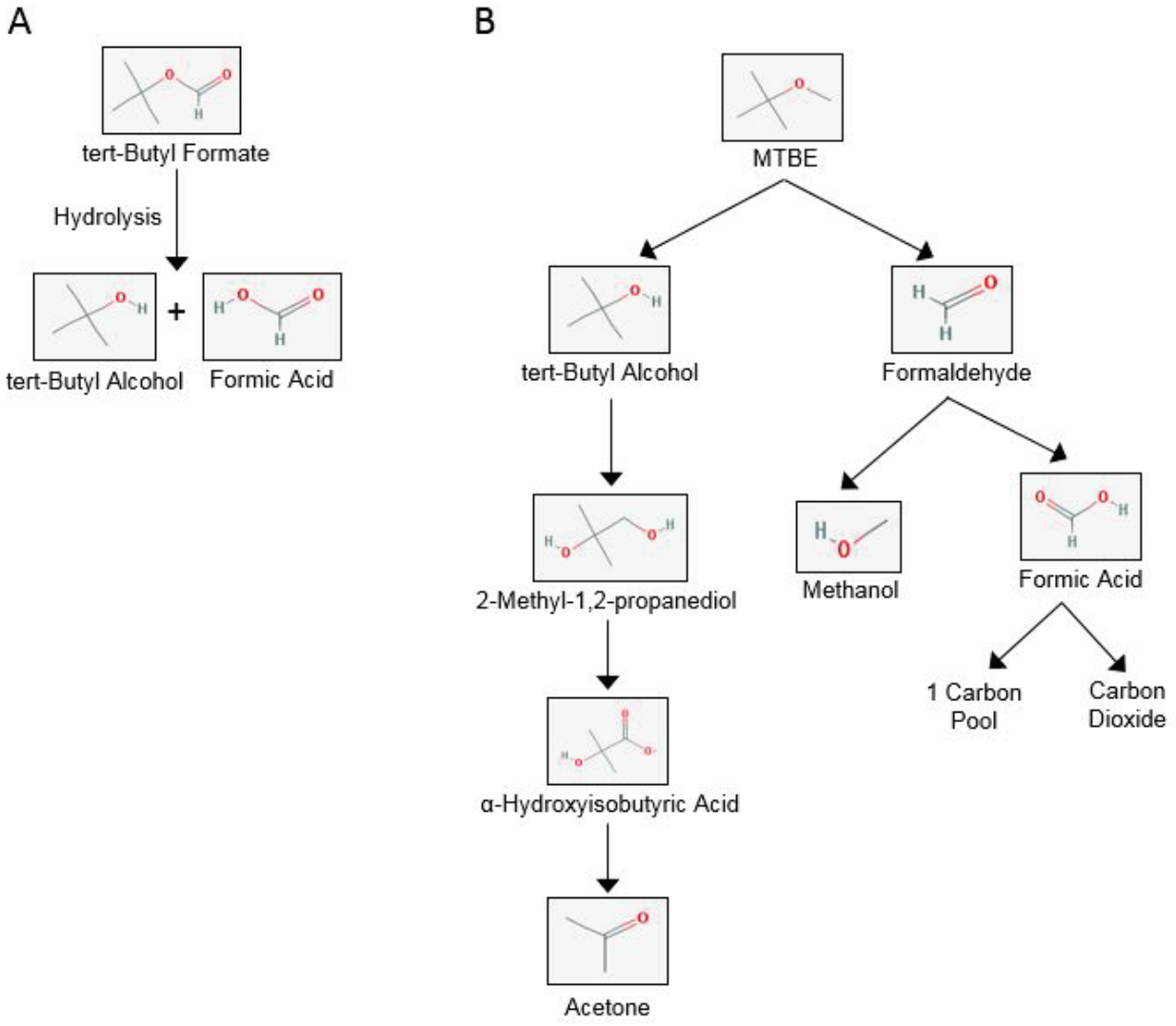


Figure A-1. (A) Proposed Environmental Breakdown Pathway of *tert*-Butyl Formate based on Information Described in Garoma et al. (2008) and Church et al. (1999). (B) Schematic Describing MTBE Metabolism as Summarized in ATSDR (1996).

Metabolic Surrogates

Figure A-1 depicts known environmental degradation products for *tert*-butyl formate (see Figure A-1 [A]) and metabolites for MTBE (see Figure A-1 [B]). Table A-2 summarizes available toxicokinetics data for *tert*-butyl formate and the structurally similar compounds identified as potential surrogates (i.e., MTBE and formic acid).

No toxicokinetic studies have been identified for *tert*-butyl formate in mammalian species. Based on data from an environmental fate study, *tert*-butyl formate is expected to be hydrolyzed to *tert*-butyl alcohol and formic acid (hydrolysis half-life of 6 hours at pH 2 [4°C], 5 days at neutral pH [22°C], and 8 minutes at pH 11 [22°C]) (Garoma et al., 2008; Church et al., 1999). These data ultimately suggest that hydrolysis of *tert*-butyl formate can occur across a wide physiologic range. The study by Garoma et al. (2008) also identified additional

degradation products following ozone/ultra violet-mediated breakdown of MTBE. Of these, formaldehyde has specifically been determined to have a known role in the generation of formic acid from the metabolism of MTBE (see Figure A-1 [B]). MTBE was identified as a potential surrogate chemical based on structural similarities. It is initially oxidized by cytochrome P450s (CYP450s) to both *tert*-butyl alcohol and formaldehyde (ATSDR, 1996). However, unchanged MTBE was the major component in expired air, regardless of route of exposure (ATSDR, 1996). *tert*-Butyl alcohol is further oxidized to form 2-methyl-1,2-propanediol, alpha-hydroxyisobutyric acid, and acetone (BioResearch, 1990). Among in vivo metabolism studies of MTBE, formaldehyde metabolism is shown to proceed more rapidly than *tert*-butyl alcohol oxidation, and results in the production of formic acid, suggesting that the localized concentration of formaldehyde will be very low (ATSDR, 1996), and these findings are consistent with studies demonstrating no measurable formaldehyde in blood or urine following human MTBE exposure (Leuschner et al., 1991). Formic acid, the other potential surrogate of *tert*-butyl formate, is converted to carbon dioxide (CO_2) and/or rapidly taken up into the carbon pool via folic acid-dependent metabolic pathways (U.S. EPA, 2010; ATSDR, 1996). Consistent with the notion that formic acid metabolism is a rapid event and not likely to contribute significantly to the overall toxicity of *tert*-butyl formate, studies examining the intracystic infusion of MTBE (a precursor of formic acid through generation of the intermediate formaldehyde) in humans demonstrate that both formaldehyde and formic acid were undetectable in blood or urine of patients in as little as 5 hours of postclinical exposure (Leuschner et al., 1991)

As stated above, *tert*-butyl alcohol is a common primary degradation product of *tert*-butyl formate and MTBE. *tert*-Butyl alcohol remains detectable in the blood and urine of humans for 12−18 hours post intracystic MTBE infusion and likely contributes to the observed systemic effects of MTBE exposure (see "Toxicity-Like Surrogates" section below). For example, in humans exposed to MTBE via intracystic infusion for dissolution of gallstones (n = 27), mean blood levels of *tert*-butyl alcohol were 0.04 mg/mL, up to 5 hours after treatment, and 0.025 mg/mL at 12−18 hours after treatment. Mean urinary levels of *tert*-butyl alcohol were 0.036 mg/mL at 5 hours, and 0.03 mg/mL at 12−18 hours after treatment (Leuschner et al., 1991). Studies examining the biodegradation of a commonly used fuel oxygenate analog of MTBE, ethyl *tert*-butyl ether (ETBE), provide additional evidence to identify *tert*-butyl alcohol as a primary and potentially toxic metabolite of both MTBE and ETBE in humans and rats (Dekant et al., 2001). However, as stated above, there are no published toxicity values for *tert*-butyl alcohol in the IRIS, PPRTV, ATSDR, or Cal/EPA databases which ultimately precludes its consideration as a potential surrogate for *tert*-butyl formate. In summary, in vivo metabolism of MTBE produces similar compounds to those generated from the environmental breakdown of *tert*-butyl formate (e.g., *tert*-butyl alcohol and formic acid, see Figure A-1). Studies examining MTBE exposure describe a rapid return of both formaldehyde and ultimately formic acid to the carbon pool, suggesting that the longer bioavailability of *tert*-butyl alcohol could drive the toxicological response of MTBE (ATSDR, 1996). Despite the expected rapid metabolism of formic acid, the ability of MTBE to degrade into both demonstrated degradation products of *tert*-butyl formate (i.e., *tert*-butyl alcohol and formic acid) makes it a preferred metabolic surrogate in contrast to formic acid.

Table A-2. Comparison of Available ADME Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates

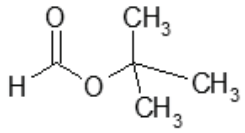
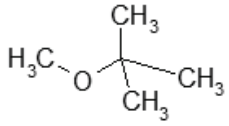
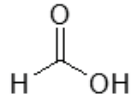
***tert*-Butyl Formate** **CASRN 762-75-4**	**MTBE** **CASRN 1634-04-4**	**Formic Acid** **CASRN 64-18-6**
		
Absorption		
ND	Rapid and extensive absorption by the GI tract postoral exposure. • Demonstrated in animal studies—at least 80% of a radiolabeled MTBE dose was excreted in expired air (principally as MTBE and *tert*-butyl alcohol) and urine (as oxidation products of *tert*-butyl alcohol) within 48 hr. Rapid and extensive absorption by the respiratory tract. • Demonstrated in human and animal studies—MTBE blood concentrations rose rapidly within 1−6-hr exposure periods.	ND
Distribution		
ND	Rapid distribution to most tissues (e.g., blood, fatty tissue, brain, liver, kidney) followed by rapid elimination with limited accumulation. • Demonstrated in animal studies following short-term inhalation or dermal exposures.	ND

Table A-2. Comparison of Available ADME Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates

***tert*-Butyl Formate** **CASRN 762-75-4**	**MTBE** **CASRN 1634-04-4**	**Formic Acid** **CASRN 64-18-6**
Metabolism		
Metabolism to *tert*-butyl alcohol and formic acid is inferred. • Chemical hydrolysis to *tert*-butyl alcohol and formic acid demonstrated in environmental fate studies (hydrolysis measured over time under acidic, basic, and neutral conditions); half-life of ~5 d at neutral pH. • Acidic conditions in stomach expected to increase rate of chemical hydrolysis (hydrolysis half-life is 6 hr at pH 2 and 4°C).	Initial metabolism by CYP450s to *tert*-butyl alcohol, and formaldehyde, followed by: (1) oxidation of *tert*-butyl alcohol to 2-methyl-1,2-propanediol and alpha-hydroxyisobutyric acid and (2) reduction of formaldehyde to methanol or oxidation of formaldehyde to formic acid and eventual production of CO_2. • *tert*-Butyl alcohol was the primary metabolite detected in blood and urine in studies of humans breathing airborne MTBE or given intracystic infusions; formaldehyde and formic acid were not detected in blood or urine in these studies. • Metabolic profile was independent of exposure route in rat studies.	Absorbed formic acid is oxidized to CO_2, partly excreted unchanged in urine, and partly metabolized and incorporated into tissue macromolecules. • Hepatic detoxifying metabolism of formate (the anion derived from formic acid) to CO_2 (via folic acid-dependent pathways) is much faster in rat liver than monkey liver due to higher levels of tetrahydrofolate. • Metabolism appears to be saturable; dogs excreted 8−9% unchanged formic acid following a 1 g oral dose and 65% unchanged following 5 g oral dose.
Excretion		
ND	Main routes of excretion are expired air (>80% of orally dosed, radiolabeled MTBE excreted as unchanged MTBE and *tert*-butyl alcohol) and some urinary excretion of oxidized metabolites of *tert*-butyl alcohol. • Metabolism and routes of excretion were independent of route of exposure in rat studies.	The half-lives of sodium formate (a sodium salt of formic acid) in blood are 12−23, 31−51, and 55 min in rats, monkeys, and humans, respectively.
Sources		
Church et al. (1999); Garoma et al. (2008)	ATSDR (1996)	U.S. EPA (2010); NTP (1992)

ADME = adsorption, distribution, metabolism, and excretion; CO_2 = carbon dioxide; CYP450 = cytochrome P450; GI = gastrointestinal; MTBE = methyl *tert*-butyl ether; ND = no data.

Toxicity-Like Surrogates (Oral)

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

Oral exposure data for *tert*-butyl formate, MTBE, and *tert*-butyl alcohol indicate that the testes are a shared site of toxicity. Data for *tert*-butyl formate are limited to a single acute gavage study in mice indicating that it can promote decreased testicular weight at doses ≥400 mg/kg (Billitti et al., 1998). Evidence for mild testicular toxicity was also observed following a 5-day exposure to MTBE (2,000 mg/kg three times) and was manifested through an increased number of tubules having gross histopathological disruption compared to controls (Billitti et al., 1998). Although the one available chronic-duration oral exposure study of MTBE showed no non-neoplastic effects in the testes of male rats, an increase in the incidence of testicular Leydig cell tumors was observed at 1,000 mg/kg-day (ATSDR, 1996). In a one-generation oral reproductive toxicity study, *tert*-butyl alcohol exposure promoted a significant decrease in sperm motility in Sprague-Dawley (S-D) rats (Lyondell Chemical Co., 2004). Importantly, no evidence of impaired reproductive function or systemic toxicity was observed in rats exposed to formic acid at doses up to 277 mg/kg-day in a combined 2-year toxicity/reproduction study that included multiple generations (U.S. EPA, 2010). Taken together, these data support the notion that the testes are a shared site of toxicity between *tert*-butyl formate, MTBE, and *tert*-butyl alcohol.

Other systemic targets of toxicity, including the central nervous system (CNS), kidney, and liver, were identified following repeat exposure to MTBE at oral doses (≥100 mg/kg-day) lower than the acute dose associated with testicular toxicity (ATSDR, 1996). The neurological effects of MTBE exposure (i.e., CNS depression) are believed to be due, at least in part, to the presence of *tert*-butyl alcohol (the primary metabolite of MTBE and degradation product of *tert*-butyl formate) in the brain of male Wistar rats (Church et al., 1999; ATSDR, 1996). Subchronic- and chronic-duration oral administration studies of *tert*-butyl alcohol in rats exhibited increased absolute and relative kidney weights (Lyondell Chemical Co., 2004; NTP, 1997, 1995), as well as increased incidence and severity of histopathological lesions in the kidney (NTP, 1997, 1995). Thyroid histopathological effects were also observed in mice following chronic-duration oral exposure to *tert*-butyl alcohol (NTP, 1995). Furthermore, developmental effects in rats and mice indicate that *tert*-butyl alcohol exposure can promote loss of fetal viability (e.g., increased rates of resorption and decreased numbers of neonates per litter) (Lyondell Chemical Co., 2004; Faulkner et al., 1989; Daniel and Evans, 1982). Formic acid (≥360 mg/kg-day) is associated with decreased body weight and reduced offspring survival in other studies (U.S. EPA, 2010). Thus, there is insufficient evidence to evaluate formic acid as an oral toxicity-like surrogate due to the absence of data regarding testicular toxicity or additional sites of toxicity that may be shared with *tert*-butyl formate following oral exposure.

In summary, oral exposure studies of *tert*-butyl formate, MTBE, and *tert*-butyl alcohol indicate that the testes are a shared site of toxicity. Furthermore, repeated and longer-duration studies of exposures to MTBE and *tert*-butyl alcohol indicate additional shared sites of toxicity for MTBE and *tert*-butyl alcohol outside of the reproductive tract. However, as stated above, there are no published toxicity values for *tert*-butyl alcohol in the IRIS, PPRTV, ATSDR, or Cal/EPA databases which ultimately precludes its consideration as a potential surrogate for *tert*-butyl formate. Therefore, MTBE is considered the most appropriate toxicity-like surrogate.

Toxicity-Like Surrogates (Inhalation)

There are no inhalation toxicity data for *tert*-butyl formate. The CNS (2,000 ppm), liver (3,000 ppm), and kidney (4,000 ppm) were identified as the primary non-neoplastic targets of inhalation MTBE exposure (ATSDR, 1996). Subchronic-duration inhalation studies of *tert*-butyl alcohol in rats reported increased absolute and relative kidney weights, as well as increased incidence and severity of histopathological lesions in the kidney (NTP, 1997). Portal-of-entry effects were observed in rats (241 mg/m^3) and mice (120 mg/m^3) exposed to formic acid via inhalation for 2 or 13 weeks (U.S. EPA, 2010). Neutropenia (15 mg/m^3) was also observed in rats exposed to formic acid by inhalation for 13 weeks, although these findings were not dose related and the mechanism of toxicity is unclear, as mouse bone marrow did not display classical histopathological characteristics of neutropenia (NTP, 1992).

While the inhalation-specific effects of MTBE and formic acid are generally divergent, there is no relevant information regarding the effects of inhalation-specific *tert*-butyl formate exposure. This precludes the identification of a best toxicity-like surrogate for the inhalation route of exposure, and neither compound was selected as an inhalation toxicity-like surrogate for *tert*-butyl formate.

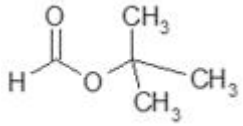
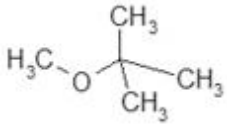
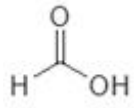
Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates			
	***tert*-Butyl Formate** **CASRN 762-75-4**	**MTBE** **CASRN 1634-04-4**	**Formic Acid** **CASRN 64-18-6**
Structure			
Repeat-dose toxicity—oral, subchronic			
POD (mg/kg-d)	NA	100	277
POD type	NA	LOAEL	NOAEL (no LOAEL was identified)
Subchronic UF_C	NA	300 (UF_H, UF_A, UF_L)	300 (UF_H, UF_A, UF_L)
Subchronic MRL (MTBE)/p-RfD (formic acid) (mg/kg-d)	NA	0.3 (MRL)	9×10^{-1} (p-RfD)
Critical effects	NA	Decreased serum BUN levels at 100 mg/kg-d (M and F).	No effects at doses up to 277 mg/kg-d.
Other effects (in principal study)	NA	Additional effects at ≥900 mg/kg-d included temporary sedation, increased serum LDH and cholesterol (F), increased AST (M), increased relative liver weight (M and F), and increased adrenal gland weight (F). All exposed males showed nephropathy associated with hyaline droplets. No other histopathological lesions or body-weight effects were associated with exposure at doses up to 1,200 mg/kg-d.	No exposure-related changes in reproductive or developmental endpoints, animal growth, or organ function (details not specified).
Species	NA	S-D rat, M and F	Rat, M and F
Duration	NA	90 d	2 yr (combined toxicity/reproductive study). NOAEL used for the derivation of the subchronic p-RfD was based on the lack of reproductive or developmental effects.
Route	NA	Gavage (in corn oil)	Drinking water

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates

	***tert*-Butyl Formate CASRN 762-75-4**	**MTBE CASRN 1634-04-4**	**Formic Acid CASRN 64-18-6**
Additional toxicity data (from other studies)	• In an acute testicular toxicity screen, a 9−25% decrease in testicular weight was observed in mice exposed to 400−2,000 mg/kg. No exposure-related changes in serum or fecal testosterone levels or testicular histology were observed.	• In a 4-wk gavage study, a NOAEL of 440 mg/kg-d and a LOAEL of 1,750 mg/kg-d were identified for increased relative liver weight and increased serum cholesterol in rats. Exposed males showed nephropathy associated with hyaline droplets. Body-weight effects were not observed at doses up to 1,750 mg/kg-d. • Biochemical changes (decreased BUN, increased AST and LDH) were observed in rats exposed to doses ≥1,071 mg/kg-d via gavage for 14 d. • Sedation has been reported in acute studies at doses as low as 400 mg/kg-d. • In an acute testicular toxicity screen, the number of tubules having gross disruption was increased in mice exposed to 2,000 mg/kg (6%) compared with controls (0%). No exposure-related changes in serum or fecal testosterone levels or testicular weight were observed.	• Numerous human case studies report irritation and corrosive effects of ingested formic acid, including ulceration and perforation of the GI tract. • Acute doses of 429−673 mg/kg are potentially lethal in humans, attributed to corrosive perforations of the abdominal viscera, gastrointestinal hemorrhage, or acute renal failure. Survivors of high acute exposures show acute renal failure, liver impairment, and hematemesis. • Decreased body-weight and food consumption were observed in rats following exposure to 360 mg/kg-d in drinking water for 9−15 wk. • Reduced offspring survival was observed in rats following chronic parental exposure to 1,360 mg/kg-d in drinking water (7 mo). • Additional short-term-, subchronic-, and chronic-duration oral studies report no adverse effects following oral exposure to formic acid; however, these studies have limited reporting or are available only from secondary sources.
Source	Billitti et al. (1998)	ATSDR (1996)	U.S. EPA (2010)
Repeat-dose toxicity—oral, chronic			
POD (mg/kg-d)	NA	NA	277
POD type	NA	NA	NOAEL (freestanding)
Chronic UF_C	NA	NA	300 (UF_H, UF_A, UF_L)
Chronic p-RfD (mg/kg-d)	NA	NA	9×10^{-1}
Critical effects	NA	NA	No adverse effects at doses up to 277 mg/kg-d.
Other effects (in principal study)	NA	NA	No exposure-related changes in reproductive or developmental endpoints, animal growth, or organ function (details not specified).

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates			
	***tert*-Butyl Formate CASRN 762-75-4**	**MTBE CASRN 1634-04-4**	**Formic Acid CASRN 64-18-6**
Species	NA	NA	Rat, M and F
Duration	NA	NA	2 yr (combined toxicity/reproductive study)
Route	NA	NA	Drinking water
Additional toxicity data (from other studies)	ND	The only available chronic-duration oral study reported decreased survival in female rats accompanied by dysplastic proliferation of lymphoreticular tissues at all tested doses (250 or 1,000 mg/kg-d, 4 times/wk for 104 wk via gavage), compared with control. These findings were associated with statistically significant increases ($p < 0.01$) in lymphoma and leukemia in female rats at ≥250 mg/kg-d. No adverse non-neoplastic effects were observed in male rats, but a statistically significant increase in the incidence of testicular Leydig cell tumors was observed at 1,000 mg/kg-d.	See "*Repeat-dose toxicity—oral, subchronic*" section above.
Source	ND	ATSDR (1996)	U.S. EPA (2010)
Repeat-dose toxicity—inhalation, subchronic			
POD (mg/m^3)	NA	260 (71 ppm)	2.7
POD type	NA	NOAEL (HEC)	LOAEL (HEC)
Subchronic UF_C	NA	100 (UF_H, UF_A)	3,000 (UF_H, UF_A, UF_L, UF_D)
Subchronic p-RfC/MRL (mg/m^3)	NA	3 (0.7 ppm)	9×10^{-4}
Critical effects	NA	Sedation (hypoactivity, lack of startle response) and blepharospasm in parental animals at 3,000 ppm (LOAEL [HEC] = 1,900 mg/m^3).	Neutropenia and increased serum ALP at 15 mg/m^3 (LOAEL [HEC] = 2.7 mg/m^3).

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates

	***tert*-Butyl Formate CASRN 762-75-4**	**MTBE CASRN 1634-04-4**	**Formic Acid CASRN 64-18-6**
Other effects (in principal study)	NA	Reduced F1 and F2 pup weight was observed at the same administered concentration that elicited CNS effects in parental animals. Increased relative liver weight was observed at 3,000 ppm in F1 parental males and at 8,000 ppm in F1 parental females (duration-adj = 1,900 and 5,200 mg/m^3, respectively). Reduced body weight was observed in parental males at 8,000 ppm (duration-adj = 5,200 mg/m^3). No adverse effects on reproduction at concentrations up to 8,000 ppm (duration-adj = 5,200 mg/m^3).	Mild nasal lesions (olfactory epithelium degeneration, respiratory epithelium squamous metaplasia) were increased in males and females at a higher administered concentration (241 mg/m^3) than selected critical effects. No other exposure-related effects were observed.
Species	NA	Rat, M and F	Rat, M and F
Duration	NA	14−19 wk (2-generation reproduction study)	13 wk
Route	NA	Whole-body inhalation	Whole-body inhalation

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates

	***tert*-Butyl Formate CASRN 762-75-4**	**MTBE CASRN 1634-04-4**	**Formic Acid CASRN 64-18-6**
Additional toxicity data (from other studies)	ND	• Effects observed in 13-wk studies in rats include altered motor activity (increased then decreased) and increased relative liver and kidney weights at ≥800 ppm (duration-adj = 510 mg/m^3); sedation, ataxia, and decreased hind-limb grip strength at ≥4,000 ppm (duration-adj = 2,600 mg/m^3); and hyperplasia of submandibular lymph nodes in males at 8,000 ppm (duration-adj = 5,100 mg/m^3). No body-weight effects were observed at any concentration. • Effects observed in 4−5-wk studies in rats and mice include sedation and increased absolute and relative liver and kidney weight at ≥3,000 ppm (duration-adj = 1,900 mg/m^3); centrilobular hepatocellular hypertrophy was observed at 8,000 ppm in mice (duration-adj = 5,100 mg/m^3). Decreased body weight was observed in male mice only at 8,000 ppm (duration-adj = 5,100 mg/m^3). • In a 1-generation rat study, no adverse reproductive or developmental effects were observed at concentrations up to 2,500 ppm (9,010 mg/m^3; duration-adj = 1,600 mg/m^3).	• Effects observed in the companion 13-wk mouse study included nasal lesions and decreased body weight female mice at ≥120 mg/m^3, respectively. No other exposure-related effects were noted. • Effects observed in 2-wk dose range-finding studies included nasal lesions in rats and mice at ≥118 mg/m^3; clinical signs of toxicity, decreased body weight, and reduced thymus weight in rats and mice at ≥470 mg/m^3; and corneal opacity in rats and mice at 941 mg/m^3.

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates			
	***tert*-Butyl Formate** **CASRN 762-75-4**	**MTBE** **CASRN 1634-04-4**	**Formic Acid** **CASRN 64-18-6**
Continued:	Continued:	Continued: • In gestational exposure studies in mice, reduced fetal body weight and skeletal ossification were observed at 4,000 ppm (14,000 mg/m^3); this concentration also produced maternal toxicity (sedation, ataxia). At 8,000 ppm (28,000 mg/m^3), increased number of nonviable implants/litter, increased late absorptions, and increased incidence of cleft palate were observed. No developmental effects were observed at ≤2,500 ppm (9,000 mg/m^3). • No developmental effects were observed in rats or rabbits exposed to concentrations up to 2,500 ppm (9,000 mg/m^3) or 8,000 ppm (28,000 mg/m^3), respectively. Maternal toxicity (reduced body weight, sedation) was observed in rabbits at ≥4,000 ppm (14,000 mg/m^3).	Continued:
Source	ND	ATSDR (1996)	U.S. EPA (2010)
Repeat-dose toxicity—inhalation, chronic			
POD (mg/m^3)	NA	259	2.7
POD type	NA	NOAEL (HEC)	LOAEL (HEC)
Chronic UF_C	NA	100 (UF_H, UF_A, UF_D)	10,000 (UF_H, UF_A, UF_S, UF_L, UF_D)
Chronic p-RfC/RfC (mg/m^3)	NA	3	3×10^{-4} (screening)
Critical effects	NA	Increased absolute and relative liver and kidney weights and increased severity of spontaneous renal lesions (F), increased prostration (F), and swollen periocular tissue (M and F) at 10,899 mg/m^3 (LOAEL [HEC] = 1,946 mg/m^3).	Neutropenia and increased serum ALP at 15 mg/m^3 (LOAEL [HEC] = 2.7 mg/m^3).

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates			
	***tert*-Butyl Formate** **CASRN 762-75-4**	**MTBE** **CASRN 1634-04-4**	**Formic Acid** **CASRN 64-18-6**
Other effects (in principal study)	NA	Additional effects noted at higher concentrations in both sexes included additional signs of clinical toxicity (ataxia, salivation) and decreased body weight. Male rats showed dose-related increases in α2u-g-mediated nephropathy and an associated decrease in survival. No additional organ-weight or histopathological changes were associated with exposure.	See "*Repeat-dose toxicity—inhalation, subchronic*" section above.
Species	NA	Rat, M and F	Rat, M and F
Duration	NA	24 mo	13 wk
Route	NA	Whole-body inhalation	Whole-body inhalation
Additional toxicity data (from other studies)	ND	• In an 18-mo mouse study, an NOAEL (HEC) of 1,288 mg/m^3 and an LOAEL (HEC) of 2,575 mg/m^3 were based on anesthetic effects, decreased body weight, increased absolute and relative liver weights, and hepatocellular hypertrophy (M). • Effects associated with short-term-duration, subchronic-duration, and reproductive/developmental studies are reported in "*Repeat-dose toxicity—inhalation, subchronic*" section above. *Note*: ATSDR (1996) derived a chronic inhalation MRL of 0.7 ppm (3 mg/m^3) using the same principal study and the critical endpoint of increased severity of chronic progressive nephropathy in female rats.	See "*Repeat-dose toxicity—inhalation, subchronic*" section above.
Source	NA	U.S. EPA (1993)	U.S. EPA (2010)
Acute lethality studies			
Rat oral LD_{50} (mg/kg)	NA	4,000	1,100

Table A-3. Comparison of Available Toxicity Data for *tert*-Butyl Formate (CASRN 762-75-4) and Potential Surrogates			
	tert-Butyl Formate CASRN 762-75-4	**MTBE CASRN 1634-04-4**	**Formic Acid CASRN 64-18-6**
Toxicity at rat oral LD_{50}	NA	NA	General depressed activity, dyspnea
Mouse oral LD_{50} (mg/kg)	NA	4,410	700
Toxicity at mouse oral LD_{50}	NA	NA	General depressed activity, dyspnea
Rat inhalation LC_{50} (mg/m^3)	NA	85,000	15,000
Toxicity at rat inhalation LC_{50}	NA	NA	General depressed activity, dyspnea
Mouse inhalation LC_{50} (mg/m^3)	NA	141,000	6,200
Toxicity at mouse inhalation LC_{50}	NA	CNS (anesthesia)	General depressed activity, dyspnea
Source	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)

α2u-g = alpha 2u-globulin; ADJ = adjusted; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; F = female(s); GI = gastrointestinal; HEC = human equivalent concentration; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = minimal risk level; MTBE = methyl *tert*-butyl ether; NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; S-D = Sprague-Dawley; 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—Oral

MTBE is selected as the surrogate compound for deriving the screening subchronic provisional reference dose (p-RfD). While formic acid (a second potential candidate surrogate) is a degradation product of *tert*-butyl formate, MTBE is a better metabolic surrogate for *tert*-butyl formate because MTBE and *tert*-butyl formate are both expected to degrade and/or metabolize to *tert*-butyl alcohol and formic acid. Importantly, evidence suggests that *tert*-butyl alcohol is primarily responsible for the oral toxicity associated with exposure to MTBE and is presumed to be associated with the toxicity of *tert*-butyl formate. Structural similarity scores (as determined by OECD toolbox) were 6% for formic acid and 40% for MTBE, further supporting the selection of MTBE as a more appropriate chemical surrogate. Additionally, the MTBE database provides evidence for a potential common target of toxicity (testes) with *tert*-butyl formate, while formic acid has a limited oral database only describing decreased body weight and food consumption in rats, in a single, poorly-reported study.

Weight-of-Evidence Approach—Inhalation

The absence of inhalation toxicity data for *tert*-butyl formate precludes the development of a surrogate-driven inhalation value for *tert*-butyl formate. Therefore, screening provisional reference concentrations (p-RfCs) were not derived.

ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall surrogate approach presented in this PPRTV assessment, MTBE was selected as the surrogate for *tert*-butyl formate for deriving a screening subchronic p-RfD. The study used to derive the ATSDR intermediate-duration oral minimal risk level (MRL) for MTBE was a 90-day gavage study in rats [Robinson et al. (1990) as cited in ATSDR (1996)]. The ATSDR profile for MTBE described this study as follows:

> *Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were treated by gavage with MTBE in corn oil at doses of 0, 100, 300, 900, and 1,200 mg/kg/day, 7 days/week for 90 days.*
>
> *Effects noted in study and corresponding doses: Relative and absolute lung weights were significantly increased in males at 1,200 mg/kg/day. Treated rats in all dose groups had diarrhea throughout the exposure period. Heart weight was significantly increased in female rats at 900 mg/kg/day. In females at 1,200 mg/kg/day, erythrocyte counts, hemoglobin, and hematocrit values were significantly increased, while leukocyte counts were significantly decreased. In male rats at 1,200 mg/kg/day, mean corpuscular volume values were significantly decreased and monocyte values were significantly elevated. Significant increases in relative liver weights were found in females at 900 mg/kg/day and in males at 900 and 1,200 mg/kg/day. Serum lactate dehydrogenase levels were significantly elevated in females at 300 mg/kg/day, and serum aspartate aminotransferase levels were significantly elevated in males at 300 and 1,200 mg/kg/day. Blood urea nitrogen (BUN) levels were significantly decreased in males and females at all dose levels, i.e., at ≥100 mg/kg/day. No histopathological lesions were found in the liver. Relative kidney weights were significantly elevated in female rats at ≥300 mg/kg/day, and absolute and relative kidney weights were significantly elevated in male rats at ≥900 mg/kg/day. Significant microscopic changes were*

observed in kidneys from treated male rats. Tubular changes, which were more severe in the 1,200 mg/kg/day dose-group males compared with controls, consisted of mild increases in cytoplasmic hyaline droplets in proximal tubular cells and small numbers of intratubular granular casts at the junction of the outer and inner stripe of the outer medulla. Female rats given 1,200 mg/kg/day had significantly elevated adrenal gland weights. Final body weight in both males and females decreased in a dose-dependent manner compared with controls, but the decrease in final body weight was significant only in females at 1,200 mg/kg/day. Cholesterol was significantly elevated in all treated female rats and in 900 mg/kg/day males. Profound anesthesia was observed immediately following dosing with 1,200 mg/kg/day, but the rats recovered in approximately 2 hours.

The critical effect for the 90-day rat study (Robinson et al., 1990) was decreased BUN levels in female and male Sprague-Dawley (S-D) rats at the lowest administered dose; the lowest-observed-adverse-effect level (LOAEL) of 100 mg/kg-day was used as the point of departure (POD) (a no-observed-adverse-effect level [NOAEL] was not identified). Furthermore, because the current practice is to only adopt existing PODs, benchmark dose modeling is not performed when applying the alternative surrogate approach (Wang et al., 2012) in PPRTV assessments. The LOAEL of 100 mg/kg-day was converted to a human equivalent dose (HED) according to current U.S. EPA (2011b) guidance. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving a p-RfD from effects that are not portal-of-entry effects.

Following U.S. EPA (2011b) guidance, the POD for decreased serum BUN in rats is converted to an HED through the application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.267 and 0.204 kg for male and female S-D rats, respectively, in a subchronic-duration study and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAFs are 0.25 for males and 0.23 for females (U.S. EPA, 2011b). The female DAF of 0.23 was applied to the LOAEL of 100 mg/kg-day, since it yields the most health-protective POD (HED):

$$\text{POD (HED)} = \text{LOAEL (mg/kg-day)} \times \text{DAF}$$
$$= 100 \text{ mg/kg-day} \times 0.23$$
$$= 23 \text{ mg/kg-day}$$

For *tert*-butyl formate, a UF_A of 3 is applied because cross-species dosimetric adjustment was performed. A UF_H of 10 is applied to account for intraspecies human-to-human variability. Additionally, for the derivation of the screening subchronic p-RfD for *tert*-butyl formate, a database uncertainty factor (UF_D) of 10 is used to account for the absence of any toxicity information for *tert*-butyl formate, and a LOAEL-to-NOAEL uncertainty factor (UF_L) of 10 is employed due to the use of a LOAEL as the POD. Thus, the screening subchronic p-RfD for *tert*-butyl formate is derived using the surrogate POD (HED) and a composite uncertainty factor (UF_C) of 3,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 10, and a UF_L of 10):

$$\textbf{Screening Subchronic p-RfD} = \text{Surrogate POD (HED)} \div UF_C$$
$$= 23 \text{ mg/kg-day} \div 3{,}000$$
$$= \mathbf{8 \times 10^{-3} \text{ mg/kg-day}}$$

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfD for *tert*-butyl formate.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfD for *tert*-Butyl Formate (CASRN 762-75-4)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for the absence of repeat-dose toxicity data for *tert*-butyl formate.
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 *tert*-butyl formate in humans.
UF_L	10	A UF_L of 10 is applied because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies variability uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose

Derivation of a screening chronic p-RfD is not proposed due to the following reasons: (1) a lack of any chronic-duration data for the target chemical, *tert*-butyl formate; (2) a lack of distinctly adverse non-neoplastic effects following chronic-duration, oral MTBE exposure; and (3) a lack of a published chronic-duration toxicity value for MTBE (see "Weight-of-Evidence Approach—Oral" section above for rationale).

Consideration of Potential Carcinogenicity

As discussed above, MTBE was selected as the surrogate for *tert*-butyl formate for derivation of a screening subchronic p-RfD using an alternative surrogate approach (Wang et al., 2012). The Cal/EPA has previously derived the following cancer potency estimates for MTBE: an oral slope factor (OSF), inhalation unit risk (IUR), and an inhalation slope factor (ISF) (Cal/EPA, 2009). Furthermore, the Cal/EPA's drinking water Public Health Goal is based on a carcinogen risk assessment (Cal/EPA, 1999). This information suggests that *tert*-butyl formate 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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