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Provisional Peer-Reviewed Toxicity Values for

Isobutyl Alcohol
(CASRN 78-83-1)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

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
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
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
CPHEA	Center for Public Health and Environmental Assessment
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
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

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV assessment.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ISOBUTYL ALCOHOL (CASRN 78-83-1)

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 U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

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.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at https://ecomments.epa.gov/chemicalsafety/.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV assessment was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

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 U.S. EPA ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

2-Methyl-1-propanol (isobutyl alcohol), CASRN 78-83-1, is one of four possible butanols of 4-carbon alcohol isomers. The other three butanols are 1-butanol, 2-butanol, and *tert*-butyl alcohol (Billig, 2001). Isobutyl alcohol is used as a solvent or as an intermediate in the flavor, fragrance, pharmaceutical, and pesticide industries. Other reported uses of isobutyl alcohol are as a process solvent (replacement for 1-butanol); a diluent and additive for nitrocellulose and synthetic resins and lacquers; a solvent in paint strippers, cleaners, hydraulic fluids, and wetting agents; and a component of printing inks and related products (NLM, 2019; Hahn et al., 2013; Billig, 2001). Isobutyl alcohol is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2021), and it is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2019).

The primary isobutyl alcohol production method is through propene hydroformylation, in which carbon monoxide and hydrogen are added to propene in the presence of catalysts. Selection of the catalyst and manufacturing processes determines the ratio of isobutyl alcohol produced compared to other isomers. Rhodium has been found to be a more favorable catalyst when optimizing the reaction for isobutyraldehyde, the isobutyl alcohol precursor. Another commercial production method of isobutyl alcohol is the Reppe process in which olefins, carbon monoxide, and water react in the presence of a catalyst. Isobutyl alcohol occurs in natural products and can be isolated from fusel oils (Hahn et al., 2013).

The empirical formula for isobutyl alcohol is $C_4H_{10}O$ and its structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of isobutyl alcohol. Isobutyl alcohol is a clear, colorless liquid at environmental temperatures with a high vapor pressure and high water solubility. Volatilization of isobutyl alcohol from water and moist surfaces is expected based on a measured Henry's law constant of 9.78×10^{-6} atm-m^3/mol. Hydrolysis of isobutyl alcohol in aqueous conditions is not expected based upon the chemical structure, which lacks functional groups that hydrolyze under environmental conditions. Adsorption of isobutyl alcohol to suspended solids and sediment in water is not expected based on its estimated soil adsorption coefficient (K_{oc}) of 10.3 L/kg. Volatilization of isobutyl alcohol from dry surfaces is also expected based on its measured vapor pressure. In the atmosphere, isobutyl alcohol will exist solely as a vapor, where it will be degraded by reaction with photochemically produced hydroxyl radicals corresponding to a half-life of 1.7 days. Direct photolysis is not expected because isobutyl alcohol does not contain chromophores that absorb at wavelengths >290 nm (wavelengths necessary for sunlight photolysis). Isobutyl alcohol is expected to have high mobility in soil based on its soil adsorption coefficient (estimated K_{oc} of 10.3 L/kg), which indicates that it may leach to groundwater.

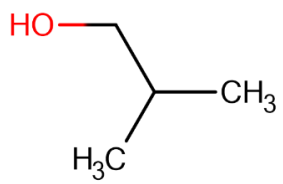


Figure 1. Isobutyl Alcohol (CASRN 78-83-1) Structure

Table 1. Physicochemical Properties of Isobutyl Alcohol (CASRN 78-83-1)

Property (unit)	Value
Physical state	Liquid[a]
Boiling point (°C)	108[b]
Melting point (°C)	−108[b]
Density (g/cm^3)	0.822[b] (predicted average)
Vapor pressure (mm Hg)	10.4[b]
pH (unitless)	NV
Acid dissociation constant (pKa) (unitless)	NV
Solubility in water (mol/L)	1.12[b]
Octanol-water partition coefficient (log K_{ow})	0.760[b]
Henry's law constant (atm-m^3/mole)	9.78×10^{-6} [b]
Soil adsorption coefficient (K_{oc}) (L/kg)	10.3[c] (predicted average)
Atmospheric OH rate constant (cm^3/molecule-sec)	1.17×10^{-11} [b]
Atmospheric half-life (d)	1.7 (calculated based on the measured OH rate constant)[b]
Relative vapor density (air = 1)	2.56[c]
Molecular weight (g/mol)	74.123[b]
Flash point (closed cup in °C)	28.6[b] (predicted average)

[a]O'Neil (2013).
[b]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (2-methyl-1-propanol; CASRN 78-83-1; https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID0021759; accessed December 15, 2021). All listed values represent experimentally determined averages unless otherwise noted.
[c]NLM (2019).

NV = not available; U.S. EPA = U.S. Environmental Protection Agency.

A summary of available toxicity values for isobutyl alcohol from the U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Isobutyl Alcohol (CASRN 78-83-1)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS (RfD)	0.3 mg/kg-d	Based on hypoactivity and ataxia in rats exposed orally for 13 wk	U.S. EPA (2002a)
HEAST (sRfD)	3 mg/kg-d	Based on hypoactivity and ataxia in rats exposed orally for 13 wk	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR	NV	NA	ATSDR (2019)
IPCS	NV	NA	IPCS (1987)
CalEPA	NV	NA	CalEPA (2020); CalEPA (2019)
OSHA (PEL)	100 ppm (300 mg/m^3)	8-h TWA for general industry, construction, and shipyard employment	OSHA (2020); OSHA (2018a); OSHA (2018b)
NIOSH (REL)	50 ppm (150 mg/m^3)	10-h TWA	NIOSH (2018)
NIOSH (IDLH)	1,600 ppm	Based on acute inhalation toxicity data in rats	NIOSH (1994)
ACGIH (TLV)	50 ppm	8-h TWA based on skin and eye irritation	ACGIH (2018); ACGIH (2001)
USAPHC (air-MEG)	1-h critical: 5,000 mg/m^3 1-h marginal: 5,000 mg/m^3 1-h negligible: 3,500 mg/m^3 8-h negligible: 150 mg/m^3 14-d negligible: 52 mg/m^3 1-yr negligible: 52 mg/m^3	1-h values based on TEELs; 8-h,14-d, and 1-yr values based on ACGIH TLV for eye and skin irritation	U.S. APHC (2013)
Cancer			
IRIS	NV	NA	U.S. EPA (2002a)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2019)

Table 2. Summary of Available Toxicity Values for Isobutyl Alcohol (CASRN 78-83-1)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
CalEPA	NV	NA	CalEPA (2020); CalEPA (2019)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = 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; USAPHC = U.S. Army Public Health Command.
[b]Parameters: IDLH = immediately dangerous to life or health concentrations; MEG = military exposure guideline; PEL = permissible exposure level; REL = recommended exposure level; RfD = reference dose; sRfD = subchronic reference dose; TEEL = temporary emergency exposure limit; TLV = threshold limit value; TWA = time-weighted average.
[c]Reference date is the publication date for the database and not the date the online source was accessed.

NA = not applicable; NV = not available.

Systematic review methods were used to identify studies relevant to the derivation of inhalation provisional toxicity values and oral and inhalation cancer weight of evidence (WOE) for isobutyl alcohol, CASRN 78-83-1. Details and results of systematic literature review can be found in Appendix B.

2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant inhalation noncancer and inhalation and oral cancer evidence bases, respectively, for isobutyl alcohol, and include all potentially relevant repeated-dose subchronic, and chronic studies, as well as reproductive and developmental toxicity studies, evaluated as *medium* or *high confidence* during systematic review (see Appendix C for more details). Oral noncancer data were not reviewed or included in this document because there is an existing Integrated Risk Information System (IRIS) oral reference dose (RfD). Principal studies used in the PPRTV assessment for derivation of provisional toxicity values are identified in bold. The phrase "statistical significance" and term "significant," used throughout the document, indicate a p-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Isobutyl Alcohol (CASRN 78-83-1)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
NV							
2. Inhalation (mg/m^3)							
NV							
Animal							
1. Oral (mg/kg-d)							
NV							
2. Inhalation (mg/m^3)							
Subchronic	10−20 M/20 F, Sprague Dawley rat, whole-body vapor inhalation, 6 h/d, 4−5 d/wk, 3 mo (14 wk) Reported analytical concentrations: 0, 258, 1,044, 2,548 ppm	0, 140, 565.2, 1,379	No toxicologically relevant effects	1,379	NDr	Li et al. (1999); Li and Kaempfe (1996)	PR; NPR, GLP
Subchronic	10 M, Sprague Dawley rat, whole-body vapor inhalation, 6 h/d, 5 d/wk, 3 mo (13 wk)) Reported analytical concentrations: 0, 258, 1,045, 2,547 ppm	0, 140, 565.7, 1,379	No toxicologically relevant effects	1,379	NDr	Li et al. (1999); Branch et al. (1996)	PR; NPR, GLP

Table 3A. Summary of Potentially Relevant Noncancer Data for Isobutyl Alcohol (CASRN 78-83-1)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive/ Developmental	**30 M/30 F, Crl:CD (SD) IGS BR rat, whole-body vapor inhalation, 6 h/d, 7 d/wk, 70 d prior to mating through weaning (F_0) with the exception of GD 20 to LD 5; exposure in utero to LD 28, direct exposure from weaning through mating to LD 21 (F_1); exposure in utero to LD 21 (F_2)** **Reported analytical concentrations: 0, 500, 1,008, 2,522 ppm (F_0 adults/F_1 pups); 0, 494, 1,012, 2,521 ppm (F_1 adults/F_2 pups)**	**0, 369.0, 743.8, 1,861 (F_0/F_1 pups)** **0, 364.5, 746.8, 1,861 (F_1 adults/F_2 pups)**	**Biologically significant decreases (≥5%) in F_1 and F_2 male and female pup body weights at multiple postnatal time points**	**NDr**	**369.0 (F_1 pups)** **364.5 (F_2 pups)**	Nemec (2003)	**NPR, PS, GLP**
Developmental	25 F SPF-Wistar rat, whole-body vapor inhalation, 6 h/d, GDs 6−15 Reported analytical concentrations: 0, 0.49, 2.50, 10.10 mg/L	0, 123, 625.0, 2,525	No toxicologically relevant effects	2,525	NDr	Klimisch and Hellwig (1995)	PR, GLP
Developmental	15 F Himalayan rabbits, whole-body vapor inhalation, 6 h/d, GDs 7−19 Reported analytical concentrations: 0, 0.5, 2.51, 10.00 mg/L	0, 125, 627.5, 2,500	No toxicologically relevant effects	2,500	NDr	Klimisch and Hellwig (1995)	PR, GLP

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002b).

[b]Dosimetry: Doses are presented as HECs (in mg/m^3) for inhalation noncancer effects. The HEC was calculated by treating isobutyl alcohol as a Category 3 gas and using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 880 is greater than the range of 541−578 reported for human blood-air partition coefficients and a blood-air partition coefficient for isobutyl alcohol in rabbits has not been determined.

[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study; GLP = reported as adhering to Good Laboratory Practices standards.

Table 3A. Summary of Potentially Relevant Noncancer Data for Isobutyl Alcohol (CASRN 78-83-1)							
Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]

ER = extrarespiratory; F = female(s); GD = gestation day; HEC = human equivalent concentration; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; NV = not evaluated.

Table 3B. Summary of Potentially Relevant Cancer Data for Isobutyl Alcohol (CASRN 78-83-1)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**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					

ND = no data.

2.1. HUMAN STUDIES

The three human studies identified in the literature search were considered *low confidence* or *uninformative* during study evaluation (see Figure C-2). The results from these studies are briefly summarized in Section 2.3.2 but they were not considered adequate for derivation of a provisional toxicity value.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures (Cancer Studies Only)

One animal oral cancer study was identified from the literature search (Dow Chemical, 1992); however, it was considered *uninformative* (see Figure C-2). The results from this study are briefly summarized in Section 2.3.3 but the study was not considered adequate for derivation of a provisional toxicity value.

2.2.2. Inhalation Exposures

Five inhalation publications, including two subchronic inhalation studies in rats (Li et al., 1999), one rat and one rabbit developmental study (Klimisch and Hellwig, 1995), and one two-generation study in rats (Nemec, 2003), were identified from the literature search and considered either *medium* or *high confidence*.

Subchronic Studies

Li et al. (1999); Li and Kaempfe (1996): Experiment 1

The subchronic general toxicity and neurotoxicity effects of isobutyl alcohol were evaluated in adult male and female rats in a peer-reviewed, published study by Li et al. (1999). Additional methodological details and data were available in an unpublished report by Li and Kaempfe (1996).

Commercially obtained Sprague Dawley rats (10−20/sex/group), 8 weeks of age at the start of exposure, were exposed whole body to isobutyl alcohol (99.9% purity) vapors at nominal concentrations of 0, 250, 1,000, or 2,500 ppm for 6 hours/day for 14 weeks (at least 70 exposures). Exposure occurred 4 days/week during Weeks 4, 8, and 13 (when neurobehavioral tests were conducted) and 5 days/week for remaining weeks. Measured analytical concentrations were 0, 258, 1,044, and 2,548 ppm (0, 782, 3,165, and 7,725 mg/m^3, respectively, as calculated by the U.S. EPA using a molecular weight of 74.123 g/mol). Twenty rats/sex/group were included in the control and high-exposure groups; 10/sex/group were included in the low- and mid-exposure groups. Experimental groups included Group 1, a neuropathology group consisting of 5 randomly selected rats/sex/group; Group 2, a general toxicity group consisting of 5/sex/group; and Group 3, consisting of the remaining 10 animals in the control and high-exposure groups.

The animals were observed twice daily for mortality and clinical signs of toxicity, including subjective assessments of reaction to brushing and tapping of the exterior walls of the chamber during the last hour of exposure. During weekly body-weight measurements, more detailed observations for signs of toxicity were recorded, including palpation for masses. Food consumption was recorded weekly. Ophthalmoscopic examinations were performed prior to study initiation and during Week 14 of exposure in the control and high-exposure animals only. Behavioral tests (functional observational battery [FOB] and motor activity) were conducted prior to initiation of exposure and during Weeks 4, 8, and 13 on all but five animals/sex in the control and high-exposure groups. The animals were not exposed to isobutyl alcohol on the days

of behavioral testing. At the end of exposure, Group 1 was sacrificed for the collection of a complete set of neurological tissues, including the brain (olfactory bulbs, forebrain, cerebrum, cerebellum, midbrain, pons, and medulla oblongata), spinal cord (cervical, thoracic, and lumbar segments), dorsal and ventral spinal nerve roots with dorsal root ganglia (C3−C6, L1−L4), Gasserian ganglion, sciatic, tibial, and sural nerves. However, only tissues from the control and high-exposure groups were examined microscopically. The one female sacrificed moribund from the high-exposure group was also examined for neuropathological lesions. Testes and epididymides of males from Group 1 were also removed, weighed, and fixed for histopathological examination.

In Group 2, blood was drawn at terminal necropsy for hematology (total erythrocyte count [red blood cells (RBCs)], total leukocyte count [white blood cells (WBCs)], hematocrit [Hct], hemoglobin [Hb], platelets, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], activated partial thromboplastin time [APTT], and leukocyte differential), and serum clinical chemistry (blood urea nitrogen [BUN], creatinine, glucose, total protein, albumin, globulin, glutamic pyruvic transaminase [SGPT]/alanine aminotransferase [ALT], alkaline phosphatase, gamma glutamyl transpeptidase, glutamic oxaloacetic transaminase [SGOT]/aspartate aminotransferase [AST], creatine phosphokinase, total and direct bilirubin, cholesterol, sodium, potassium, calcium, chloride, and phosphorus). Group 2 animals were grossly examined, and organs (brain, lungs, liver, kidneys, adrenals, testes, and epididymides) were weighed. Select tissues (adrenals, brain, epididymides, eyes, gross lesions, heart, kidneys, liver, lungs, nose sections, ovaries, skin, spleen, testes, uterus, and vagina) were fixed for histological analysis.

While Group 3 was intended as a recovery group for neurobehavior, these animals were sacrificed instead at the end of the exposure along with Groups 1 and 2 because no persistent neurobehavioral effects were observed during the study. Males from Group 3 underwent gross necropsy, and testes and epididymides were weighed and fixed for histopathological examination. Females from Group 3 underwent gross necropsy only. Statistical analysis of FOB, motor activity, and rearing data consisted of Levene's test for homogeneity, Dunnett's multiple comparison test, and analyses of variance (ANOVAs) using baseline values as covariates (analyses of covariance [ANCOVAs]) for parameters with repeated measures. For other endpoints, Bartlett's test was used for homogeneity of variances, followed by either Dunnett's test and linear regression, or nonparametric Kruskal-Wallis, Jonckheere's, and/or Mann-Whitney U test for trend. Incidence data were analyzed using Fisher's exact test (one-tailed). The Grubb's test was used to detect outliers in organ-weight data.

Quantitative data extraction for Experiment 1 can be found in the Health Assessment Workspace Collaborative (HAWC) database; links to specific data sets are included below for ease of review. One moribund female from the high-exposure group was sacrificed at approximately 2 months due to development of lymphoblastic leukemia of the vertebral column and surrounding tissues; all other males and females survived. A decrease in response to chamber brushing was subjectively observed in all examined males and females exposed to isobutyl alcohol when tested during the last hour of daily exposure (every exposure day throughout the study); control animals responded normally to chamber brushing. Some rats from the high-exposure group also showed a decrease in response to chamber tapping during the last hour of daily exposure (first 3 days of exposure only), with three males and four females affected during Day 1 of exposure and 0−2 rats/sex affected during Exposure Days 2 and 3. All

high-exposure animals responded normally to cage tapping after the first 3 exposure days, and all control animals and animals in the lower exposure groups responded normally throughout the study. No abnormal clinical signs were observed immediately after cessation of daily exposures or during weekly detailed clinical assessments. No ophthalmological changes were reported in the control or high-exposure animals. Body weight and body-weight gain were comparable across study groups. Statistically significant increases in food consumption in males in the mid-exposure group were sporadic, and no exposure-response relationship was observed. No changes in food consumption were observed in females.

There were no statistically significant differences between treated and control groups in the FOB or motor activity testing at any time point throughout the study. No biologically relevant changes in hematology or clinical chemistry were observed. The few sporadic findings that reached statistical significance, including a 9−10% increase in RBC, Hct, and Hb in high-dose females and a <5% increase in serum calcium in mid-dose males, were not considered biologically relevant given the direction of change (increased) and a lack of exposure-response, respectively. A statistically significant trend for increased absolute kidney weight was observed in exposed males (increases of 4, 17, and 16% in low-, mid-, and high-exposure males, respectively); however, pairwise statistics did not identify any statistically significant effects between individual exposure groups and controls. No statistically significant trend or pairwise effects were observed in relative kidney weights in males (kidney:body weight [6, 9, 8%] or kidney:brain [4, 15, 15%]). Statistically significant positive trends were observed in absolute liver weight (−5, 9, 17%), liver:body weight (−3, 1, 9%), and liver:brain weight (−4, 9, 18%) in low-, mid-, and high-exposure males, respectively, but again, pairwise comparisons did not identify any statistically significant changes between groups. While select kidney and liver weights in males were elevated by >10%, these findings were not considered indicative of a biologically relevant effect because (1) there were no exposure-related changes in liver or kidney serum biochemistry indicative of a functional impairment, (2) there were no associated histochemical lesions in the liver or kidney, and (3) organ-weight changes were not observed in females. No exposure-related gross or microscopic lesions were identified in any of the evaluated organs. All observed gross and microscopic lesions, including those in perfusion-fixed neuronal tissues, were sporadic, occurred in small numbers, and/or did not exhibit concentration dependence.

The highest exposure concentration (7,725 mg/m^3) is a no-observed-adverse-effect level (NOAEL) associated with repeated exposure. No biologically relevant effects were noted in body weight, hematology, clinical chemistry, or histopathology. Biologically significant increases in liver and kidney weights in male animals were noted but not identified as lowest-observed-adverse-effect levels (LOAELs) because corroborating evidence was lacking. The transient central nervous system (CNS) depression observed only during daily exposure periods was considered an acute response to isobutyl alcohol by the study authors, and not an indicator of an emerging subchronic neurological effect. The absence of persistent subchronic neurological effects is supported by the lack of exposure-related findings in the FOB and motor activity analyses and no evidence of damage to neurological tissues. Analytical concentrations of

0, 782, 3,165, and 7,725 mg/m^3 correspond to extrarespiratory effects human equivalent concentration (HEC_{ER}) values of 0, 140, 565.2, and 1,379 mg/m^3.[1]

Li et al. (1999); Branch et al. (1996): Experiment 2

Li et al. (1999) studied the subchronic neurotoxic effects of isobutyl alcohol in adult male Sprague Dawley (CD) rats using schedule-controlled operant behavior (SCOB) training. Additional methodological details and data are available in an unpublished report by Branch et al. (1996).

Commercially sourced Sprague Dawley rats were obtained at 5 weeks of age. After a 1-week acclimation period, 40 male rats were placed on a restricted diet (11−14 g/day, 7 days/week); water was available ad libitum. Male rats were trained to perform on the SCOB test in automated operant chambers. Briefly, SCOB training included 47-minute sessions in which the animals were trained to press a lever for food reinforcement using both fixed ratio (FR; rewarded only after a certain number of lever presses), and fixed interval (FI; rewarded for lever press only after a specified amount of time has elapsed). Rats were fully trained prior to exposure to isobutyl alcohol, starting with small ratios/intervals and progressing to a final schedule of four consecutive FR periods of 20 lever presses followed by two consecutive FI periods of 120 seconds. Most rats reached training criteria within 30 days; however, an additional 6 weeks of training was required for performance to be stable. The baseline performance for each animal was established 1 week prior to exposure (during Week 10 of training).

At 16 weeks of age, groups of trained male rats (10/group) were exposed to isobutyl alcohol (99.9% purity) vapors at nominal concentrations of 0, 250, 1,000, or 2,500 ppm for 6 hours/day, 5 days/week for 13 weeks (65 exposures), with sacrifice 1 week after the final exposure. Reported analytical concentrations were 0, 258, 1,045, and 2,547 ppm (782, 3,168, and 7,722 mg/m^3, respectively, as calculated by the U.S. EPA using a molecular weight of 74.123 g/mol). Starting 1 week before the first exposure and continuing throughout the study, the animals were tested 5 days/week (before the daily exposure session) for SCOB performance (e.g., whether rats pushed the lever the appropriate number of times during the FR period and waited the appropriate amount of time between lever presses during FI periods). Overall motor activity and habituation were also recorded during SCOB testing. The animals were observed twice daily for mortality and clinical signs of toxicity, including subjective assessments of reactions to brushing and tapping of the exterior walls of the chamber during the last hour of exposure. Ophthalmoscopic examinations were conducted on all rats prior to study initiation and 3 days after the last exposure. Body weights were recorded weekly and prior to SCOB testing. During weekly body-weight measurements, more detailed observations for signs of toxicity were recorded, including palpation for masses. Gross necropsy was performed only in the event of a finding during detailed clinical observations. Only the SCOB data collected during the pretest week and during Weeks 4, 8, and 13 of exposure were statistically analyzed, including measures of SCOB performance, total motor activity, and motor activity habituation. Repeated measures

[1]HEC calculated by treating isobutyl alcohol as a Category 3 gas (based on the lack of respiratory effects and the ability of similar alcohols to produce systemic effects when inhaled) using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 880 is greater than the range of 541−578 reported for human blood-air partition coefficients according to Kaneko et al. (1994) and Fiserova-Bergerova and Diaz (1986).

analysis of covariance (REPANCOVA) using baseline values as covariates was used to analyze weekly mean values across time and exposure concentration. Levine's test ($p \leq 0.01$) was used to analyze homogeneity of variance, and Dunnett's multiple comparison test was used to compare groups. Positive control data for SCOB tests were collected from 40 male rats prior to the study using d-amphetamine sulfate and chlorpromazine hydrochloride. The same dependent variables were measured in the experimental and positive control studies.

Quantitative data extraction for Experiment 2 can be found in the HAWC database; links to specific data sets are included below for ease of review. No mortalities were observed. A decrease in response to chamber brushing was subjectively observed in all examined rats exposed to isobutyl alcohol when tested during the last hour of daily exposure (every exposure day throughout the study); control animals responded normally to chamber brushing. Control and exposed animals both responded normally to chamber tapping during the last hour of daily exposure throughout the study. No other exposure-related clinical signs were observed immediately before, during, or after daily exposure. No palpable masses were identified during detailed clinical observations, and no ophthalmological abnormalities were found. There were no consistent, exposure-related changes in body weight or body-weight gain in exposed animals, compared with controls. Results from SCOB testing indicated no statistically significant differences in SCOB performance between controls and treatment groups during any of the testing weeks. Positive control animals performed as expected in SCOB testing. The only notable observation at necropsy was swollen testes in one mid-exposure male; this finding was considered incidental.

The U.S. EPA has identified the highest exposure concentration (7,722 mg/m^3) as a NOAEL based on a lack of toxicologically relevant effects associated with repeated exposure. As discussed for Experiment 1, the slight, transient CNS depression observed during daily exposure was considered by the study authors to be an acute response to isobutyl alcohol, and not an anticipated indicator of an emerging subchronic neurological effect; however, it is unclear if these transient effects would manifest under longer-duration exposures due to lack of experimental data. The absence of subchronic neurological effects is supported by the lack of exposure-related findings in the SCOB testing. The analytical concentrations of 782, 3,168, and 7,722 mg/m^3 correspond to HEC_{ER} values of 0, 140, 565.7, and 1,379 mg/m^3.[2]

Chronic Studies

No chronic inhalation studies of isobutyl alcohol have been identified.

Reproductive/Development Studies

Nemec (2003)

In an unpublished two-generation study, groups of Crl:CD (SD) IGS BR rats (30/sex/group) were exposed to clean filtered air or to isobutyl alcohol vapor concentrations of 500, 1,000, or 2,500 ppm (nominal) for 6 hours/day, 7 days/week via whole-body exposure (Nemec, 2003). Reported analytical mean concentrations were 500, 1,008, and 2,522 ppm

[2]HEC calculated by treating isobutyl alcohol as a Category 3 gas (based on the lack of respiratory effects and the ability of similar alcohols to produce systemic effects when inhaled) and using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 880 is greater than the range of 541−578 reported for human blood-air partition coefficients according to Kaneko et al. (1994) and Fiserova-Bergerova and Diaz (1986).

(1,476, 2,975, and 7,444 mg/m^3, respectively, as determined by the study authors) for the parental (F_0) generation and F_1 pups, and 494, 1,012, and 2,521 ppm (1,458, 2,987, and 7,442 mg/m^3, respectively, as determined by the study authors) for F_1 adults and F_2 pups. Exposure for F_0 rats began ~70 days prior to mating, and continued in both sexes throughout mating, gestation, and lactation periods until postnatal day (PND) 28. During this time, exposure was stopped in F_0 females between gestation day (GD) 20 and lactation day (LD) 5 to allow for parturition. On PND 4, F_1 litters were culled to eight rats (preferably to four per sex). Prior to weaning, 30 F_1 pups/sex/group were randomly selected to generate the F_2 generation. Additional weanlings were kept as potential replacement animals. Mated F_0 males and females were necropsied after F_1 weaning. The remaining F_0 animals were sacrificed on Study Day 133. The F_1 offspring not selected for mating were sacrificed at weaning (PND 28). F_1 animals selected for mating began direct exposure at weaning and were exposed in the same manner as F_0 animals from at least 70 days prior to mating until sacrifice. Second-generation (F_2) offspring were exposed in utero, and during lactation until sacrifice. Mated F_1 adults and F_2 pups were sacrificed on PND 21.

All animals were observed twice daily and within 1 hour of exposure for mortality and clinical signs of toxicity. Subjective assessments of state of arousal and response to a loud-noise stimulus were included in the evaluations and were difficult to interpret due to reporting outcomes as results combined from different stimuli. Female estrous cycles were monitored beginning 21 days prior to pairing until evidence of mating was observed. F_0 and F_1 male and female body weights were recorded on Study Days 0, 1, 4, and 7, and weekly (males) thereafter. After mating, female body weights and food consumption were recorded on GDs 0, 4, 7, 11, 14, and 20 and LDs 1, 4, 7, 14, 21, and 28 (F_0 females only). Gross necropsies were performed on all adult animals. Organ (adrenals, brain, epididymides, kidneys, liver, ovaries, pituitary, prostate, seminal vesicles with coagulating glands, spleen, testes, thymus gland, and uterus with oviducts and cervix) weights were recorded. Microscopic examinations were done on all gross lesions and select tissues (adrenal glands, cortex and medulla, brain, cervix, epididymis, caput, corpus and cauda, kidneys, liver, ovaries, pituitary, prostate, seminal vesicles, spleen, testis, thymus, uterus, and vagina) from 10 adults/sex/group from the control and high-exposure groups. Reproductive performance parameters included mating and fertility indices for F_0 and F_1 generations. Spermatogenic endpoints, including mean testicular and epididymal sperm counts, sperm production rate, motility, progressive motility, and percentage of morphologically normal sperm, were evaluated in F_0 and F_1 males. Litter endpoints examined included litter size, postnatal survival, and pup body weights on PNDs 1, 4, 7, and 21 for F_1 and F_2 pups and PNDs 28, 32, and 35 for F_1 pups. Complete necropsies were performed on F_1 and F_2 pups that were sacrificed on PNDs 28 and 21, respectively. Select organ weights (brain, spleen, thymus gland) were recorded in pups at each sacrifice. Gross lesions were retained for histopathologic examination.

Mating and fertility data were analyzed using the χ^2 test with Yates' correction factor. For other endpoints, one-way ANOVA was used to determine intergroup differences followed by the Dunnett's test if significant. The litter was used as the experimental unit where appropriate. Nonparametric data were subjected to the Kruskal-Wallis nonparametric ANOVA test followed by the Mann-Whitney U test, if significant. Using litter size as a covariant, parametric one-way ANCOVA was used to determine intergroup differences in mean offspring weights, followed by the Student's *t*-test, if significant. The two-tailed Fisher's exact test was used on histological findings to compare test groups to the control.

Quantitative data extraction for the two-generation study can be found in the HAWC database; links to specific data sets are included below for ease of review. One F_0 female in the low-exposure group was sacrificed in extremis after 91 days of exposure. No other F_0 generation mortalities were observed, and there were no significant clinical signs of toxicity in any exposure group. Responses to stimuli (ear flick) were comparable between exposed and control animals. Overall, there were no exposure-related changes in body weights or body-weight gains for F_0 males or females, and terminal body weights were comparable across all groups. Sporadic, but statistically significant, body-weight changes that did not exhibit a dose-response relationship included a 55% reduction in body-weight gain in middle exposure concentration F_0 males during Study Days 84−91, a 7% increase in body weight in low-exposure F_0 females on LD 28, and an 18-fold increase in body-weight gain in low-exposure F_0 females during LDs 1−28. These changes in low-exposure females coincided with an increase in food efficiency in this group during lactation. Mean body weights and body-weight gains were comparable between all other exposure groups and controls throughout the study. Statistically significant reductions in food consumption were observed sporadically during the study in the high-exposure group, particularly in males, but the reductions were small (generally <5% decrease from controls) and did not coincide with statistically significant changes in body weight. There were no dose-response associations observed in F_0 adult organ weights; however, sporadic statistically significant changes were observed. These sporadic changes in males included a 20% increase in absolute prostate weight in the mid-exposure group and 14−23% increases in relative prostate weight in the low- and mid-exposure groups, compared with controls. The study authors reported that because similar effects were not observed in high-exposure group animals, these changes were not attributable to the test article. In low-exposure females, the sporadic changes were limited to a 16% decrease in absolute pituitary weight. No statistically significant organ-weight changes were observed in the high-exposure groups for either sex. The single female euthanized in extremis had renal and liver necrosis; no exposure-related microscopic changes were observed in remaining F_0 animals that survived until scheduled sacrifice.

The mating and fertility indices in F_0 animals were not affected by exposure to isobutyl alcohol. The fertility index of 97% in low-exposure F_0 females was statistically significantly higher than the fertility index of 73% in controls, but this was not considered biologically relevant. There were no differences in estrous cyclicity, time to coitus, or gestation length between exposed animals and controls. Overall, there were no statistically significant effects of exposure on any sperm parameters, including motility, sperm count, sperm production rates, or morphology in F_0 males. Examination of sperm identified one F_0 male in the high-exposure group with a low percentage of morphologically normal sperm (0.5% vs. a mean of 97.9% in controls). The study authors concluded that the percentages of morphologically normal sperm from other males in this exposure group were within the normal biological range for this species and strain.

No exposure-related effects were observed in F_1 litter endpoints. Litter size, sex ratios, and mean number of pups were comparable across exposure groups. F_1 pups in the low-exposure group showed a 10% decrease in survival between PND 4 and 28, but survival in this group was comparable to controls on PNDs 0−4. In the higher-exposure groups, survival was comparable to control on PNDs 0−4 and PNDs 4−28. Reductions in F_1 pup body weights and body-weight gains were observed at various times during the postnatal period in all exposure groups. For the purposes of this PPRTV assessment, a ≥5% decrease in pup body weight is considered biologically significant by the U.S. EPA. In the low-exposure group, statistically and/or

biologically (i.e., ≥5%) significant decreases in pup weight (7−18%) were observed in F_1 males on PNDs 4−35 and F_1 females on PNDs 1−35. In the mid-exposure group, statistically and/or biologically significant decreases in pup weight (7−13%) were observed in F_1 males and F_1 females on PNDs 7−35. Biologically relevant reductions in pup weight (5−8%) were also observed in the high-exposure group in F_1 males and F_1 females on PNDs 7−28. For body-weight gain, statistically significant decreases were observed in low-exposure F_1 males (14−34%) on PNDs 4−7, 14−21, and PNDs 1−28 and females (10−40%) on PNDs 4−7, 14−21, 21−28, and 28−35. In the mid-exposure group, statistically significant decreases in body-weight gains (11−26%) were observed in F_1 males on PNDs 4−7, 14−21, 28−32, and 28−35 and females on PNDs 4−7, 14−21, 28−35, and 32−35. In the high-exposure group, body-weight gains were significantly decreased by 12% in F_1 males on PNDs 14−21. There were no notable necropsy findings or exposure-related organ-weight changes in F_1 pups on PND 28. Sporadic organ-weight changes included a statistically significant 19% reduction in absolute thymus weight in low-exposure males and a 6% decrease in absolute brain weight in low-exposure females, with no significant effects at higher exposure levels. The mean days to balanopreputial separation in males and vaginal patency in females were not affected by exposure. Vaginal patency was slightly, but statistically significantly, delayed by 6% relative to controls in low-exposure females only; this was likely secondary to the observed decreases in body weight in this exposure group.

There were no significant exposure-related clinical findings, including response to stimuli, in either F_1 males or females. Like the F_0 animals, sporadic and transient changes in body weights and food consumption occurred in F_1 adults, but without indication of concentration dependence. Reductions in body weights and/or body-weight gains that were evident in low- and mid-exposure groups during lactation persisted into adulthood, with small reductions (≤10%) occurring primarily in low- and mid-exposure males and only sporadically in females. At terminal sacrifice, statistically significant 7−8% decreases in F_1 adult male body weight were observed in low- and mid-exposure groups, and a statistically significant 8% decrease in cumulative body-weight gain was observed in the low-exposure group only. No statistically significant changes were observed for F_1 adult female terminal body weight or cumulative body-weight gain. Slight (≤10%), but statistically significant, reductions in relative food consumption occurred in high-exposure F_1 females during GDs 0−4, 11−14, and 0−20. Sporadic statistically significant changes in organ weights in F_1 adults were not considered related to treatment due to lack of a clear exposure-related response (increased relative brain weight and relative thymus weight and decreased absolute liver weight in low-exposure males; reduced absolute pituitary weights in low- and mid-exposure females). At sacrifice, there were no gross or microscopic findings attributed to exposure. The mating and fertility indices in exposed adult F_1 animals were comparable with controls. No exposure-related changes were observed in any other reproductive performance measures or in male sperm parameters.

Clinical observations and survival of F_2 pups were comparable between exposed and control animals. Reductions in F_2 pup body weight and body-weight gains were observed at various times during the postnatal period in all exposure groups. In the low- and mid-exposure groups, statistically and/or biologically (i.e., ≥5%) significant decreases in body weight (7−17%) were observed in F_2 males and F_2 females on PNDs 1−21. In the high-exposure group, statistically and/or biologically significant decreases in body weight (5−14%) were observed in F_2 males and F_2 females on PNDs 14 and 21 only. For body-weight gain, statistically significant decreases were observed in low-exposure F_2 males (23−31%) on PNDs 1−4, 4−7, and 14−21 and

females (21−25%) on PNDs 1−4, 4−7, and 14−21. In the mid-exposure group, statistically significant decreases in body-weight gain of 25−27% were observed on PNDs 14−21 in males and females. In the high-exposure group, a statistically significant 21% decrease in body-weight gain was observed in F_2 female pups on PNDs 14−21.

No notable necropsy findings in F_2 pups were reported. Sporadic, but statistically significant, changes in organ weights in F_2 pups on PND 21 were not considered related to treatment due to lack of a clear exposure-response relationship. Sporadic changes in F_2 male pups included a 15−16% increase in relative brain weight, but not absolute brain weight, in the low- and mid-exposure groups and a 24% decrease in absolute spleen weight, but not relative spleen weight, in the mid-exposure group only. Similarly, sporadic changes in F_2 female pups included a 13% increase in relative brain weight, but not absolute brain weight in the low-, mid-, and high-exposure groups; a 19−28% decrease in absolute spleen weight across all exposure groups; and a 24% decrease in relative spleen weight in the mid-exposure group only. At gross necropsy, there were no exposure-related findings in F_2 pups. Dilated renal pelvis was observed in two pups each in the low- and mid-exposure groups, but the incidences were not significant if analyzed at either the individual or litter level.

The U.S. EPA considers the lowest concentration (1,476 mg/m^3 in F_1 pups and 1,458 mg/m^3 in F_2 pups) a developmental LOAEL based on decreased F_1 and F_2 male and female pup body weights at multiple postnatal time points. There were biologically significant (≥5%) decreases in body weights of pups of both sexes at all concentrations in both generations. The highest concentration (7,444 mg/m^3 in F_0 adults/F_1 pups and 7,442 mg/m^3 in F_1 adults/F_2 pups) is a systemic and reproductive NOAEL based on a lack of toxicologically relevant effects on systemic and reproductive endpoints. Analytical concentrations of 0, 1,476, 2,975, and 7,444 mg/m^3 for F_0 adults and F_1 pups correspond to HEC values of 0, 369.0, 743.8, and 1,861 mg/m^3, for extrarespiratory effects. Analytical concentrations of 0, 1,458, 2,987, and 7,442 mg/m^3 for F_1 adults and F_2 pups correspond to HEC values of 0, 364.5, 746.8, and 1,861 mg/m^3, respectively, for extrarespiratory effects.[3]

Klimisch and Hellwig (1995): Rats

A published, peer-reviewed developmental toxicity study by Klimisch and Hellwig (1995) was conducted in female SPF-Wistar rats. Mated females (25/group) were exposed whole body to nominal concentrations of isobutyl alcohol (99.8% purity) vapors at 0, 0.5, 2.5, or 10 mg/L (0, 500, 2,500, or 10,000 mg/m^3, respectively, as converted by the U.S. EPA) for 6 hours/day on GD 6−15. Control groups were exposed to clean air. Measured analytical mean concentrations were 0, 0.49, 2.50, or 10.10 mg/L (0, 490, 2,500, or 10,100 mg/m^3, respectively, as converted by the U.S. EPA). The animals were weighed at 3-day intervals and observed daily for clinical signs of toxicity. At sacrifice on GD 20, all dams underwent gross necropsy, and the uteri were weighed. The numbers of corpora lutea, implants, live fetuses, and early and late resorptions were recorded. Fetuses were sexed, weighed, and examined externally. Visceral examinations were conducted on approximately half of the fetuses, and skeletal examinations on

[3]HEC calculated by treating isobutyl alcohol as a Category 3 gas (based on the lack of respiratory effects and the ability of similar alcohols to produce systemic effects when inhaled) and using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 880 is greater than the range of 541−578 reported for human blood-air partition coefficients according to Kaneko et al. (1994) and Fiserova-Bergerova and Diaz (1986).

the remaining fetuses from each litter. Statistical analysis of data included the Dunnett's test for maternal body weights, fetal body weights, and survival data. The Fisher's exact test was used to evaluate maternal mortality, conception, and fetal examinations.

Quantitative data extraction for this rat developmental toxicity study can be found in the HAWC database; links to specific data sets are included below for ease of review. No mortalities were observed, and no clinical signs of toxicity related to exposure were reported. No exposure-related changes were observed in maternal body-weight gains during exposure or through GD 20 (with or without correction for gravid uterine weight); absolute body weights were not reported. Uterine weights were comparable across all groups. Litter parameters, including corpora lutea, dead implants, live fetuses, implantation, and placental weight, were comparable across all groups. A statistically significant decrease in postimplantation loss was observed in the high-exposure group (4.2%) compared with controls (10%); however, this effect is not considered toxicologically relevant. No statistically significant changes in preimplantation loss were observed. Fetal body weights were comparable between exposure and control groups. There were no exposure-dependent increases in visceral or skeletal abnormalities. The only statistically significant change was a decreased fetal incidence in dilated renal pelvis in the low-exposure group (31%), compared with controls (47%); however, this effect is not considered toxicologically relevant, and no changes were observed at higher exposure levels.

The U.S. EPA considers the highest concentration (10,100 mg/m^3) a maternal and developmental NOAEL, based on the lack of toxicologically relevant effects. The reported concentrations of 0, 490, 2,500, and 10,100 mg/m^3 correspond to HEC values of 0, 123, 625.0, and 2,525 mg/m^3 for extrarespiratory effects.[4]

Klimisch and Hellwig (1995): Rabbits

A published, peer-reviewed developmental toxicity study by Klimisch and Hellwig (1995) was conducted in female Himalayan rabbits. Inseminated females (15/group) were exposed whole body to isobutyl alcohol (purity 99.8%) vapors at 0, 0.5, 2.5, or 10 mg/L (0, 500, 2,500, or 10,000 mg/m^3, respectively, as converted by the U.S. EPA) for 6 hours/day on GD 7−19. Reported analytical mean concentrations were 0, 0.5, 2.51, or 10.00 mg/L (0, 500, 2,510, and 10,000 mg/m^3, respectively, as converted by the U.S. EPA). Animals in control groups were exposed to clean air. The animals were observed daily for clinical signs of toxicity, and body weights were recorded at 3-day intervals. All dams underwent gross necropsy on GD 29 and the uteri were weighed. The numbers of corpora lutea, implants, live fetuses, and early and late resorptions were recorded. Fetuses were sexed, weighed, and examined externally. Soft tissue and skeletal examinations were conducted on all fetuses. Statistical analysis of data included the Dunnett's test for maternal body weights, fetal body weights, and survival data. The Fisher's exact test was used to evaluate maternal mortality, conception, and fetal examinations.

Quantitative data extraction for the rabbit developmental toxicity study can be found in the HAWC database; links to specific data sets are included below for ease of review. One doe in

[4]HEC calculated by treating isobutyl alcohol as a Category 3 gas (based on the lack of respiratory effects and the ability of similar alcohols to produce systemic effects when inhaled) and using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 880 is greater than the range of 541−578 reported for human blood-air partition coefficients according to Kaneko et al. (1994) and Fiserova-Bergerova and Diaz (1986).

the mid-exposure group died on Day 24, and a single doe in the high-exposure group was sacrificed on Day 21 due to spontaneous abortion. The deaths were not considered exposure-related. No clinical signs of toxicity were reported. There were no statistically significant changes in maternal body weight, body-weight gain, or uterine weight between the exposed and control does. Litter parameters were comparable across all groups, including corpora lutea, implantations, dead implants, pre- and postimplantation loss, and live fetuses. There was a slight, but statistically significant, 12% increase in mean placental weight in the mid-exposure group, compared with control, but statistically significant changes were not observed in the low- or high-exposure groups. There were no statistically or biologically significant changes in fetal body weights. No exposure-dependent increases in visceral or skeletal abnormalities were observed. A statistically significant increase in the overall fetal incidence of a specific heart variation (traces of interventricular foramen/septum membranaceum) occurred in the high-exposure group (12/92 = 13%), compared with concurrent controls (2/105 = 2%); however, the litter incidence for this variation in the high-exposure group (5/13 = 38%) was not statistically different from concurrent controls (2/15 = 13%).

The highest concentration (10,000 mg/m^3) is a maternal and developmental NOAEL based on the lack of toxicologically relevant effects. Although there was a significant increase in the fetal incidence of traces of interventricular foramen/septum membranaceum in the heart, the biological relevance of this effect is unclear. Among an unexposed rat model system examining this biological phenomenon, alterations of the cardiac membranous ventricular septum were found to not affect postnatal survival and these alterations resolved spontaneously during neonatal life, suggesting a lack of toxicity associated with the presence of these membranous tissues (Solomon et al., 1997). As there were no other potential toxicologically relevant effects identified, the U.S. EPA did not identify a LOAEL. The reported concentrations of 0, 500, 2,510, and 10,000 mg/m^3 correspond to HEC values of 0, 125, 627.5, and 2,500 mg/m^3 for extrarespiratory effects.[5]

Carcinogenicity

No adequate inhalation carcinogenicity studies of isobutyl alcohol in animals have been identified.

2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

2.3.1. Genotoxicity

The genotoxicity potential for isobutyl alcohol has been evaluated in a limited number of in vitro and in vivo studies (see Table 4A for more details). Overall, the available data indicate that isobutyl alcohol is not a genotoxic agent.

[5]HEC calculated by treating isobutyl alcohol as a Category 3 gas (based on the lack of respiratory effects and the ability of similar alcohols to produce systemic effects when inhaled) and using the following equation from the U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the blood-air partition coefficient for isobutyl alcohol in rabbits has not been determined. The human blood-air partition coefficient ranges between 541 and 578 according to Kaneko et al. (1994) and Fiserova-Bergerova and Diaz (1986).

Table 4A. Summary of Isobutyl Alcohol Genotoxicity

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	0, 10, 33.3, 100, 333, 1,000, 3,330, 5,000 µg/plate	−	−	Plate incorporation assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	American Cyanamid (1992)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.001−5 µL/plate	−	−	Plate incorporation assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	Litton Bionetics (1978a)
Mutation	*S. typhimurium* TA1535	0, 1 mg/plate	−	NDr	Ames assay. No evidence of mutagenicity.	Mirvish et al. (1993)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5, 10, 50, 100, 500, 1,000, 5,000 µg/plate	−	−	Preincubation assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	Shimizu et al. (1985)
Mutation	*S. typhimurium* TA97 TA98, TA100, TA1535, TA1537	0, 100, 333, 1,000, 3,333, 10,000 µg/plate, or to an upper dose defined by solubility	−	−	Preincubation assay. No evidence of mutagenicity in any of the strains tested, with or without rat and hamster S9 activation.	Zeiger et al. (1988)
Mutation	*Escherichia coli* WP2uvrA	5, 10, 50, 100, 500, 1,000, 5,000 µg/plate	−	−	Ames assay. No evidence of mutagenicity with or without S9 activation.	Shimizu et al. (1985)
Mutation	*Saccharomyces cerevisiae* D4	0.001, 0.01, 0.1, 1.0, 5 µL/plate	−	−	Plate incorporation assay. No evidence of mutagenicity with or without S9 activation.	Litton Bionetics (1978a)
DNA damage (SOS induction)	*S. typhimurium* TL210	NR	(+)	NDr	Luminescent *umu* microplate assay. TL210 is a phenotypic transformation of *S. typhimurium* TA1535 that contains a plasmid with luminescent genes *LuxA–E* extracted from *Vibrio fischeri*. Increased luminescence was observed using DMSO or methanol for dilution. The data table indicates that the finding was positive (defined as >twofold increase); however, the text indicates that the finding was "pseudopositive" (defined as 1.5−2-fold increase).	Nakajima et al. (2006)

Table 4A. Summary of Isobutyl Alcohol Genotoxicity						
Endpoint	**Test System**	**Doses/Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
DNA damage (SOS induction)	*S. typhimurium* TA1535/pSK1002	NR	–	NDr	Light absorption *umu* test. Negative after a 4-h incubation using DMSO or methanol for dilution.	Nakajima et al. (2006)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	L5178Y mouse lymphoma cells	0, 0.78, 1.56, 3.13, 6.25, 12.5 µL/mL (without activation) and 0, 0.39, 0.78, 1.56, 3.13, 6.25 µL/mL (with activation)	–	–	Forward mutation assay. No dose-related increase in mutation frequencies with or without S9 metabolic activation. Cytotoxicity was observed at >12.5 µL/mL with activation and at >3.13 and >6.25 µL/mL without activation, in two separate trials. Assays were conducted twice due to contamination issues in the first trial.	Litton Bionetics (1978b)
Mutation	V79 Chinese hamster fibroblasts	0, up to 270 mM	–	–	HPRT assay. No genotoxicity was observed following a 2-h treatment with the test substance. The highest nontoxic concentration tested was 107 mM.	Kreja and Seidel (2002)
DNA damage	V79 Chinese hamster fibroblasts	0, 53, 270 mM	–	NDr	Comet assay. No DNA damage was observed following a 4-h treatment with 53 mM; 270 mM was cytotoxic.	Kreja and Seidel (2002)
DNA damage	Human lung carcinoma epithelial A549 cells	0, 53, 270 mM	–	NDr	Comet assay. A significant increase in DNA damage was only seen following a 4-h treatment with 270 mM. The cytotoxic IC_{50} was 11 mM; therefore, these results are considered negative (not tested below cytotoxic concentrations).	Kreja and Seidel (2002)
DNA damage	Primary human peripheral blood cells	0, 53, 270 mM	–	NDr	Comet assay. No DNA damage was observed following a 4-h treatment with 53 mM; 270 mM was cytotoxic.	Kreja and Seidel (2002)
Clastogenicity (MN)	V79 Chinese hamster fibroblasts	0, 11, 53 mM	–	NDr	MN were not induced following a 4-h treatment with the test substance.	Kreja and Seidel (2002)

Table 4A. Summary of Isobutyl Alcohol Genotoxicity

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies—mammalian species in vivo						
Clastogenicity (CA)	White rats (8 M) were administered a single dose of isobutyl alcohol via gavage	0, 40% aqueous solution equivalent to 1/5 LD_{50}.	−	NA	Without activation, CAs in rat bone marrow cells 48-h after treatment were described by the study authors as "less pronounced" than alcohols with high molecular masses. The twofold increase in the rate of polyploid cells, 1.3-fold increase in cells with chromosome gaps, and 1.6% increase in cells with CAs were interpreted by OECD (2004) as negative.	Barilyak and Kozachuk (1988)
Clastogenicity (MN)	NMRI mice (M/F) were administered single oral doses of isobutyl alcohol via gavage	0, 500, 1,000, 2,000 mg/kg	−	NA	No increase in polychromatic erythrocytes containing small or large MN after treatment. Positive controls (cyclophosphamide, vincristine) produced the expected response.	Engelhardt and Hoffmann (2000) as cited in OECD (2004)

[a](+) = weak positive, − = negative.

CA = chromosomal aberration; DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; F = female(s); IC_{50} = half maximal inhibitory concentration; LD_{50} = median lethal dose; M = male(s); MN = micronuclei; NA = not applicable; NDr = not determined; NR = not reported.

Available in vitro studies indicate that isobutyl alcohol is not mutagenic to bacteria, yeast, or mammalian cells. Isobutyl alcohol was not mutagenic with or without metabolic activation in *Salmonella typhimurium* (Mirvish et al., 1993; American Cyanamid, 1992; Zeiger et al., 1988; Shimizu et al., 1985; Litton Bionetics, 1978a), *Escherichia coli* (Shimizu et al., 1985), or *Saccharomyces cerevisiae* (Litton Bionetics, 1978a). In a German study by Hilscher et al. (1969), available only from secondary sources (OECD, 2004; U.S. EPA, 1986), a sevenfold increase in reversions in *E. coli* CA274 cells was observed following a 72-hour incubation with 2.5% isobutyl alcohol. However, both secondary sources indicated that the methods were inadequate and considered the study unreliable; therefore, the study was not included in Table 4A. In mammalian cells, isobutyl alcohol was not mutagenic in mouse lymphoma cells or Chinese hamster fibroblasts, with or without metabolic activation (Kreja and Seidel, 2002; Litton Bionetics, 1978b).

Available in vitro studies also indicate that isobutyl alcohol is not clastogenic to mammalian cells, has a low potential to cause deoxyribonucleic acid (DNA) damage in bacteria, and does not induce DNA damage in mammalian cells. Isobutyl alcohol did not induce micronuclei (MN) in Chinese hamster fibroblasts, without metabolic activation (Kreja and Seidel, 2002). In a study that evaluated DNA damage in bacteria, the SOS response was assessed using the light absorption *umu* test and a more sensitive luminescent *umu* test in a recombinant *S. typhimurium* TA1535 strain (Nakajima et al., 2006). The SOS response was not increased using the light absorption test. Data reporting for the more sensitive luminescent test were inconsistent; isobutyl alcohol was reported as positive (>twofold increase in SOS response) in the data tables but "pseudopositive" (1.5−2-fold increase in SOS response) in the resulting discussion. Isobutyl alcohol did not induce DNA damage at noncytotoxic doses in human lung carcinoma epithelial A549 cells, V79 Chinese hamster fibroblasts, or primary human peripheral blood cells without metabolic activation (Kreja and Seidel, 2002).

In vivo studies were limited to two cytogenic studies, one with limited details in White rats and an Organisation for Economic Cooperation and Development (OECD) guideline mouse MN test in NMRI mice. In rats, there were slight increases (≤twofold) in the rate of bone marrow polyploid cells and in cells with chromosomal gaps or aberrations (Barilyak and Kozachuk, 1988). These increases were reported by the study authors to be less pronounced than those observed when testing other alcohols; OECD (2004) interpreted the results to be negative. No increases in the rates of polychromatic erythrocytes containing small or large MN were observed in mice administered single oral doses up to 2,000 mg isobutyl alcohol/kg (Engelhardt and Hoffmann, 2000 as cited in OECD, 2004).

2.3.2. Supporting Human Toxicity Studies

Available supporting human inhalation studies are summarized in Table 4B and include a case report with insufficient details and two human studies evaluated as *low confidence* or *uniformative* during study evaluation due to major methodological limitations (see Appendix C for details).

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Supporting evidence—noncancer effects in humans following inhalation exposure				
Case series report	Four laboratory workers occupationally exposed to unspecified levels of isobutyl alcohol for short periods up to 18 mo.	Vertigo, nausea, and headache were reported. There was one case of vestibular irritation and one case of Meniere's disease.	This study is *uninformative* due to lack of available details.	Seitz (1972) as cited in U.S. EPA (1986)
Occupational cohort study	Air sampling data from 12 exposed workers and 11 unexposed workers were collected to determine levels of exposure to multiple compounds. Exposure was defined by department. Participants provided self-reported health surveys that included medical history, as well as sperm samples to examine for changes in spermatogenesis.	Exposure to isobutyl alcohol was negligible (below detection level for most participants). Therefore, no compound-specific analysis was performed. Health surveys found no abnormal effects on spermatogenesis, fertility, or liver or kidney function between exposed and control groups.	This study is *uninformative* regarding the potential effects of isobutyl alcohol on male reproductive toxicity (primary endpoint) or liver or kidney function due to negligible exposure.	Hollett and Aw (1982)
Skin irritation	In an acute patch test, a 25 µL volume of a 75% solution of isobutyl alcohol was applied to the skin of 12 participants of Asian descent, under occlusive conditions for 5 min. Prior to patch testing, subjects were preclassified as "flushers" (n = 8) or "nonflushers" (n = 4) when drinking alcohol. The sites were monitored for 60 min for signs of erythema. The conditions of a positive response were not defined. Reversibility was not evaluated.	A positive response was reported in 2/12 individuals. Both positive reactions were in individuals previously determined to have a predisposition for flushing. Severity was not described.	This study is of limited usefulness due to multiple deficiencies, including short exposure duration and assessment time, short follow-up, subjective determination of results, no description of participant selection, and lack of discussion of confounding factors.	Wilkin and Stewart (1987); Wilkin and Fortner (1985)
Supporting evidence—noncancer effects in animals following inhalation exposure				
Acute (mortality)	Acute toxicity data in rats were reported from RTECS database.	4-h ALC = 4,000 ppm (12,126 mg/m^3)		Kennedy and Graepel (1991)
Acute (mortality)	Rats were exposed to isobutyl alcohol via inhalation. No additional study details were available.	LC_{50} = 19,200 mg/m^3		Kushneva et al. (1983) as cited in OECD (2004); IPCS (1987)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Acute (mortality)	Rats (6/group) were exposed to saturated isobutyl alcohol vapors reported to be approximately 16,000 ppm (49,248 mg/m^3) for 2 h or to 8,000 ppm (24,624 mg/m^3) for 4 h.	100% survival at 49,248 mg/m^3 for 2 h. Mortality in 2/6 rats at 24,624 mg/m^3 for 4 h.		Smyth et al. (1954) as cited in IPCS (1987)
Acute (mortality)	Female rats (6/group) were exposed to saturated vapors (estimated at 14,000 ppm or 42,441 mg/m^3) of isobutyl alcohol for 2 or 4 h and were observed for 14 d.	All animals survived following a 2-h exposure. Mortality was 100% after a 4-h exposure.		Mellon Institute (1986)
Acute (mortality)	Male and female rats (6/group) were exposed to an isobutyl alcohol concentration of 8,000 ppm (24,624 mg/m^3) for 4 h. Male rats were tested twice (once with a sample from 1946 and once with a sample from 1953); females were tested once (sample NS). Mortality was recorded.	1/6 male rats died following exposure to the 1953 sample; no mortalities following exposure to the 1946 sample. No female mortalities.		Mellon Institute (1986)
Acute (mortality)	Sprague Dawley rats (10/sex) were exposed to 6.5 mg/L (2,145 ppm) isobutyl alcohol vapors for 4 h. Animals were observed for 14 d following exposure.	4-h LC_{50} >6,500 mg/m^3 No deaths or signs or toxicity were observed.		BASF (undated) as cited in OECD (2004)
Acute (mortality)	Mice were exposed to isobutyl alcohol via inhalation. No additional study details were available.	LC_{50} = 15,500 mg/m^3		Kushneva et al. (1983) as cited in IPCS (1987)
Acute (mortality)	Rabbits were exposed to isobutyl alcohol via inhalation. No additional study details were available.	LC_{50} = 26,250 mg/m^3		Kushneva et al. (1983) as cited in OECD (2004)
Acute (mortality)	Guinea pigs were exposed to isobutyl alcohol via inhalation. No additional study details were available.	LC_{50} = 19,900 mg/m^3		Kushneva et al. (1983) as cited in IPCS (1987)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Acute (neurotoxicity)	Rats (10/sex/group) were exposed to isobutyl alcohol vapor concentrations of 1,500, 3,000, or 6,000 ppm (4,547, 9,095, or 18,189 mg/m^3) for 6 h. Animals were observed for mortality and clinical signs of CNS depression. FOB and motor function tests were conducted prior to and immediately after exposure and on Days 1, 7, and 14 after dosing. At sacrifice (Day 15), animals were grossly examined, and central and peripheral nervous tissues were fixed for microscopic examination.	Rapid, but reversible general CNS depression occurred during exposure in the 3,000- and 6,000-ppm groups. Hypoactivity was observed at 1,500 ppm. At 6,000 ppm, females showed a decrease in alertness, and decreased motor activity was recorded in both sexes. One male exhibited an uncoordinated gait. All effects were transient. There were no treatment-related findings at gross necropsy.		Monsanto (1994)
Acute (neurotoxicity)	Male albino SPF rats (4/group) were exposed whole body to at least three concentrations (NS) of isobutyl alcohol vapors for 4 h. A neurotropic effect was determined based on the inhibition of propagation and maintenance of an electrically evoked seizure. Baseline durations of hindlimb tonic extensions in response to 0.2-sec, 50-Hz, 180-V electrical impulses applied through ear electrodes were established prior to exposure. The effect of exposure on the duration of maximal tonic extension was measured. Each animal was tested up to 4 times with intervals of 3 wk between exposures. Experiments were performed in duplicate. Based on a linear regression, the concentration evoking a 30% depression in the duration of tonic extension (RC_{30}) was determined.	Rat RC_{30} (30% depression of seizure activity) = 3,800 ppm (11,520 mg/m^3); this is considered a sign of CNS depression.		Frantík et al. (1994)
Acute (neurotoxicity)	Harlan Sprague Dawley rats (5/sex) were exposed to saturated isobutyl alcohol vapors for 6 h under semi-static conditions. Animals were observed for mortality and clinical signs and were necropsied 14 d following exposure.	No deaths were observed. Animals exhibited hypoactivity, lacrimation, narcosis, prostration, and abnormal breathing during exposure, and prostration, narcosis, and negative reflexes following exposure.		Union Carbide Corp. (1993) as cited in OECD (2004)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Acute (neurotoxicity)	Female H-strain mice (2/group) were exposed whole body to isobutyl alcohol vapors for 2 h. A neurotropic effect was determined based on the inhibition of propagation and maintenance of an electrically evoked seizure. Baseline durations of hindlimb tonic extensions in response to 0.2-sec, 50-Hz, 180-V electrical impulses applied through ear electrodes were established prior to exposure. The effect of exposure on the duration of maximal tonic extension was measured. Each animal was tested up to 4 times with intervals of 3 wk between exposures. Experiments were performed in duplicate. Based on a linear regression, the concentration evoking a 30% depression in the duration of tonic extension (RC_{30}) was determined.	Mouse RC_{30} (30% depression of seizure activity) = 2,500 ppm (7,579 mg/m^3); this is considered a sign of CNS depression.		Frantík et al. (1994)
Acute (eye irritation)	Groups of male and female rats were exposed to isobutyl alcohol vapor concentrations of 2,000, 6,000, or 8,000 ppm (6,063, 18,189, or 24,252 mg/m^3) for 6 h. Animals received ophthalmoscopic examinations at an unspecified time following exposure.	Inflammatory changes (iritis, vascular congestion, anterior synechia) were observed at ≥18,189 mg/m^3. Inflammatory changes were accompanied by unilateral or bilateral corneal opacities, with the greatest severity at 24,252 mg/m^3.		Chemical Manufacturers Association (1994)
Acute (respiratory irritation)	Male Swiss OF_1 mice (6/group) were exposed head only to four concentrations of isobutyl alcohol vapors for 5 min (concentrations NR). Respiratory rates were monitored and the concentration resulting in a 50% reduction in the breathing rate (RC_{50}) was determined.	Mouse RD_{50} (50% decrease in respiratory rate) = 1,818 ppm (5,511 mg/m^3); this is considered an indication of respiratory irritation.		de Ceaurriz et al. (1981)
Acute (systemic)	Rats and rabbits were exposed to isobutyl alcohol concentrations of 100, 1,300, 8,000, or 15,700 mg/m^3 via inhalation for 4 h. Animals were sacrificed 3 d later. Results were reported for both species together (no species-specific data).	Altered breathing frequency at ≥100 mg/m^3; decreased number of lymphocytes at ≥1,300 mg/m^3; airway irritation, hematological changes, and dystrophia of hepatocytes and olfactory neurons in the brain at ≥8,000 mg/m^3; and similar but more severe effects at 15,700 mg/m^3.		Kushneva et al. (1983) as cited in IPCS (1987)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Short-term	Male CD rats (5/group) were exposed to 0, 2,274, 4,550, or 9,095 mg/m^3 for 6 h/d, 5 d/wk for 2 wk. Animals were examined for changes in mortality, clinical signs (including subjective evaluations of response to external stimuli), food consumption, body weights, and hematological parameters. Animals were subject to ophthalmoscopic examinations and FOB testing. Complete necropsies, organ weights, and histopathological analyses were done.	A marginal decrease in response to chamber wall tapping was observed during exposure starting at 2,274 mg/m^3 with more pronounced effects at higher concentrations. General CNS depression and labored breathing occurred at the two higher exposure levels.	Observed CNS depression was transient and considered by the study authors to be due to acute exposure rather than an indication of neurotoxicity resulting from repeated exposures.	Kaempfe and Li (1996)
Subchronic	Rats (sex, strain, and number NS) were exposed to isobutyl alcohol vapor concentrations of 0.1, 0.5, or 3.0 mg/m^3 continuously for 4 mo.	Reductions in erythrocyte numbers, hemoglobin content, cholinesterase, and catalase activity were reported at 0.5 and 3.0 mg/m^3. At 3.0 mg/m^3, there was an increased stimulus threshold to trigger avoidance response, and increased ALT and AST activities.	Data reporting was inadequate for independent analysis.	Tsulaya (1978) as cited in OECD (2004)
Undefined duration	Mice (sex, strain, and number NS) were intermittently exposed to 2,125 ppm (6,442 mg/m^3) of isobutyl alcohol for a total of 223 h (9.25 h/exposure). An additional group was also given repeated exposures to 6,400 ppm (19,400 mg/m^3); duration of exposure for this group was NS.	No deaths were reported in the group exposed to 6,442 mg/m^3 (no further details on this group). Transient narcosis was observed at 19,400 mg/m^3.	Data reporting was inadequate for independent analysis.	Weese (1928) as cited in U.S. EPA (1986)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Comments	References
Supporting evidence—cancer effects in animals following oral exposure				
Carcinogenicity	Male and female Wistar rats (19 in treatment group, 25 in control group; number per sex NS) were administered isobutyl alcohol via gavage at 0.2 mL/kg or 0.9% NaCl (control) twice/wk for a lifetime.	The average survival was 643 d for controls and 495 d for the treatment group. Three animals in the treatment group had malignant tumors (an antestomach carcinoma and a liver cell carcinoma, an antestomach carcinoma with myeloid leukemia, and myeloid leukemia). No tumors were reported in controls. Liver damage, including steatosis, necrosis, fibrosis, and cirrhosis, hyperplasia of blood forming tissues, and damage to heart tissue were also reported.	This study was *uninformative*. Overall, the study has major design and reporting deficiencies. Evidence was not presented clearly or transparently. Dosing frequency, animal number, and tumor incidences are too low to draw meaningful conclusions regarding the carcinogenic potential of isobutyl alcohol.	Dow Chemical (1992); Gibel et al. (1975)

[a]Acute = exposure for ≤24 hours; short term = repeated exposure for >24 hours ≤30 days; subchronic = repeated exposure for >30 days ≤10% life span (>30 days up to approximately 90 days in typically used laboratory animal species); chronic = repeated exposure for >10% life span for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002b).

ALC = approximate lethal concentration; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; FOB = functional observation battery; LC_{50} = median lethal concentration; NaCl = sodium chloride; NR = not reported; NS = not specified; RC_x = concentration to cause *x* change in response (e.g., RC_{30} = concentration to cause 30% change in response); RTECS = Registry of Toxic Effects of Chemical Substances.

In a case-series report available only from a secondary source, vertigo, nausea, and headache were reported by workers occupationally exposed to isobutyl alcohol; no additional details regarding exposure levels or duration were available (Seitz, 1972 as cited in U.S. EPA, 1986). In an occupational cohort study, sperm analysis, renal and liver function tests, and medical health survey reports of birth defects in offspring, infertility, miscarriages, and stillbirths were evaluated in workers exposed to a variety of chemicals; however, air sampling from potentially exposed factory workers indicated that exposure to isobutyl alcohol was negligible (Hollett and Aw, 1982). Therefore, no assessments of isobutyl alcohol were made in this study.

The only other available human studies both describe an acute patch test in 12 Asian volunteers; 8 of these volunteers were classified as "flushers" with a predisposition to skin redness when drinking alcohol (Wilkin and Stewart, 1987; Wilkin and Fortner, 1985). Subjects were dermally exposed to isobutyl alcohol for 5 minutes on presoaked skin. Results were reported as positive or negative for erythema (as opposed to a graded scoring system), but no clear definition of erythema was provided. Two of the volunteers, both "flushers," were classified as positive. Overall, it can be concluded that a 5-minute exposure to isobutyl alcohol under the test conditions did not cause skin redness in most subjects and that the two subjects with redness were predisposed as described by the study authors, increasing the uncertainty surrounding results from these two individuals. However, the usefulness of this study is limited due to several deficiencies, including short exposure duration and assessment time, short follow-up, subjective determination of results, no description of participant selection, and lack of discussion of confounding factors.

2.3.3. Supporting Animal Toxicity Studies

Supporting animal toxicity studies include several acute and short-term inhalation studies, which indicate CNS depression and eye and respiratory irritation as toxicologically relevant effects following exposure to high air levels. Other supporting studies include a 4-month foreign language study in rats available only as a brief description in a secondary source and an inadequately reported developmental probe study in rats and rabbits. For carcinogenicity, the database is limited to an oral cancer study with methodological inadequacies and limited data reporting. See Table 4B for more details.

Supporting Studies for Noncarcinogenic Effects in Animals

Acute lethality studies on isobutyl alcohol indicate that isobutyl alcohol has relatively low lethality via the inhalation route. Reported median lethal concentration (LC_{50}) values were 19,200 mg/m^3 in rats, 15,500 mg/m^3 in mice, 26,250 mg/m^3 in rabbits, and 19,900 mg/m^3 in guinea pigs (Kushneva et al., 1983 as cited in OECD, 2004; Kushneva et al., 1983 as cited in IPCS, 1987; Mellon Institute, 1986). The acute exposure at which mortality first occurred (approximate lethal concentration [ALC]) for rats was reported as 12,126 mg/m^3 (Kennedy and Graepel, 1991). Other lethality studies in rats reported no mortalities following exposure to saturated vapors (~42,441−49,248 mg/m^3) for 2 hours and 0, 33, and 100% mortality following a 4-hour exposure to 6,500, 24,624, and 42,441 mg/m^3, respectively (BASF, undated as cited in OECD, 2004; Smyth et al., 1964 as cited in IPCS, 1987; Mellon Institute, 1986). In contrast, no deaths were reported in rats exposed to saturated vapors (estimated exposure not reported) for 6 hours (Union Carbide Corp., 1993 as cited in OECD, 2004). No mortalities were observed in mice following repeated exposure to 6,442 mg/m^3 for a total of 223 hours (9.25 hours/exposure) (Weese, 1928 as cited in U.S. EPA, 1986).

Neurotoxicity is the primary effect reported in available acute and short-term inhalation studies. Transient hypoactivity was reported at acute concentrations ≥4,547 mg/m^3, with more pronounced CNS depression (e.g., decreased alertness, uncoordinated gait, prostration, narcosis) occurring at ≥7,579 mg/m^3 (Frantík et al., 1994; Monsanto, 1994; Union Carbide Corp., 1993 as cited in IPCS, 1987). In an unpublished 2-week study in rats, transient decreases in response to stimuli (cage tapping) were observed during exposure to ≥2,274 mg/m^3, with general CNS depression at ≥4,550 mg/m^3; the effects ceased after the rats were removed from the chamber (Kaempfe and Li, 1996). A specialized study by Frantík et al. (1994) evaluated CNS depressant potential of isobutyl alcohol by evaluating inhibition of the propagation and maintenance of an electrically evoked seizure in rats and mice. The concentration required for a 30% decrease in seizure activity (RC_{30}), measured by duration of hindlimb tonic extensions, in rats and mice was 11,520 and 7,579 mg/m^3, respectively. One study, available only from a secondary source, reported dystrophia of olfactory neurons in the brain of rats and rabbits exposed to ≥8,000 mg/m^3 for 4 hours (Kushneva et al., 1983 as cited in IPCS, 1987).

High air concentrations of isobutyl alcohol vapor are irritating to the eyes and airways. Exposure to isobutyl alcohol vapors for 6 hours resulted in inflammatory changes in the eye and corneal opacities in rats at ≥18,189 mg/m^3 (Chemical Manufacturers Association, 1994). Respiratory irritation, indicated by altered breathing frequency, was reported in both rats and rabbits after exposure to ≥100 mg/m^3 for 4 hours (Kushneva et al., 1983 as cited in IPCS, 1987). In another study, the 50% reduction in respiratory rates (RC_{50}) in mice after 5 minutes of exposure to isobutyl alcohol vapors was 5,511 mg/m^3 (de Ceaurriz et al., 1981). In the 2-week study by Kaempfe and Li (1996), labored breathing was reported during exposure to concentrations ≥4,550 mg/m^3; effects ceased upon removal from the chamber.

One acute inhalation study, available only from a secondary source, reported hematological changes, dystrophia of hepatocytes, and a reduced number of lymphocytes in both rats and rabbits exposed to ≥1,300 mg/m^3 for 4 hours (Kushneva et al., 1983 as cited in IPCS, 1987). No further details on these effects are available.

In a foreign-language study available only from a secondary source, transient narcosis was observed in mice following repeated exposures to 19,400 mg/m^3 (number and duration of exposures not reported) (Weese, 1928 as cited in U.S. EPA, 1986). In a foreign-language subchronic study also available only from a secondary source, leg withdrawal response to electrical stimuli was depressed in rats exposed for 4 months to 3.0 mg/m^3 (Tsulaya, 1978 as cited in OECD, 2004). Minor hematological changes (reduced hemoglobin content, decreased erythrocyte count) and increased serum ALT and AST were also reported at ≥0.5 mg/m^3. No effects were observed at 0.1 mg/m^3. Available data from these studies are too limited for independent analysis.

Supporting Studies for Developmental Effects in Animals

No supporting studies for developmental effects in animals have been identified. The literature search did identify a technical report (Eastman Kodak, 1992) that, upon analysis, was found to be the same study as the Klimisch and Hellwig (1995) study.

Supporting Studies for Carcinogenic Effects in Animals

Data on the carcinogenic potential for isobutyl alcohol are limited to a single foreign language study by Gibel et al. (1975), with an English translation by Dow Chemical (1992). In this study, 19 male and female rats (number per sex not specified) were administered isobutyl alcohol at 0.2 mL/kg via gavage twice weekly until natural death. Twenty-five male and female controls were similarly treated with 0.9% sodium chloride (NaCl). Three animals in the treated group had malignant tumors (an antestomach carcinoma and a liver cell carcinoma, an antestomach carcinoma with myeloid leukemia, and myeloid leukemia). No tumors were reported in the controls. This study was evaluated as *critically deficient* (*uninformative*) during systematic review because of its limited reporting and several methodological inadequacies (e.g., inadequate dosing frequency, animal number, and tumor incidences); see Appendix C for more details.

2.3.4. Metabolism/Toxicokinetic Studies

The toxicokinetic properties of isobutyl alcohol have been evaluated in a limited number of published studies, and also reviewed by OECD (2004), IPCS (1987), and U.S. EPA (1986); these secondary sources cite a number of foreign language studies and unpublished data sources that were not available for independent review. An overview based both on published studies and these reviews is presented below.

Absorption

Isobutyl alcohol is readily absorbed through the lungs and gastrointestinal tract and is expected to be readily absorbed through the skin, consistent with general principles associated with the identified physicochemical properties. Experimental data in rats show rapid absorption of isobutyl alcohol based on detection of the parent compound and isobutyl alcohol metabolites in the blood within 5 minutes of inhalation exposure (OECD, 2004; IPCS, 1987; U.S. EPA, 1986). Peak blood concentrations of isobutyl alcohol were observed 15 minutes after inhalation exposure in rats (OECD, 2004). The blood-air partition coefficient for isobutyl alcohol was determined to be 541−578 in humans and 880 in rats (Kaneko et al., 1994; Fiserova-Bergerova and Diaz, 1986); see Table 5. Experimental data from humans and laboratory animals indicate that isobutyl alcohol is also rapidly absorbed through the gastrointestinal tract based on detection of the parent compound and isobutyl alcohol metabolites in the blood and urine <1 hour after oral administration (OECD, 2004; U.S. EPA, 1986). In humans, blood levels of isobutyl alcohol peak 45−120 minutes after the start of oral exposure (OECD, 2004). Similarly, peak blood levels in rabbits were observed 1 hour after oral administration (U.S. EPA, 1986). No in vivo dermal studies measuring absorption of isobutyl alcohol have been identified; however, dermal absorption was computationally predicted to be high following direct dermal contact with isobutyl alcohol liquid or vapors (Fiserova-Bergerova et al., 1990).

Table 5. Partition Coefficients for Isobutyl Alcohol

Species	Muscle	Kidney	Lung	Brain	Fat	Liver	Blood	Reference
Tissue-gas partition coefficients for isobutyl alcohol								
Human	343 ± 46	371 ± 28	400 ± 42	White matter: 337 ± 57 Gray matter: 387 ± 29	388 ± 33	NDr	541 ± 134	Fiserova-Bergerova and Diaz (1986)
Human	NDr	NDr	NDr	NDr	NDr	NDr	578 ± 75	Kaneko et al. (1994)
Rat	850 ± 66	875 ± 42	NDr	868 ± 22	720 ± 52	880 ± 100	880 ± 37	Kaneko et al. (1994)
Tissue-blood partition coefficients for isobutyl alcohol								
Rat (measured)	0.97	0.99	NDr	0.99	0.82	1.00	NA	Kaneko et al. (1994)
Human (predicted)	0.38−0.76	0.41−0.82	0.45−0.88	0.43−0.85	0.43−0.85	NDr	NA	Poulin and Krishnan (1995)

NA = not applicable; NDr = not determined.

Distribution

Data regarding distribution of isobutyl alcohol or its metabolites to specific tissues following in vivo exposure were not available. In a developmental toxicity study, Klimisch and Hellwig (1995) stated that isobutyl alcohol is distributed to both hydrophilic and lipophilic compartments, but did not cite the source of this information. It is assumed that isobutyl alcohol in blood can cross the placental barrier, but no specific data to test this hypothesis were available. Tissue-gas and tissue-blood coefficients have been determined experimentally in rat tissues, and tissue-blood coefficients have been predicted in human tissues (Poulin and Krishnan, 1995; Kaneko et al., 1994) (see Table 5).

Metabolism

The primary metabolites identified in blood and urine in humans and laboratory animals following exposure include isobutyraldehyde and isobutyric acid (OECD, 2004; U.S. EPA, 1986). Metabolism is rapid, with peak metabolite concentrations in blood observed at 2−4 hours after the start of oral dosing in humans and 25 minutes after the start of inhalation exposure in rats (OECD, 2004). Other urinary metabolites identified include acetaldehyde, acetic acid, and unspecified glucuronic acid conjugates (OECD, 2004; IPCS, 1987; U.S. EPA, 1986). Metabolism may be dose-dependent because aldehydes were only observed in rabbits following exposure to drinking water saturated with isobutyl alcohol, but not to single gavage doses of ~618−1,600 mg/kg (U.S. EPA, 1986). Isovaleric acid was also identified in the urine of rabbits following exposure to drinking water saturated with isobutyl alcohol; however, this unexplainable metabolite may have been identified in error because of potential co-elution of a metabolite with isovaleric acid on the chromatogram (OECD, 2004).

Based on identified metabolites in blood and urine following exposure to isobutyl alcohol, it is proposed that isobutyl alcohol is oxidized into isobutyraldehyde by alcohol dehydrogenase (ADH), which is further oxidized into isobutyric acid via aldehyde dehydrogenases (ALDH) (OECD, 2005; U.S. EPA, 1986). Subsequently, isobutyric acid reacts with Coenzyme A (CoA), enters the tricarboxylic acid cycle, and results in liberation of carbon dioxide (CO_2) (U.S. EPA, 1986). ADH inhibition studies confirm the primary role of ADH in isobutyl alcohol oxidation. Using the ADH inhibitors, 4-methylpyrazole and isobutyramide, Plapp et al. (2015) estimated that ADH is responsible for approximately 66% of isobutyl alcohol metabolism in vivo in rats. Pyrazole, another ADH inhibitor, was also effective at reducing breakdown of isobutyl alcohol by approximately 50% (Lester and Benson, 1970). ADH metabolism is rapid in both in situ rat liver perfusions and in vitro rat liver homogenates (2−7 µmol/g liver/minute) (OECD, 2005; U.S. EPA, 1986). Based on in vitro studies with human liver Class I, II, and III ADHs, Class I ADH isoenzymes are the most active for isobutyl alcohol (Ehrig et al., 1988). Human skin ADH enzymes also have demonstrated the ability to oxidize isobutyl alcohol (Wilkin and Stewart, 1987).

Excretion

Excretion of isobutyl alcohol and its metabolites is primarily via urine, with small amounts of unchanged isobutyl alcohol and CO_2 in expired air (OECD, 2005; IPCS, 1987; U.S. EPA, 1986). Blood and urine samples collected from humans who were administered approximately 5 mg/kg isobutyl alcohol in an ethanol/water mixture over a 2-hour time period indicated rapid elimination of unchanged isobutyl alcohol and its primary metabolites in urine (OECD, 2004). Urinary levels of isobutyl alcohol, isobutyraldehyde, and isobutyric acid peaked 1, 8, and 2 hours after the start of oral exposure in humans, respectively (OECD, 2004). Isobutyl alcohol was no longer detected in the blood of humans 12 hours after drinking an orange juice, isobutyl alcohol, and ethanol mixture, although ethanol consumption likely altered toxicokinetics (U.S. EPA, 1986). Excretion of $^{14}CO_2$ in expired air was used to determine an excretion rate of 6.9 mmol/kg-hour in rats following an intraperitoneal (i.p.) injection of 6.8 mmol/kg of [^{14}C]-labelled isobutyl alcohol (Lester and Benson, 1970). Another study in rats determined a first-order elimination rate of 3.8 ± 0.5 mmol/kg-hour following an i.p. injection of 1 M isobutyl alcohol (Plapp et al., 2015). Clearance of isobutyl alcohol from blood following intravenous (i.v.) exposure is 0.13 L/kg-minute in rats (Kielbasa and Fung, 2000).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

Provisional reference dose (p-RfD) values are not derived because an RfD value is available on the U.S. EPA's IRIS database (U.S. EPA, 1987).

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

Available inhalation studies include peer-reviewed subchronic neurotoxicity studies in rats (Li et al., 1999), peer-reviewed developmental studies in rats and rabbits (Klimisch and Hellwig, 1995), and an unpublished, two-generation study in rats (Nemec, 2003).

In peer-reviewed studies, the only treatment-related effect identified was slightly decreased response to stimuli during daily exposures at ≥782 mg/m^3 (HEC_{ER} = 140 mg/m^3) in the 13- and 14-week rat studies by Li et al. (1999). However, this transient CNS depression was considered an acute response by the study authors, and no additional information was identified to suggest that these effects are an indicator of an emerging subchronic neurological effect. Rapid, reversible CNS depression has been observed in animals following acute exposure to very high concentrations of isobutyl alcohol (see Table 4B). None of the available inhalation studies indicate more serious or permanent alterations in the nervous system following exposure to isobutyl alcohol. However, due to a lack relevant chronic exposure characterization, it is not possible to definitively conclude that these transient effects will not manifest at later life stages. In the Li et al. (1999) study, the absence of subchronic neurological effects is supported by the lack of exposure assessed outside of the daily exposure period (FOB, motor activity, SCOB) and no supporting morphological or histological evidence of damage to neurological tissues. However, a subjectively observed (non-quantitated) decrease in response to chamber brushing was observed for all exposed rats on days of exposure. Therefore, the highest concentration of 7,725 mg/m^3 (HEC_{ER} = 1,379 mg/m^3) in the subchronic studies by Li et al. (1999) is considered by the U.S. EPA to be a NOAEL for subchronic effects. No toxicologically relevant effects (including decreased fetal pup body weight) were noted in the developmental studies by Klimisch and Hellwig (1995) at concentrations up to 10,100 mg/m^3 (HEC_{ER} = 2,525 mg/m^3) in rats or 10,000 mg/m^3 (HEC_{ER} = 2,500 mg/m^3) in rabbits.

In the unpublished two-generation study by Nemec (2003), the U.S. EPA identified the lowest concentration as a LOAEL based on decreased F_1 and F_2 male and female pup postnatal body weight at concentrations ≥1,476 and 1,458 mg/m^3 (HEC_{ER} = 369.0 and 364.5 mg/m^3), respectively. Because the only toxicologically relevant effect following repeated inhalation exposure to isobutyl alcohol was identified in an unpublished study, the inhalation database is considered inadequate to support derivation of provisional reference values. However, the non-peer-reviewed, two-generation study provides sufficient data to develop screening subchronic and chronic provisional reference concentration (p-RfC) values based on developmental effects (see Appendix A).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

A summary of the noncancer provisional reference values is shown in Table 6.

Table 6. Summary of Noncancer Reference Values for Isobutyl Alcohol (CASRN 78-83-1)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	Oral RfD value of 0.3 mg/kg-d is available on IRIS (U.S. EPA, 1987)						
Screening subchronic p-RfC (mg/m^3)	Rat/both	Developmental (decreased F_2 pup body weights)	**1**	LOAEL	364.5	300	Nemec (2003)
Screening chronic p-RfC (mg/m^3)	Rat/both	Developmental (decreased F_2 pup body weights)	**4×10^{-1}**	LOAEL	364.5	1,000	Nemec (2003)

HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; NOAEL = no-observed-adverse-effect level; NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfD = oral reference dose; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for isobutyl alcohol. No adequate cancer data are available. In general, available genotoxicity assays of isobutyl alcohol (see Table 4A) indicate that isobutyl alcohol is not a genotoxic agent. Under the U.S. EPA (2005) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential, so the cancer WOE descriptor for isobutyl alcohol is "*Inadequate Information to Assess the Carcinogenic Potential*" (for both the oral and inhalation routes of exposure).

Table 7. Cancer WOE Descriptor for Isobutyl Alcohol

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human carcinogenicity data identified to support this descriptor.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no animal carcinogenicity studies identified to support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no animal carcinogenicity studies identified to support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any adequate studies evaluating carcinogenicity of isobutyl alcohol.**
"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.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Due to lack of adequate carcinogenicity data for isobutyl alcohol, derivation of cancer risk estimates is precluded (see Table 8).

Table 8. Summary of Cancer Risk Estimates for Isobutyl Alcohol (CASRN 78-83-1)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	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.

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main provisional peer-reviewed toxicity value (PPRTV) assessment, it is inappropriate to derive provisional reference concentrations (p-RfCs) for isobutyl alcohol. However, some 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 Center for Public Health and Environmental Assessment (CPHEA) 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 provisional reference values 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 could be more uncertainty associated with deriving 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 CPHEA.

DERIVATION OF SCREENING PROVISIONAL REFERENCE CONCENTRATIONS

As discussed in the main body of the report, toxicologically relevant effects identified in inhalation studies are limited to a non-peer-reviewed study. While non-peer-reviewed data are considered inappropriate to derive p-RfCs, these data are adequate to derive screening p-RfCs.

Derivation of Screening Subchronic Provisional Reference Concentration

Decreased body weight in F_1 and F_2 male and female pups in the unpublished two-generation rat study (Nemec, 2003) is the most sensitive target of inhalation toxicity identified for isobutyl alcohol. There were biologically significant (≥5%) decreases in body weights of pups of both sexes at all concentrations in both generations. Similar alterations to pup body weight were not observed in a developmental study in rats by Klimisch and Hellwig (1995), although the exposure regimens and experimental design were significantly different among the two studies (two-generations vs. 10 days). For the purposes of this PPRTV assessment, a ≥5% decrease in pup body weight is considered biologically significant by the U.S. Environmental Protection Agency (U.S. EPA). Due to lack of clear dose-response, these data were not amenable to benchmark dose (BMD) modeling. Therefore, the U.S. EPA selected the LOAEL of 1,458 mg/m^3 (HEC_{ER} = 364.5 mg/m^3), based on F_2 pup exposure, as the point of departure (POD) for derivation of the screening subchronic p-RfC.

The screening subchronic p-RfC of **1 mg/m^3** for isobutyl alcohol is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, a database uncertainty factor [UF_D] of 1, and a LOAEL-to-no-observed-adverse-effect level (NOAEL) uncertainty factor [UF_L] of 10) to the selected POD of 364.5 mg/m^3, as follows:

Screening Subchronic p-RfC = POD (HEC) ÷ UF_C
= 364.5 mg/m^3 ÷ 300
= **1 mg/m^3**

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfC for isobutyl alcohol.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfC for Isobutyl Alcohol

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, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a Category 3 gas, as specified in the U.S. EPA (1994) guidelines for deriving p-RfCs.
UF_D	1	A UF_D of 1 is applied to account for deficiencies and uncertainties in the database. The database includes a comprehensive two-generation toxicity study in rats, that has not been published or peer-reviewed. Other available studies include a subchronic study in rats and developmental studies in rats and rabbits. The database lacks documentation that portal-of-entry effects were evaluated. Based on the available subchronic information (Li et al. (1999), it appears that developmental toxicity is more sensitive than systemic toxicity at least in a subchronic setting, and it is unlikely that additional subchronic studies would provide a lower POD. Therefore, a UF_D of 1 was selected.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of isobutyl alcohol 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 the POD is a developmental effect observed in a two-generation study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; 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.

Derivation of Screening Chronic Provisional Reference Concentration

The screening chronic p-RfC is derived using the same POD for decreased body weight (LOAEL of 1,458 mg/m^3 [HEC_{ER} = 364.5 mg/m^3]), based on F_2 pup exposure in the unpublished two-generation study by Nemec (2003) that serves as the basis for the screening subchronic p-RfC. Therefore, the lowest LOAEL of 1,458 mg/m^3 (HEC_{ER} = 364.5 mg/m^3), based on F_2 pup exposure, was selected as the POD for derivation of the screening chronic p-RfC.

The screening chronic p-RfC of $\mathbf{4 \times 10^{-1}}$ mg/m^3 for isobutyl alcohol is derived by applying a UF_C of 1,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 3, and a UF_L of 10) to the selected POD of 364.5 mg/m^3, as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{POD (HEC)} \div UF_C \\ &= 364.5 \text{ mg/m}^3 \div 1{,}000 \\ &= \mathbf{4 \times 10^{-1} \text{ mg/m}^3} \end{aligned}$$

Table A-2 summarizes the uncertainty factors for the screening chronic p-RfC for isobutyl alcohol.

Table A-2. Uncertainty Factors for the Screening Chronic p-RfC for Isobutyl Alcohol

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, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a Category 3 gas, as specified in the U.S. EPA (1994) guidelines for deriving p-RfCs.
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies and uncertainties in the database. The database includes a comprehensive two-generation toxicity study in rats, that has not, however, been published or peer-reviewed. Other available studies include a subchronic study in rats and developmental studies in rats and rabbits. The database lacks documentation that portal-of-entry effects were evaluated and is considered to be overall limited in scope. No chronic inhalation exposure studies were identified to inform the sensitivity of potential systemic effects compared to the identified reproductive/developmental toxicities characterized in Nemec (2003).
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of isobutyl alcohol 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 the POD is based on a developmental effect observed in a two-generation study. While the exposure period was less-than-chronic, 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 lifetime exposure (U.S. EPA, 1991).
UF_C	1,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; 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.

APPENDIX B. SYSTEMATIC LITERATURE SEARCH METHODS AND RESULTS

As discussed in the main body of the Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, a systematic review was conducted to identify studies relevant to the derivation of inhalation provisional toxicity values and oral and inhalation cancer weight of evidence (WOE) for isobutyl alcohol. Because an oral reference dose (RfD) value is available on the U.S. Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) database (U.S. EPA, 1987), oral noncancer data for isobutyl alcohol were not reviewed.

LITERATURE SEARCH

Literature searches were conducted in April 2019 and updated in August 2022 for studies relevant to the derivation of provisional toxicity values for isobutyl alcohol. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[6] (including TSCATS1), and Web of Science (see Table B-1). The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), the U.S. EPA Chemical Data Access Tool (CDAT), the U.S. EPA ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume (HPV), Chemicals via IPCS INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO) (see Table B-2).

[6]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search updates performed after April 2019.

Table B-1. Database Query Strings for Isobutyl Alcohol (CASRN 78-83-1) (PubMed, TOXLINE, WOS, TSCATS)

Database (search date)	Query String
PubMed 8/1/2022	(78-83-1[rn] OR "isobutyl alcohol"[nm]) OR (("1-Hydroxymethylpropane"[tw] OR "1-Propanol, 2-methyl-"[tw] OR "2-METHYL PROPANOL"[tw] OR "2-Methyl-1-propanol"[tw] OR "2-Methylpropan-1-ol"[tw] OR "2-methylpropane-1-ol"[tw] OR "2-Methylpropanol"[tw] OR "2-Methylpropyl alcohol"[tw] OR "Butanol (iso)"[tw] OR "BUTYL ISO ALCOHOL"[tw] OR "Fermentation butyl alcohol"[tw] OR "iso-butanol"[tw] OR "iso-Butyl alcohol"[tw] OR "Isobutanol"[tw] OR "Isobutyl alcohol"[tw] OR "Isopropyl carbinol"[tw] OR "Isopropylcarbinol"[tw]) NOT medline[sb])
WOS 8/1/2022	TS=("1-Propanol, 2-methyl-" OR "2-METHYL PROPANOL" OR "2-Methyl-1-propanol" OR "2-Methylpropan-1-ol" OR "2-Methylpropanol" OR "iso-butanol" OR "iso-Butyl alcohol" OR "Isobutanol" OR "Isobutyl alcohol" OR "1-Hydroxymethylpropane" OR "2-methylpropane-1-ol" OR "2-Methylpropyl alcohol" OR "Butanol (iso)" OR "BUTYL ISO ALCOHOL" OR "Fermentation butyl alcohol" OR "Isopropyl carbinol" OR "Isopropylcarbinol") AND ((WC=("Toxicology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Neurosciences" OR "Obstetrics & Gynecology" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Respiratory System" OR "Urology & Nephrology" OR "Anatomy & Morphology" OR "Andrology" OR "Pathology" OR "Otorhinolaryngology" OR "Ophthalmology" OR "Pediatrics" OR "Oncology" OR "Reproductive Biology" OR "Developmental Biology" OR "Biology" OR "Dermatology" OR "Allergy" OR "Public, Environmental & Occupational Health") OR SU=("Anatomy & Morphology" OR "Cardiovascular System & Cardiology" OR "Developmental Biology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Immunology" OR "Neurosciences & Neurology" OR "Obstetrics & Gynecology" OR "Oncology" OR "Ophthalmology" OR "Pathology" OR "Pediatrics" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Public, Environmental & Occupational Health" OR "Respiratory System" OR "Toxicology" OR "Urology & Nephrology" OR "Reproductive Biology" OR "Dermatology" OR "Allergy")) OR (WC="veterinary sciences" AND (TS="rat" OR TS="rats" OR TS="mouse" OR TS="murine" OR TS="mice" OR TS="guinea" OR TS="muridae" OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS="dog" OR TS="dogs" OR TS=beagle* OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset*)) OR (TS=toxic* AND (TS="rat" OR TS="rats" OR TS="mouse" OR TS="murine" OR TS="mice" OR TS="guinea" OR TS="muridae" OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS="dog" OR TS="dogs" OR TS=beagle* OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset* OR TS="child" OR TS="children" OR TS=adolescen* OR TS=infant* OR TS="WORKER" OR TS="WORKERS" OR TS="HUMAN" OR TS=patient* OR TS=mother OR TS=fetal OR TS=fetus OR TS=citizens OR TS=milk OR TS=formula OR TS=epidemio* OR TS=population* OR TS=exposure* OR TS=questionnaire OR SO=epidemio*)) OR TI=toxic*) Indexes=SCI-EXPANDED, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years

Table B-1. Database Query Strings for Isobutyl Alcohol (CASRN 78-83-1) (PubMed, TOXLINE, WOS, TSCATS)

Database (search date)	Query String
TOXLINE 4/9/2019	(78-83-1 [rn] OR "1-propanol 2-methyl-" OR "2-methyl propanol" OR "2-methyl-1-propanol" OR "2-methylpropan-1-ol" OR "2-methylpropanol" OR "iso-butanol" OR "iso-butyl alcohol" OR "isobutanol" OR "isobutyl alcohol") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HAPAB [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	"1-Hydroxymethylpropane" OR "2-methylpropane-1-ol" OR "2-Methylpropyl alcohol" OR "Butanol (iso)" OR "BUTYL ISO ALCOHOL" OR "Fermentation butyl alcohol" OR "Isopropyl carbinol" OR "Isopropylcarbinol"
TSCATS 1 4/9/2019	78-83-1 [rn] AND tscats[org]

TSCATS = Toxic Substances Control Act Test Submission; WOS = Web of Science.

Table B-2. Resources Searched to Augment the Database Search Strings for Isobutyl Alcohol (CASRN 78-83-1)

Additional Strategies	Query and/or Link
ChemView	https://chemview.epa.gov/chemview/?tf=2&ch=78-83-1&su=2-5-6-7&as=3-10-9-8&ac=1-15-16-6378999&ma=4-11-1981377&tds=0&tdl=10&tas1=1&tas2=asc&tas3=undefined&tss=&modal=detail&modalId=99839&modalSrc=2-5-10-4
NTP	• https://ntp.niehs.nih.gov/testing/status/agents/ts-78831.html • 78-83-1 • "isobutanol" "isobutyl alcohol" "2-methyl propanol" "2-methyl-1-propanol" • "1-propanol, 2-methyl-" "2-methylpropan-1-ol" "2-methylpropanol" "iso-butanol" • "iso-butyl alcohol" • "1-hydroxymethylpropane" "2-methylpropane-1-ol" "2-methylpropyl alcohol" "butanol (iso)" • "butyl iso alcohol" "fermentation butyl alcohol" "isopropyl carbinol" "isopropylcarbinol"
	https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html
ACGIH	ACGIH. 2018. 2018 TLVs and BEIs: Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists
ATSDR	http://www.atsdr.cdc.gov/toxprofiles/index.asp
CalEPA	http://www.oehha.ca.gov/tcdb/index.asp
DWSHA	https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf
ECETOC	http://www.ecetoc.org/publications
ECHA	https://echa.europa.eu/substance-information/-/substanceinfo/100.001.044
	http://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation
HEAST	http://epa-heast.ornl.gov/heast.php
HPVIS	https://iaspub.epa.gov/oppthpv/public_search.html_page

Table B-2. Resources Searched to Augment the Database Search Strings for Isobutyl Alcohol (CASRN 78-83-1)

Additional Strategies	Query and/or Link
IARC	http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf
InChem—OECD SIDS	http://www.inchem.org/pages/sids.html
IRIS	http://www.epa.gov/iris/
JECDB	http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
NIOSH	http://www.cdc.gov/niosh/npg/npgdcas.html
OECD (HPV, SIDS, IUCLID)	http://webnet.oecd.org/hpv/ui/Search.aspx
OSHA	http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992
	http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10629
	https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286
WHO	https://www.who.int/publications/

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure index; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA = European Chemicals Agency; HEAST = Health Effects Assessment Summary Tables; HPV = High Production Volume; HPVIS = High Production Volume Information System; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; IUCLID = International Uniform Chemical Information Database; JECDB = Japan Existing Chemical Data Base; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OECD = Organisation for Economic Cooperation and Development; OSHA = Occupational Safety and Health Administration; SIDS = Screening Information Data Sets; TLV = threshold limit value; WHO = World Health Organization.

SCREENING PROCESS

Two screeners independently conducted a title and abstract screening of the search results using DistillerSR[7] to identify study records that met the Population, Exposure, Comparator, and Outcome (PECO) eligibility criteria (see Table B-3).

[7]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

Table B-3. PECO Criteria for Isobutyl Alcohol (CASRN 78-83-1)	
PECO Element	**Evidence**
Population	Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity.
Exposure	In vivo (all routes), ex vivo, and in vitro exposure to isobutyl alcohol, including mixtures to which isobutyl alcohol may contribute significantly to exposure or observed effects.
Comparator	Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls).
Outcome	Any endpoint suggestive of a toxic effect on any bodily system, or mechanistic change associated with such effects. Any endpoint relating to disposition of the chemical within the body.

PECO = Population, Exposure, Comparator, and Outcome.

Records that were included based on title and abstract screening advanced to full-text review using the same PECO eligibility criteria. Full-text copies of potentially relevant records identified from title and abstract screening were retrieved, stored in the HERO database, and independently assessed by two screeners using DistillerSR to confirm eligibility. If studies were considered PECO-relevant based on full-text review, screeners tagged the studies as one of the following study types: human (all studies); animal (oral route); animal (inhalation chronic/ carcinogenicity); animal (inhalation subchronic); animal (inhalation reproductive/ developmental); animal (inhalation acute); animal (other routes besides oral or inhalation); absorption, distribution, metabolism, and excretion/physiologically based pharmacokinetic (ADME/PBPK); genotoxicity; mechanistic; or reviews/secondary sources. If "animal (oral route)" was selected, reviewers were asked to indicate whether the study was a chronic/ carcinogenicity study (yes/no). Because the focus of the PPRTV assessment was to assess data relevant to derivation of provisional reference concentrations (p-RfCs) and inhalation and oral cancer assessment (but not provisional reference doses [p-RfDs]), only studies tagged as animal (inhalation subchronic), animal (inhalation reproductive/developmental), and animal (oral chronic/carcinogenicity study) moved onto the study evaluation stage. All other PECO-relevant studies were retained as supplemental information.

At both title/abstract and full-text review levels, screening conflicts were resolved by discussion between the primary screeners in consultation with a third reviewer to resolve any remaining disagreements.

RESULTS

Literature searches yielded 1,298 unique records (see Figure B-1). Of the 1,298 studies identified, 1,099 were excluded during title and abstract screening, while 199 were reviewed at the full-text level. After full-text review, 114 studies were excluded, and 74 studies were tagged as supplemental including acute inhalation studies, studies evaluating routes other than inhalation or oral, mechanistic studies, toxicokinetic studies, genotoxicity studies, and reviews and secondary sources of information. Eleven studies were considered further as relevant to inhalation provisional toxicity values and oral and inhalation cancer assessment for isobutyl alcohol, including three human health studies (described in three publications), three subchronic

animal inhalation studies (described in one peer-reviewed and two non-peer-reviewed publications), three reproductive/developmental animal inhalation studies (described in one peer-reviewed publication and one non-peer-reviewed publication), and two oral cancer study in animals (described in one foreign language publication and one English translation report).

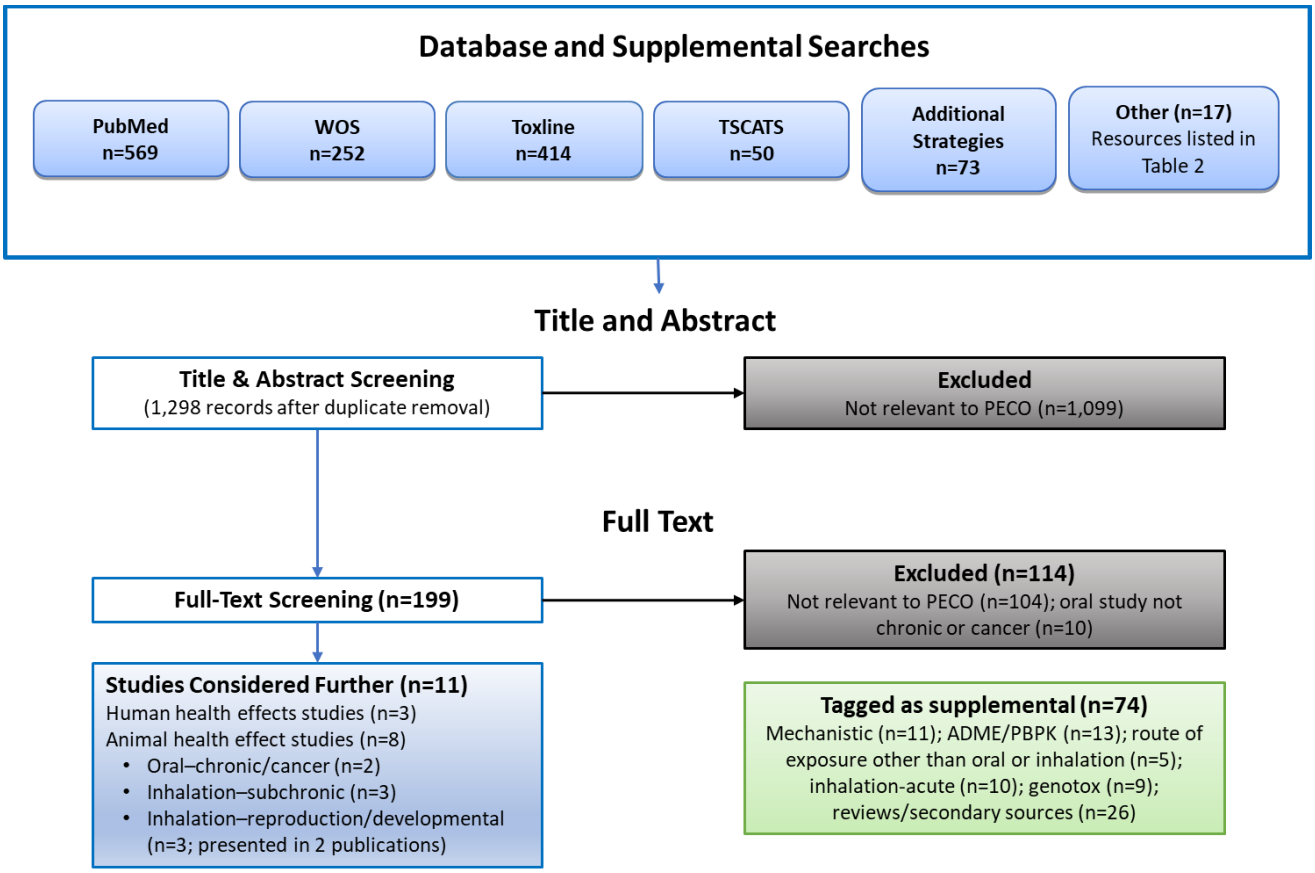


Figure B-1. Literature Search and Screening Flow Diagram for Isobutyl Alcohol (CASRN 78-83-1)

APPENDIX C. DATA EVALUATION METHODS AND RESULTS

METHODOLOGY

Based on the literature screen, there were 11 separate studies considered relevant to inhalation provisional toxicity values and oral and inhalation cancer weight of evidence (WOE) for isobutyl alcohol. Study evaluation proceeded for eight studies, including a cross-sectional occupational exposure study (Hollett and Aw, 1982), a human patch-test study (Wilkin and Stewart, 1987; Wilkin and Fortner, 1985), two subchronic inhalation studies in rats (Li et al., 1999; Branch et al., 1996; Kaempfe and Li, 1996), a two-generation inhalation study in rats (Nemec, 2003), a developmental inhalation study in rats and rabbits (Klimisch and Hellwig, 1995), and an oral cancer study in rats (Dow Chemical, 1992).

Study evaluations were conducted by two independent reviewers using the U.S. Environmental Protection Agency (U.S. EPA) version of the Health Assessment Workspace Collaborative (HAWC) database, a free and open-source, web-based software application designed to manage and facilitate the process of conducting literature assessments.[8] Study evaluation conflicts were resolved by discussion between the primary reviewers in consultation with a third reviewer to resolve any remaining disagreements.

The general approach for evaluating human health and animal toxicology studies is presented in Figure C-1. For each of the outcomes in a study, reviewers evaluated each of the domains shown in Figure C-1. Reviewers reached a consensus judgment of *good*, *adequate*, *deficient*, *not reported*, or *critically deficient* in each domain, as defined in Figure C-1. Questions used to guide the development of criteria for each domain in human health and animal toxicology studies are presented in Tables C-1 and C-2, respectively. Evaluations were focused on the methodological approaches and adequacy of reporting in the individual studies and did not consider either the direction or the magnitude of the study results. Key concerns for the review of epidemiology and animal toxicology studies are potential sources of bias (factors that could systematically affect the magnitude or direction of an effect) and insensitivity (factors that limit the ability of a study to detect a true effect). Once the evaluation domains were rated, a study confidence rating of *high*, *medium*, *low*, or *uninformative* for a specific health outcome was determined by considering the strengths and limitations, as defined in Figure C-1. Study confidence ratings were based on reviewer judgments across the evaluation domains, including the likely impact that the noted deficiencies in bias and sensitivity, or inadequate reporting, may have on the results.

[8]HAWC: A modular web-based interface to facilitate development of human health assessments of chemicals (https://hawcprd.epa.gov).

Individual Study Level Domains

Epidemiological	Animal
Exposure Measurement	Reporting Quality
Outcome Ascertainment	Selection or Performance Bias
Population Selection	Confounding/Variable Control
Confounding	Reporting or Attrition Bias
Analysis	Exposure Methods Sensitivity
Sensitivity	Outcome Measures and Results Display
Selective Reporting	

Domain Judgments

	Judgement	Interpretation
++	**Good**	The study was conducted appropriately in relation to the evaluation domain and any deficiencies, if present, are minor and would not be expected to influence the study results.
+	**Adequate**	There are methodological limitations relating to the evaluation domain, but that those limitations are not likely to be severe or to have a notable impact on the results.
-	**Deficient**	Identified biases or deficiencies that are interpreted as likely to have had a notable impact on the results or that prevent interpretation of the study findings.
NR	**Not reported**	The information necessary to evaluate the domain was not available in the study. Generally, this term carries the same functional interpretation as deficient for the purposes of the study confidence classification.
--	**Critically Deficient**	The study conduct introduced a serious flaw that makes the observed effect(s) uninterpretable. Studies with a determination of critically deficient in an evaluation domain will almost always cause the study to be considered overall "uninformative".

Overall Study Rating

Rating	Domain Judgments	Interpretation
High	**Good** across all or most evaluation domains	A well-conducted study with no notable deficiencies or concerns were identified; the potential for bias is unlikely or minimal, and the study used sensitive methodology.
Medium	**Good** or **Adequate** across most domains; may have a **Deficient** evaluation in domain(s) considered to minimal influence on the magnitude or direction of effect	A satisfactory (acceptable) study in which deficiencies or concerns were noted, but the limitations are unlikely to be of a notable degree.
Low	**Deficient** in one or more domains	A substandard study in which deficiencies or concerns were noted, and the potential for bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	**Critically Deficient** in one or more domains	An unacceptable study in which serious flaw(s) make the study results unusable for informing hazard identification.

Figure C-1. Approach for Evaluating Epidemiological and Animal Toxicology Studies

Table C-1. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions

Exposure Measurement
Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?
	• For all:
	  ○ Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency, and duration of exposure?
	  ○ Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably?
	  ○ Was the exposure measurement likely to be affected by a knowledge of the outcome?
	  ○ Was the exposure measurement likely to be affected by the presence of the outcome (i.e., reverse causality)?
	• For case-control studies of occupational exposures:
	  ○ Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials?
	• For biomarkers of exposure, general population:
	  ○ Is a standard assay used? What are the intra- and interassay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately?
	• What exposure time period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?
		• Is the degree of exposure misclassification likely to vary by exposure level?
		• If the correlation between exposure measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurements?
		• If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Outcome Ascertainment
Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?
	• For all:
	  ○ Is outcome ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)?
	• For case-control studies:
	  ○ Is the comparison group without the outcome (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease?
	• For mortality measures:
	  ○ How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease?
	• For diagnosis of disease measures:
	  ○ Is diagnosis based on standard clinical criteria? If based on self-report of diagnosis, what is the validity of this measure?
	• For laboratory-based measures (e.g., hormone levels):
	  ○ Is a standard assay used? Does the assay have an acceptable level of interassay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population?
		• Is there a concern that any outcome misclassification is nondifferential, differential, or both?
		• What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Table C-1. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions

Participant Selection
Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?
	• For longitudinal cohort:
	  ○ Did participants volunteer for the cohort based on knowledge of exposure and/or preclinical disease symptoms? Was entry into the cohort or continuation in the cohort related to exposure and outcome?
	• For occupational cohort:
	  ○ Did entry into the cohort begin with the start of the exposure?
	  ○ Was follow-up or outcome assessment incomplete, and if so, was follow-up related to both exposure and outcome status?
	  ○ Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")?
	• For case-control study:
	  ○ Were controls representative of population and time periods from which cases were drawn?
	  ○ Are hospital controls selected from a group whose reason for admission is independent of exposure?
	  ○ Could recruitment strategies, eligibility criteria, or participation rates result in differential participation relating to both disease and exposure?
	• For population-based survey:
	  ○ Was recruitment based on advertisement to people with knowledge of exposure, outcome, and hypothesis?
		• Were differences in participant enrollment and follow-up evaluated to assess bias?
		• If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
		• Were appropriate analyses performed to address changing exposures over time in relation to symptoms?
		• Is there a comparison of participants and nonparticipants to address whether differential selection is likely?

Confounding
Is confounding of the effect of the exposure likely?
	• Is confounding adequately addressed by considerations in…
	  ○ participant selection (matching or restriction)?
	  ○ accurate information on potential confounders, and statistical adjustment procedures?
	  ○ lack of association between confounder and outcome, or confounder and exposure in the study?
	  ○ information from other sources?
	• Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing), minimizing potential overcontrol (e.g., inclusion of a variable on the pathway between exposure and outcome)?
		• If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Analysis Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?	• Are missing outcome, exposure, and covariate data recognized, and if necessary, accounted for in the analysis? • Does the analysis appropriately consider variable distributions and modeling assumptions? • Does the analysis appropriately consider subgroups of interest (e.g., based on variability in exposure level or duration, or susceptibility)? • Is an appropriate analysis used for the study design? • Is effect modification considered, based on considerations developed a priori? • Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	• If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Table C-1. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions
Sensitivity Is there a concern that sensitivity of the study is not adequate to detect an effect?	• Is the exposure range adequate? • Was the appropriate population included? • Was the length of follow-up adequate? Is the time/age of outcome ascertainment optimal given the interval of exposure and the health outcome? • Are there other aspects related to risk of bias or otherwise that raise concerns about sensitivity?	
Selective Reporting Is there reason to be concerned about selective reporting?	• Are the results needed for the IRIS analysis (based on a priori specification) presented? If not, can these results be obtained? • Are only statistically significant results presented?	

IRIS = Integrated Risk Information System.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Reporting Quality	**Reporting Quality—** Does the study report information for evaluating the design and conduct of the study for the endpoint(s)/outcome(s) of interest? *Notes: Reviewers should reach out to study authors to obtain missing information when studies are considered key for hazard evaluation and/or dose-response. This domain is limited to reporting. Other aspects of the exposure methods, experimental design, and endpoint evaluation methods are evaluated using the domains related to risk of bias and study sensitivity.*	Does the study report the following? • **Critical information** necessary to perform study evaluation: o Species, test article name, levels and duration of exposure; route (e.g., oral; inhalation), qualitative or quantitative results for at least one endpoint of interest. • **Important information** for evaluating the study methods: o Test animal: strain, sex, source, and general husbandry procedures. o Exposure methods: source, purity, method of administration. o Experimental design: frequency of exposure, animal age and life stage during exposure and at endpoint/outcome evaluation. o Endpoint evaluation methods: assays or procedures used to measure the endpoint(s)/outcome(s) of interest.	These considerations typically do not need to be refined by assessment teams, although in some instances the **important information** may be refined depending on the endpoint(s)/outcome(s) of interest or the chemical under investigation. A judgment and rationale for this domain should be given for the study. Typically, these will not change regardless of the endpoint(s)/outcome(s) investigated by the study. **In the rationale, reviewers should indicate whether the study adhered to GLP, OECD, or other testing guidelines.** • *Good*: All **critical** and **important information** is reported or inferable for the endpoint(s)/outcome(s) of interest. • *Adequate*: All **critical information** is reported, but some **important information** is missing. However, the missing information is not expected to significantly impact the study evaluation. • *Deficient*: All **critical information** is reported but **important information** is missing that is expected to significantly reduce the ability to evaluate the study. • *Critically deficient*: Study report is missing any pieces of **critical information**. Studies that are *critically deficient* for reporting are *uninformative* for the overall rating and not considered further for evidence synthesis and integration.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Risk of Bias: Selection and Performance Bias	**Allocation—** Were animals assigned to experimental groups using a method that minimizes selection bias?	For each study: • Did each animal or litter have an equal chance of being assigned to any experimental group (i.e., random allocation)? • Is the allocation method described? • Aside from randomization, were any steps taken to balance variables across experimental groups during allocation?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. • *Good*: Experimental groups were randomized, and any specific randomization procedure was described or inferable (e.g., computer-generated scheme). (Note that normalization is not the same as randomization [see response for *adequate*].) • *Adequate*: Study authors reported that groups were randomized but did not describe the specific procedure used (e.g., "animals were randomized"). Alternatively, study authors used a nonrandom method to control for important modifying factors across experimental groups (e.g., body-weight normalization). • *Not reported* (interpreted as *deficient*): No indication of randomization of groups or other methods (e.g., normalization) to control for important modifying factors across experimental groups. • *Critically deficient*: Bias in the animal allocations was reported or inferable.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations

Risk of Bias: Selection and Performance Bias	**Observational Bias/Blinding—** Did the study implement measures to reduce observational bias?	For each endpoint/outcome or grouping of endpoints/outcomes in a study:
		• Does the study report blinding or other methods/procedures for reducing observational bias?
		• If not, did the study use a design or approach for which such procedures can be inferred?
		• What is the expected impact of failure to implement (or report implementation) of these methods/procedures on the results?
			These considerations typically do not need to be refined by the assessment teams. (Note that it can be useful for teams to identify highly subjective measures of endpoint[s]/outcome[s] where observational bias may strongly influence results prior to performing evaluations.)
			
			A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study.
			
			• *Good*: Measures to reduce observational bias were described (e.g., blinding to conceal treatment groups during endpoint evaluation; consensus-based evaluations of histopathology lesions).[a]
			• *Adequate*: Methods for reducing observational bias (e.g., blinding) can be inferred or were reported but described incompletely.
			• *Not reported*: Measures to reduce observational bias were not described.
			  o Interpreted as *adequate*—The potential concern for bias was mitigated based on use of automated/computer-driven systems, standard laboratory kits, relatively simple, objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology.
			  o Interpreted as *deficient*—The potential impact on the results is major (e.g., outcome measures are highly subjective).
			• *Critically deficient*: Strong evidence for observational bias that could have impacted results.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Risk of Bias: Confounding/Variable Control	**Confounding—** Are variables with the potential to confound or modify results controlled for and consistent across all experimental groups?	For each study: • Are there differences across the treatment groups (e.g., co-exposures, vehicle, diet, palatability, husbandry, health status, and so forth) that could bias the results? • If differences are identified, to what extent are they expected to impact the results?	These considerations may need to be refined by assessment teams, as the specific variables of concern can vary by experiment or chemical. A judgment and rationale for this domain should be given for each cohort or experiment in the study, noting when the potential for confounding is restricted to specific endpoint(s)/outcome(s). • *Good*: Outside of the exposure of interest, variables that are likely to confound or modify results appear to be controlled for and consistent across experimental groups. • *Adequate*: Some concern that variables that were likely to confound or modify results were uncontrolled or inconsistent across groups but are expected to have a minimal impact on the results. • *Deficient*: Notable concern that potentially confounding variables were uncontrolled or inconsistent across groups and are expected to substantially impact the results. • *Critically deficient*: Confounding variables were presumed to be uncontrolled or inconsistent across groups and are expected to be a primary driver of the results.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Risk of Bias: Reporting and Attrition Bias	**Selective Reporting and Attrition—** Did the study report results for all prespecified outcomes and tested animals? *Note: This domain does **not** consider the appropriateness of the analysis/results presentation. This aspect of study quality is evaluated in another domain.*	For each study: • Selective reporting bias: o Are all results presented for endpoint(s)/outcome(s) described in the methods (see note)? • Attrition bias: o Are all animals accounted for in the results? o If there are discrepancies, do study authors provide an explanation (e.g., death or unscheduled sacrifice during the study)? o If unexplained results, omissions, and/or attrition are identified, what is the expected impact on the interpretation of the results?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. • *Good*: Quantitative or qualitative results were reported for all prespecified outcomes (explicitly stated or inferred), exposure groups, and evaluation time points. Data not reported in the primary article is available from supplemental material. If results, omissions, or animal attrition is identified, the study authors provide an explanation, and these are not expected to impact the interpretation of the results. • *Adequate*: Quantitative or qualitative results are reported for most prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points. Omissions and/or attrition are not explained but are not expected to significantly impact the interpretation of the results. • *Deficient*: Quantitative or qualitative results are missing for many prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points and/or high animal attrition; omissions and/or attrition are not explained and may significantly impact the interpretation of the results. • *Critically deficient*: Extensive results omission and/or animal attrition is identified and prevents comparisons of results across treatment groups.

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Sensitivity: Exposure Methods Sensitivity	**Characterization—** Did the study adequately characterize exposure to the chemical of interest and the exposure administration methods? *Note: Consideration of the appropriateness of the route of exposure is not evaluated at the individual study level. Relevance and utility of the routes of exposure are considered in the PECO criteria for study inclusion and during evidence synthesis.*	For each study: • Does the study report the source and purity and/or composition (e.g., identity and percent distribution of different isomers) of the chemical? If not, can the purity and/or composition be obtained from the supplier (e.g., as reported on the website)? • Was independent analytical verification of the test article purity and composition performed? • Did the study authors take steps to ensure the reported exposure levels were accurate? o For inhalation studies: Were target concentrations confirmed using reliable analytical measurements in chamber air? o For oral studies: If necessary, based on consideration of chemical-specific knowledge (e.g., instability in solution; volatility) and/or exposure design (e.g., the frequency and duration of exposure), were chemical concentrations in the dosing solutions or diet analytically confirmed? • Are there concerns about the methods used to administer the chemical (e.g., inhalation chamber type, gavage volume, etc.)?	It is essential that these criteria are considered and potentially refined by assessment teams, as the specific variables of concern can vary by chemical. A judgment and rationale for this domain should be given for each cohort or experiment in the study. • *Good*: Chemical administration and characterization is complete (i.e., source, purity, and analytical verification of the test article are provided). There are no concerns about the composition, stability, or purity of the administered chemical or the specific methods of administration. For inhalation studies, chemical concentrations in the exposure chambers are verified using reliable analytical methods. • *Adequate*: Some uncertainties in the chemical administration and characterization are identified, but these are expected to have minimal impact on interpretation of the results (e.g., source and vendor-reported purity are presented, but not independently verified; purity of the test article is suboptimal but not concerning). For inhalation studies, actual exposure concentrations are missing or verified with less reliable methods. • *Deficient*: Uncertainties in the exposure characterization are identified and expected to substantially impact the results (e.g., source of the test article is not reported; levels of impurities are substantial or concerning; deficient administration methods such as use of static inhalation chambers or a gavage volume considered too large for the species and/or life stage at exposure). • *Critically deficient*: Uncertainties in the exposure characterization are identified, and there is reasonable certainty that the results are largely attributable to factors other than exposure to the chemical of interest (e.g., identified impurities are expected to be a primary driver of the results).

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Sensitivity: Outcome Measures and Results Display	**Endpoint Sensitivity and Specificity—** Are the procedures sensitive and specific for evaluating the endpoint(s)/outcome(s) of interest? *Note: Sample size alone is not a reason to conclude an individual study is* critically deficient.	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Are there concerns regarding the specificity and validity of the protocols? • Are there serious concerns regarding the sample size (see note)? • Are there concerns regarding the timing of the endpoint assessment?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: • Selection of protocols that are insensitive or nonspecific for the endpoint of interest. • Use of unreliable methods to assess the outcome. • Assessment of endpoints at inappropriate or insensitive ages, or without addressing known endpoint variation (e.g., due to circadian rhythms, estrous cyclicity, etc.). • Decreased specificity or sensitivity of the response due to the timing of endpoint evaluation, as compared to exposure (e.g., short-acting depressant or irritant effects of chemicals; insensitivity due to prolonged period of nonexposure prior to testing).

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Sensitivity: Outcome Measures and Results Display	**Results Presentation—** Are the results presented in a way that makes the data usable and transparent?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Does the level of detail allow for an informed interpretation of the results? • Are the data analyzed, compared, or presented in a way that is inappropriate or misleading?	Considerations for this domain are highly variable depending on the outcomes of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: • Nonpreferred presentation such as developmental toxicity data averaged across pups in a treatment group when litter responses are more appropriate. • Failing to present quantitative results. • Pooling data when responses are known or expected to differ substantially (e.g., across sexes or ages). • Failing to report on or address overt toxicity when exposure levels are known or expected to be highly toxic. • Lack of full presentation of the data (e.g., presentation of mean without variance data; concurrent control data are not presented).

Table C-2. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

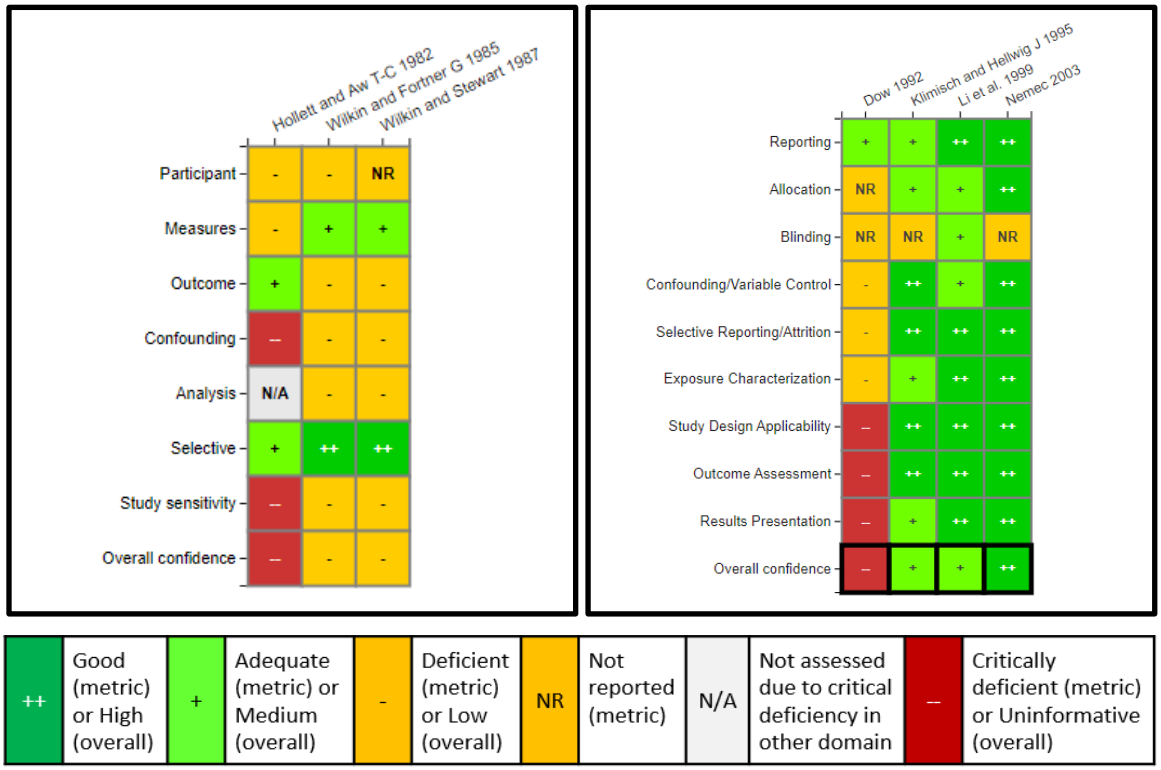
Evaluation Type	Domain−Core Question	Prompting Questions	Basic Considerations
Overall Confidence	**Overall Confidence—** Considering the identified strengths and limitations, what is the overall confidence rating for the endpoint(s)/outcome(s) of interest? *Note: Reviewers should mark studies that are rated lower than* high *confidence only due to low sensitivity (i.e., bias towards the null) for additional consideration during evidence synthesis. If the study is otherwise well conducted and an effect is observed, the confidence may be increased.*	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Were concerns (i.e., limitations or uncertainties) related to the reporting quality, risk of bias, or sensitivity identified? • If yes, what is their expected impact on the overall interpretation of the reliability and validity of the study results, including (when possible) interpretations of impacts on the magnitude or direction of the reported effects?	The overall confidence rating considers the likely impact of the noted concerns (i.e., limitations or uncertainties) in reporting, bias, and sensitivity on the results. A confidence rating and rationale should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. • *High*: No notable concerns are identified (e.g., most or all domains rated *good*). • *Medium*: Some concerns are identified but expected to have minimal impact on the interpretation of the results (e.g., most domains rated *adequate* or *good*; may include studies with *deficient* ratings if concerns are not expected to strongly impact the magnitude or direction of the results). Any important concerns should be carried forward to evidence synthesis. • *Low*: Identified concerns are expected to have significant impact on the study results or their interpretation (e.g., generally, *deficient* ratings for one or more domains). The concerns leading to this confidence judgment must be carried forward to evidence synthesis (see note). • *Uninformative*: Serious flaw(s) that make the study results unusable for informing hazard identification (e.g., generally, *critically deficient* rating in any domain; many *deficient* ratings). *Uninformative* studies are considered no further in the synthesis and integration of evidence.

[a]For nontargeted or screening-level histopathology outcomes often used in guideline studies, blinding during the initial evaluation of tissues is generally not recommended as masked evaluation can make "the task of separating treatment-related changes from normal variation more difficult" and "there is concern that masked review during the initial evaluation may result in missing subtle lesions." Generally, blinded evaluations are recommended for targeted secondary review of specific tissues or in instances when there is a predefined set of outcomes that is known or predicted to occur (Crissman et al., 2004).

GLP = Good Laboratory Practice; OECD = Organisation for Economic Co-operation and Development; PECO = Population, Exposure, Comparator, Outcome.

RESULTS

Based on the study evaluations, all human studies and the animal oral cancer study (Dow Chemical, 1992) were considered *low confidence* or *uninformative* (see Figure C-2); therefore, these studies were only briefly discussed in Section 2.3 of this document (see Table 4B).



Click to see human interactive data graphic and animal interactive data graphic for rating rationales.

Figure C-2. Evaluation Results for Human (A) and Animal (B) Studies Assessing Effects of Isobutyl Alcohol

The remaining five in vivo animal studies are represented in three publications, including one rat and one rabbit developmental study (Klimisch and Hellwig, 1995), two subchronic inhalation studies in rats [Branch et al. (1996); Li and Kaempfe (1996); both studies also presented in Li et al. (1999)], and one two-generation study in rats (Nemec, 2003), which were included in Section 2 of this document (see Table 4A). As shown in Figure C-2, these studies were rated as *high* or *medium confidence*.

DATA EXTRACTION

Information on study design, methods, results, and data from animal toxicology studies were extracted into HAWC and are available at https://hawcprd.epa.gov/assessment/100500033/.

Visual graphics prepared from HAWC are embedded as hyperlinks and are fully interactive when viewed online by way of a "click to see more" capability. Clicking on content allows access to study evaluation ratings, methodological details, and underlying study data. The action of clicking on content contained in those visual graphics (e.g., data points, endpoint, and study design) will yield the underlying data supporting the visual content. *Note: The following*

browsers are fully supported for accessing HAWC: Google Chrome (preferred), Mozilla Firefox, and Apple Safari. There are errors in functionality when viewed with Internet Explorer. Any discrepancies in data extraction were resolved by discussion or consultation with a third member of the evaluation team. Analytical concentrations were extracted as reported in the study and converted to mg/m^3 human equivalent concentrations (HECs).

APPENDIX D. REFERENCES

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