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Provisional Peer-Reviewed Toxicity Values for

n-Heptanal
(CASRN 111-71-7)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

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

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-HEPTANAL (CASRN 111-71-7)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

n-Heptanal, CASRN 111-71-7, is obtained commercially from the pyrolysis or catalytic dehydration of ricinoleic acid (from castor oil). It also occurs naturally in various fruits, including cassava, plums, and Bisbee Delicious apples, and in flowers, such as clary sage (HSDB, 2014). *n*-Heptanal is primarily used as a chemical intermediate to make α-amylcinnamaldehyde and esters of heptanoic acid (HSDB, 2014). Additionally, it has direct applications as a food additive and a fragrance (HSDB, 2014). The U.S. Food and Drug Administration and the World Health Organization (WHO) have approved *n*-heptanal as a synthetic flavoring agent for human consumption (FDA, 2015; WHO, 2002). According to estimates from the WHO, oral intake of *n*-heptanal (3.2 µg/day) in the United States is below the human intake threshold for class I substances (1,800 µg/day); therefore, *n*-heptanal was determined to pose no safety concerns from use as a flavoring agent on the basis of its structural class and low levels of estimated intake (WHO, 1999; IPCS, 1998).

At room temperature, *n*-heptanal is a liquid with a penetrating fruity odor (HSDB, 2014). In the environment, *n*-heptanal will partition primarily to air where it will exist in the gas phase (HSDB, 2014). Its atmospheric half-life is approximately 13 hours based on its experimental rate constant for reaction with hydroxyl radicals. If released to dry soil, it will readily volatilize due to its high vapor pressure. Based on its measured Henry's law constant, *n*-heptanal will also exhibit moderate volatility from moist soil and water surfaces. In addition, *n*-heptanal deposited on soil may leach to groundwater or undergo runoff after a rain event based on its high water solubility and moderate soil absorption coefficient. Removal of *n*-heptanal from soil by leaching with water will likely compete with volatilization and biodegradation, depending on the local conditions (wet, dry, etc.). The empirical formula for *n*-heptanal is $C_7H_{14}O$ (see Figure 1). A table of physicochemical properties for *n*-heptanal is provided below (see Table 1).

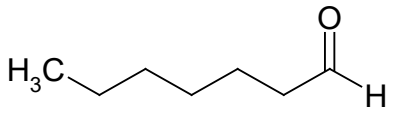


Figure 1. *n*-Heptanal Structure

Table 1. Physicochemical Properties of *n*-Heptanal (CASRN 111-71-7)[a]

Property (unit)	Value
Physical state	Colorless liquid[b]
Boiling point (°C)	152.8
Melting point (°C)	−43.3
Density (g/cm^3)	0.82162[b]
Vapor pressure (mm Hg at 25°C)	3.52
pH (unitless)	NA
Solubility in water (g/L at 25°C)	1.25
Octanol-water partition constant (log K_{ow})	2.8[c]
Henry's law constant (atm-m^3/mol at 25°C)	2.7×10^{-4}
Soil adsorption coefficient K_{oc} (mL/g) (estimated)	176 (estimated)
Relative vapor density (air = 1)	3.9[b]
Molecular weight (g/mol)	114.19

[a]Data was gathered from the PHYSPROP database unless otherwise noted (U.S. EPA, 2012b).
[b]HSDB (2014).
[c]U.S. EPA (2015).

NA = not applicable.

A summary of available toxicity values for *n*-heptanal from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *n*-Heptanal (CASRN 111-71-7)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
WHO (ADI)	Acceptable	No safety concern at current levels of intake when used as a flavoring agent; secondary components do not raise a safety concern.	WHO (2002)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2016)
Cancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: ADI = acceptable daily intake.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in May 2015 and updated in June 2017 for studies relevant to the derivation of provisional toxicity values for *n*-heptanal (CASRN 111-71-7). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science (WOS). The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

As shown in Tables 3A and 3B, there are no potentially relevant and repeated short-term-, subchronic-, or chronic-duration studies, or developmental or reproductive toxicity studies in humans or animals.

Table 3A. Summary of Potentially Relevant Noncancer Data for *n*-Heptanal (CASRN 111-71-7)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							

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

Table 3B. Summary of Potentially Relevant Cancer Data for *n*-Heptanal (CASRN 111-71-7)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

HUMAN STUDIES

The literature search revealed no studies of humans exposed to *n*-heptanal via oral or inhalation routes. Human volunteers were exposed dermally to *n*-heptanal (4% concentration in petrolatum) in a 48-hour patch test (RIFM, 1974). No evidence of irritation or sensitization were observed in the subjects. Lawson et al. (1956) briefly reported experiments in which *n*-heptanal was injected intramuscularly into breast cancer patients to explore *n*-heptanal's possible therapeutic function and/or use for early diagnosis. The experiments were not rigorously performed or documented, and provide no information on potential health effects.

ANIMAL STUDIES

The literature search did not reveal any studies of animals exposed to *n*-heptanal via oral administration or inhalation apart from acute lethality studies; the latter are discussed in the "Other Data" section below.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tables 4A and 4B provide overviews of genotoxicity and other supporting studies of *n*-heptanal, respectively. Table 4B includes:

- Acute oral and inhalation studies,
- Intraperitoneal (i.p.) injection studies (gestational and acute exposure),
- Acute and short-term-duration dermal studies, and
- Acute ocular irritation studies.

Genotoxicity

The genotoxicity of *n*-heptanal was evaluated in several in vitro studies (see Table 4A). The findings suggest that *n*-heptanal is not mutagenic or clastogenic. All available studies of *n*-heptanal using strains of *Salmonella typhimurium* and *Escherichia coli* were negative for mutagenicity with or without metabolic activation (Zeiger et al., 1992; Shell Oil Co, 1982; Florin et al., 1980; Litton Bionetics, 1980). *n*-Heptanal did not induce chromosomal aberrations (CAs) in rat liver (RL4) cells or mitotic gene conversion in strain JD1 of the yeast *Saccharomyces cerevisiae* (Shell Oil Co, 1982).

Table 4A. Summary of *n*-Heptanal (CASRN 111-71-7) Genotoxicity

Endpoint	Test System	Dose/Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA97, TA98, TA100, TA1535, and TA1537	0, 1, 3, 10, 33, 100, 166, 333, 1,000, 1,666, or 3,333 µg/plate	−	−	Preincubation assay. Cytotoxicity was observed at doses ≥1,666 µg/plate.	Zeiger et al. (1992)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538	0, 15.6, 31.3, 62.5, 125, 250, 500, 1,000, 2,000, or 4,000 µg/mL	−	−	Preincubation assay. Positive results in TA1535 and TA1538 without S9 were not reproduced in replicate assays.	Shell Oil Co (1982)
Mutation	*Escherichia coli* WP_2 and WP_2uvrA	0, 15.6, 31.3, 62.5, 125, 250, 500, 1,000, 2,000, or 4,000 µg/mL	−	−	Preincubation assay.	Shell Oil Co (1982)
Mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537	0, 3 µmol/plate	−	−	Spot test.	Florin et al. (1980)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538	0.0001−0.01 µL/plate	−	−	Cytotoxicity occurred at 0.01 µL/plate.	Litton Bionetics (1980)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Gene conversion	*Saccharomyces cerevisiae* JD1	0, 1.25, 2.5, 5, 12.5, or 25 µg/mL (without S9), and 5, 12.5, 25, 50, or 125 µg/mL (with S9)	−	−	Equivocal result at histidine locus was considered to result from instability and volatility of test compound.	Shell Oil Co (1982)
Genotoxicity studies in mammalian cells—in vitro						
CAs	RL4 cells	0, 2.5, 5, 10, or 12.5 µg/mL	−	−	NA	Shell Oil Co (1982)

Table 4A. Summary of *n*-Heptanal (CASRN 111-71-7) Genotoxicity						
Endpoint	**Test System**	**Dose/Concentration[a]**	**Results without Activation[b]**	**Results with Activation[b]**	**Comments**	**References**
Genotoxicity studies—in vivo						
ND						
Genotoxicity studies in subcellular systems						
ND						

[a]Concentrations tested in the assay.
[b]+ = positive; ± = weakly positive; – = negative.

CA = chromosomal aberration; NA = not applicable; ND = no data; RL4 = rat liver cell.

Supporting Animal Toxicity Studies

A number of supporting animal toxicity studies were identified (see Table 4B for additional details), including:

- Four acute inhalation studies in rats, with lethality observed only in a single study conducted at vapor saturation (concentration not reported) (Dow Chemical Co, 1958). The estimated median lethal concentration (LC_{50}) values were >520 mg/m^3 (Bio Dynamics, 1981), >4,700 mg/m^3 (Bio Dynamics, 1989), and >18,400 mg/m^3 (Shell Oil Co, 1982).
- An acute oral lethality study that reported an approximate median lethal dose (LD_{50}) of 3,200 mg/kg in both rats and mice (Eastman Kodak, 1985), and two other acute oral studies in rats reported no lethality at doses of 2,000 mg/kg (Dow Chemical Co, 1958) and 5,000 mg/kg (MB Research Laboratories Inc, 1974).
- A gestational exposure study using i.p. injection that reported resorption at all doses (>700 mg/kg-day) (Carruthers and Stowell, 1941) and an acute i.p. injection study that reported approximate LD_{50} values of 1,600 mg/kg for rats and 400−800 mg/kg for mice (Eastman Kodak, 1985).
- A 2-week dermal study in rabbits (500 mg/kg) that demonstrated histopathological changes restricted to the application site (no treatment-related effects were observed in the brain, heart, kidneys, liver, or lungs) (Bio Dynamics, 1991).
- Three acute dermal studies that reported skin irritation (Eastman Kodak, 1985; MB Research Laboratories Inc, 1974; Dow Chemical Co, 1958) and two acute ocular studies that reported eye irritation (Bio Dynamics, 1980; Dow Chemical Co, 1958).

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Acute oral and inhalation studies				
Acute oral (lethality)	2 rats (sex and strain not reported) received 2,000 mg/kg *n*-heptanal as a 10% solution in corn oil. Evaluations were not detailed.	Neither rat died. The study report indicated that diuresis was observed after dosing; pathology findings were negative.	This study was reported in tabular form with limited information.	Dow Chemical Co (1958)
Acute oral (lethality)	10 rats and 10 mice (sex and strain not reported) were given *n*-heptanal via oral administration at doses between 200−3,200 mg/kg. Clinical signs and body weight were recorded, and animals were observed for at least 14 d after exposure.	Numbers of deaths were not reported, but time of death was reported to be 1 hr in rats and 7 d in mice. The study reported slight or moderate muscle weakness as the only symptoms. The animals all gained weight during the observation period.	The approximate LD_{50} for both rats and mice was estimated as 3,200 mg/kg. This study was reported in tabular form with limited information.	Eastman Kodak (1985)
Acute oral (lethality)	10 rats were given *n*-heptanal orally at a dose of 5,000 mg/kg and observed for 14 d.	No rats died. Clinical signs included lethargy and piloerection. No other information was presented.	This study was reported in tabular form with limited information.	MB Research Laboratories Inc (1974)
Acute inhalation (lethality)	M and F Wistar rats (5/sex) were exposed (whole body) for 4 hr, to 0 or 18,400 mg/m^3 *n*-heptanal vapor (near saturation). The animals were observed for signs of toxicity daily over the 14-d observation period; body weights were recorded after 7 and 14 d.	1 male rat died within 5 min after the end of exposure. Autopsy of this animal revealed dark liver, hemorrhagic lung (considered a postmortem change), and hemolysis and Hb crystals in the renal cortical tubules, suggesting pre-exposure hemolysis. Clinical signs in surviving animals included rapid respiration, eye and nose irritation, salivation, and agitation. Body weights were not affected by exposure. Signs in female rats resolved within 48 hr, but males continued to exhibit some signs throughout the 14-d follow-up.	The study authors did not consider the single death to be treatment-related. The LC_{50} for *n*-heptanal was estimated to be >18,400 mg/m^3. Exposure was associated with respiratory and ocular irritation.	Shell Oil Co (1982)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute inhalation (lethality)	M and F S-D CD rats (5/sex) were exposed (whole body) for 4 hr to 230 or 520 mg/m^3 *n*-heptanal vapor. The animals were observed for signs of toxicity daily over the 14-d observation period; body weights were recorded on D 0, 1, 2, 4, 7, and 14 (exposure was on D 1). All animals were subjected to gross necropsy.	No animals died during or after exposure. Clinical signs of toxicity during exposure included matted fur, reduced activity, closed eyes, labored breathing/gasping, mucoid nasal discharge, and chromodacryorrhea in most animals of both exposure groups. The high-exposure group (but not the low) exhibited lacrimation, salivation, dried red nasal discharge, and dried material around the eyes and face. During the first 4 hr postexposure, neurological signs including body tremors, tiptoeing, and hyper-sensitivity to touch were seen in the high-exposure group, and lacrimation, ocular abnormalities, and labored or rapid breathing were seen in both groups. During the 14-d observation period, ocular abnormalities, signs of respiratory dysfunction, and body-weight loss were seen in both groups, but were more severe or at higher incidence in the high-exposure group. Necropsy findings at the low exposure included: dilated renal pelvis in 2 females, and lung and kidney discoloration in 1 male. At the high exposure, 1 male exhibited dilated renal pelvis and 1 exhibited lung discoloration; no necropsy findings in females were reported.	LC_{50} for *n*-heptanal was estimated to be >520 mg/m^3. Exposure was associated with respiratory, ocular, neurological, body weight, kidney, and lung effects.	Bio Dynamics (1981)
Acute inhalation (lethality)	M and F S-D CD rats (3/sex) were exposed (whole body) for 4 hr to 4,700 mg/m^3 *n*-heptanal vapor. The animals were observed for signs of toxicity daily over the 7-d observation period; body weights were recorded on D 1 and 8. Necropsy was not performed.	No animals died during exposure or the observation period. Irritation of the respiratory tract (evidenced by labored breathing, gasping, salivation, and decreased activity) was observed during exposure, but not after exposure ended or during the observation period. During the first 2 hr after exposure, yellow anogenital staining was noted in exposed animals. During the week-long observation period, some animals exhibited dry rales and nasal discharge. Body weight was not affected.	LC_{50} for *n*-heptanal is >4,700 mg/m^3. Rats exposed to *n*-heptanal at this concentration exhibited signs of respiratory irritation.	Bio Dynamics (1989)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute inhalation (lethality)	3 rats/group (sex and strain not reported) were exposed for 6−15 min to a saturated atmosphere of *n*-heptanal (concentration not specified). Mortality, signs of toxicity, and necropsy were evaluated. The postexposure observation period was not reported.	None of the rats exposed for 6 min died, but all 3 died shortly after 15 min of exposure. Respiratory and ocular irritation were seen in both exposure groups.	This study was reported in tabular form with limited information. *n*-Heptanal treatment was associated with respiratory and ocular irritation.	Dow Chemical Co (1958)
Other route studies				
Gestational i.p. injection (reproduction)	Pregnant rats (Wistar, piebald, and stock; 1–9/group) were injected with *n*-heptanal (in lard or acetone, with methyl salicylate at concentrations of 0.1–1% as a stabilizer) daily throughout pregnancy. Doses ranged from 700−12,000 mg/kg-d (assuming an average body weight of 0.25 kg). Dams were sacrificed and examined for resorptions at 2-d intervals from GD 6−18 or at the first appearance of bloody discharge. Body weights were measured daily.	All dose levels produced resorption (acetone and lard vehicles) in some, but not all, dams (incidence and severity data were not provided). Rats given injections with lard showed varying degrees of ascites, whitish exudates coating the liver and spleen, and adhesions (liver to diaphragm and intestine, ovaries to intestine) and pulmonary hemorrhage (associated with lipoid pneumonitis). In rats treated with heptanal in acetone, lung hemorrhages were not observed and ascites and related peritoneal changes were less severe.	Administered doses varied within each group; incidence and severity data were not provided.	Carruthers and Stowell (1941)
Acute i.p. injection (lethality)	10 rats and 10 mice (sex and strain not reported) were given *n*-heptanal via i.p. injection at doses between 200−3,200 mg/kg. Clinical signs and body weight were recorded, and animals were observed for at least 14 d after exposure.	Numbers of deaths were not reported, but time of death was reported to be 2 hr−3 d in rats, and 1−7 d in mice. The study reported moderate weakness with diarrhea in rats, and slight-to-significant weakness with rough coat and prostration in mice. The animals all gained weight during the observation period.	The approximate LD_{50} was 1,600 mg/kg for rats and 400−800 mg/kg for mice. This study was reported in tabular form with limited information.	Eastman Kodak (1985)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Short-term dermal	Rabbits (5/sex/group) were treated with dermal application (uncovered) of *n*-heptanal (25% w/w in mineral oil) for 2 wk at a dose of 0 or 500 mg/kg-d on 5 d/wk. Prior to treatment, the skin was abraded for half of the animals in each group. The animals were observed daily, and body weights were recorded weekly. 3 animals/sex were sacrificed at the end of exposure, and the remaining animals were sacrificed 2 wk after exposure ended. All animals received gross necropsy, and the brain, heart, kidneys, liver, lungs, and skin were subjected to microscopic examination.	No rabbits died prior to scheduled sacrifice. Body-weight loss was noted in most animals after 1–2 wk of exposure. Signs of dermal irritation and injury in treated rabbits included slight or moderate erythema with minimal edema during Wk 1 and necrosis, eschar formation, atonia, fissuring, desquamation, and exfoliation in all animals during Wk 2; 1 rabbit showed alopecia. Decreased food consumption was also noted in the second wk of exposure. The study authors noted that the skin changes "subsided" in the animals observed for 2 wk following exposure. Histopathology changes consisted of epidermal necrosis at the application site, accompanied by epidermal hyperplasia and hyperkeratosis, in animals exposed to *n*-heptanal.	Histopathological changes were restricted to the application site. No treatment-related effects were observed in the brain, heart, kidneys, liver, or lungs.	Bio Dynamics (1991)
Acute dermal (irritation)	10 rabbits were treated dermally with *n*-heptanal at a dose of 5,000 mg/kg and observed for 14 d.	No rabbits died. Signs of dermal irritation included moderate to marked redness and edema. No other information was presented.	This study was reported in tabular form with limited information.	MB Research Laboratories Inc (1974)
Acute dermal (irritation)	Rabbits (number, sex, and strain not reported) were exposed to undiluted or diluted (10% in Dowanol DPM) *n*-heptanal by dermal application to intact or abraded skin, of the ear or belly. Evaluations were not detailed.	Slight-to-moderate hyperemia, with slight edema and necrosis, and in some cases, a raw ulcer resulted from exposure to undiluted *n*-heptanal. With diluted *n*-heptanal, slight exfoliation, resolving within 18 d, was seen.	Undiluted *n*-heptanal was irritating to the skin of rabbits. This study was reported in tabular form with limited information.	Dow Chemical Co (1958)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute dermal (irritation)	A guinea pig (sex and strain not reported) was exposed dermally to 0.6 mL undiluted *n*-heptanal. Dermal examinations and body weight were recorded for 14 d after exposure.	The guinea pig survived treatment. Signs of dermal irritation and injury included moderate edema and necrosis, with hemorrhage at the treatment site boundary within 24 hr; eschar loss leaving raw area in 1 wk; and scarring with alopecia in the treatment area after 2 wks. The guinea pig gained weight during the observation period.	Undiluted *n*-heptanal was irritating to the skin of a guinea pig. This study was reported in tabular form with limited information.	Eastman Kodak (1985)
Acute ocular (irritation)	Rabbits (number, sex, and strain not reported) were exposed to undiluted or diluted (in 10% propylene glycol) *n*-heptanal applied to the eyes. Evaluations were not detailed.	Exposure to undiluted *n*-heptanal yielded slight pain and conjunctivitis that resolved in 48 hr. Exposure to diluted *n*-heptanal resulted in immediate slight conjunctivitis (later becoming extensive) accompanied by moderate corneal damage and iritis; with postexposure washing (but not without washing), these effects resolved in 1 wk.	In rabbits, direct contact with *n*-heptanal was irritating to the eyes, and moderately to severely injurious to the eyes in a solution with propylene glycol. This study was reported in tabular form with limited information.	Dow Chemical Co (1958)
Acute ocular (irritation)	9 adult NZW rabbits (sex not reported) were exposed to undiluted *n*-heptanal (0.1 mL) applied to the conjunctival sac of 1 eye. Eyes of 3 rabbits were washed 20 sec after treatment, and the eyes of the remaining 6 rabbits were not. Eye irritation was evaluated for up to 7 d after exposure.	Exposure to undiluted *n*-heptanal resulted in conjunctival redness, swelling, and necrosis in all rabbits. Corneal opacity and ulceration and iridial irritation were observed in some animals of both groups.	Undiluted *n*-heptanal was irritating to the eyes of rabbits after direct contact.	Bio Dynamics (1980)

F = female(s); GD = gestation day; Hb = hemoglobin; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; M = male(s); NZW = New Zealand White; S-D = Sprague-Dawley.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for *n*-Heptanal (CASRN 111-71-7)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Screening subchronic p-RfC (mg/m^3)	Rat/M	Atrophy of the olfactory epithelium	3×10^{-2}	$BMCL_{10}$ (HEC)	8 (based on surrogate POD [HEC])	300	Union Carbide (1993) as cited in U.S. EPA (2008b)
Screening chronic p-RfC (mg/m^3)	Rat/M	Atrophy of the olfactory epithelium	3×10^{-3}	$BMCL_{10}$ (HEC)	8 (based on surrogate POD [HEC])	3,000	Union Carbide (1993) as cited in U.S. EPA (2008b)

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for *n*-Heptanal (CASRN 111-71-7)

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

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

DERIVATION OF ORAL REFERENCE DOSES

Available data on oral exposure to *n*-heptanal consists of acute-duration lethality studies in rodents that are inadequate in terms of scope and length of exposure for the development of provisional reference doses (p-RfDs) (Eastman Kodak, 1985; MB Research Laboratories Inc, 1974; Dow Chemical Co, 1958). The European Chemical Agency (ECHA) registered substances database has summarized 3- and 13-week toxicity studies in rats exposed to *n*-heptanal via gavage (ECHA, 2017). The EPA was not able to obtain copies of the original studies or verify the primary source(s) and validity of the study reports. Therefore, the information is considered

insufficient for the derivation of oral reference values. In the absence of any suitable studies, the derivation of p-RfDs for *n*-heptanal is precluded. A tiered read-across approach yielded no potential surrogates with oral toxicity data for the development of screening p-RfDs (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The database for inhalation exposure to *n*-heptanal includes acute-duration lethality studies (Bio Dynamics, 1989; Shell Oil Co, 1982; Bio Dynamics, 1981; Dow Chemical Co, 1958) that are inadequate for the derivation of provisional reference concentrations (p-RfCs). However, a screening subchronic p-RfC value was derived applying a tiered surrogate approach (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 7 identifies the cancer weight-of-evidence (WOE) descriptor for *n*-heptanal.

Table 7. Cancer WOE Descriptor for *n*-Heptanal (CASRN 111-71-7)

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 absence of suitable data in humans or animals for an assessment of carcinogenicity.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected; WOE = weight of evidence.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

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

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for *n*-heptanal. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH

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

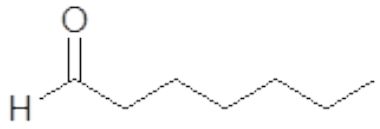
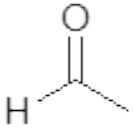
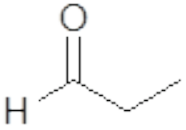
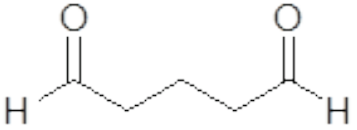
Structural Surrogates (Structural Analogs)

An initial surrogate search focused on the identification of structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. This was accomplished by searching U.S. EPA's DSSTox database (DSSTox, 2016) and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2017). The Organisation for Economic Co-operation and Development (OECD) quantitative structure-activity relationship (QSAR) toolbox was also used to calculate structural similarity using the Tanimoto method (a similar quantitative method used by ChemIDplus and DSSTox) (OECD, 2017). Three structural analogs to *n*-heptanal were identified that have inhalation toxicity values: acetaldehyde (U.S. EPA, 1998), propionaldehyde (U.S. EPA, 2008a, b), and glutaraldehyde (Cal/EPA, 2000). No potential candidates with oral toxicity values were found; therefore, the current analysis is limited to the identification of surrogate chemicals for the derivation of inhalation noncancer reference values for *n*-heptanal.

Table A-1 summarizes the physicochemical properties and similarity scores for *n*-heptanal and the structural analogs. All four compounds are straight chain, saturated aldehydes with physicochemical properties that are consistent with related aldehydes. An effect of carbon chain length on the physicochemical properties of the monoaldehyde compounds (i.e., acetaldehyde, propionaldehyde, and *n*-heptanal) is apparent. Indeed, an increasing trend in

melting point, boiling point, Henry's law constant, and lipophilicity (Log K_{ow}) is observed with the increase in carbon number, meanwhile, water solubility and vapor pressure decrease as carbon number increases. The DSSTox and OCED QSAR toolbox similarity scores for the analogs were relatively low (10−36% for OECD, 33−69% for DSSTox). Similarity estimates for the candidate analogs were not obtained from ChemIDplus, given the ≥50% cut-off threshold for similarity search within the database. A review of the similarity search output suggests that the low similarity scores are strongly biased by the descriptor for the carbon chain length (the analogs are C2−C5, and the target chemical is C7). Structural similarity metrics use a variety of structural descriptors to calculate similarity (although the nature of the descriptors may vary across different tools). Similarity scores calculated for compounds with few structural descriptors will be disproportionately influenced by changes in, or absence of, a single descriptor, while these same changes have relatively lower impact on similarity scores for compounds with many descriptors. Thus, similarity scores may be of limited use when comparing surrogates with relatively simple structures such as those evaluated in this assessment. However, more importantly, these compounds share a reactive aldehyde moiety, which has been associated with the mode of action (MOA) for the inhalation toxicity of aldehydes (U.S. EPA, 2008b). The presence of two aldehyde functional groups on glutaraldehyde is anticipated to enhance chemical reactivity in relation to the monoaldehyde analogs; therefore, acetaldehyde and propionaldehyde are considered more appropriate structural surrogates for *n*-heptanal over glutaraldehyde.

Table A-1. Structural and Physicochemical Properties of *n*-Heptanal (CASRN 111-71-7) and Candidate Analogs[a]

	***n*-Heptanal (heptaldehyde)**	**Acetaldehyde (ethanal)**	**Propionaldehyde (propanal)**	**Glutaraldehyde (pentanedial)**
Structure				
CASRN	111-71-7	75-07-0	123-38-6	111-30-8
Molecular weight	114.19	44.05	58.08	100.12
DSSTox similarity score (%)[b]	100	33	47	69
OECD QSAR Toolbox similarity score (%)[c]	100	10	33	36
Melting point (°C)	−43.3	−123.37	−80	−29.86 (estimated)[a]
Boiling point (°C)	153	20.1	48	188[c]
Vapor pressure (mm Hg at 25°C)	3.52	902	317	0.6
Henry's law constant (atm-m^3/mole at 25°C)	2.7×10^{-4}	6.7×10^{-5}	7.3×10^{-5}	3.3×10^{-8}
Water solubility (mg/L)	1,250	1,000,000	306,000	167,200 (estimated)[a]
Log K_{ow}	2.8[d]	−0.34	0.59	−0.33
pKa	NV	13.57	NV	NV

[a]Data was gathered from the PHYSPROP database for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]DSSTox (2016).
[c]OECD (2017).
[d]U.S. EPA (2015).

NV = not available.

Metabolic Surrogates

Toxicokinetic information on *n*-heptanal and the structural analogs is largely unavailable. No specific studies that inform on the absorption or distribution, of *n*-heptanal or glutaraldehyde via relevant routes of exposure (i.e., inhalation or oral) could be identified. Kinetic studies demonstrated significant uptake in the upper respiratory tract following inhalation of acetaldehyde (1−1,500 ppm) or propionaldehyde (0.4−0.6 µg/mL or ~950−1,400 ppm) in experimental animals (Stanek and Morris, 1999; Morris and Blanchard, 1992; Egle, 1972). Upon absorption, systemic distribution of inhaled aldehydes is expected to be reduced by the reactivity of the aldehyde moiety and the potential for metabolism in the respiratory tract (U.S. EPA, 2008a, b, 1998), although data examining the tissue distribution of *n*-heptanal and the structural analogs after inhalation exposure is currently lacking.

Metabolism and elimination pathways for *n*-heptanal, acetaldehyde, propionaldehyde, and glutaraldehyde (see Table A-2) are similar, as expected for most saturated aliphatic aldehydes (WHO, 1999). All four compounds appear to be substrates for aldehyde dehydrogenase (ALDH), a primary enzyme responsible for the initial oxidation to their corresponding carboxylic acids (heptanoic acid for *n*-heptanal; acetic acid for acetaldehyde; propionic acid for propionaldehyde; glutaric acid for glutaraldehyde). Glutaraldehyde is a poor substrate for certain human and rat isoforms of ALDH in relation to other aldehydes, suggesting that additional enzymes could be involved in its metabolism (Beauchamp et al., 1992). Further oxidation of the carboxylic acid analogs occurs via *β*-oxidation pathways as in the metabolism of fatty acids. Briefly, carboxylic acids condense with coenzyme A (CoA) to form thioesters that are subject to *β*-cleavage, yielding acetyl-CoA and/or propionyl-CoA. Propionyl-CoA is further metabolized to succinyl-CoA; both acetyl-CoA and succinyl-CoA enter the Krebs cycle and are eventually excreted as carbon dioxide (CO_2) and water.

The role of metabolism in the detoxification of reactive aldehydes can be inferred by the correlation between low levels of ALDH activity and increased severity of lesions in the olfactory epithelium of rats exposed to acetaldehyde (Bogdanffy et al., 1986). Additionally, mice devoid of ALDH2 activity display susceptibility to acetaldehyde-mediated histopathology in the respiratory tract (Oyama et al., 2007). Wang et al. (2002) examined metabolic ALDH2 activity for different aldehydes, including *n*-heptanal and its monoaldehyde analogs, in human liver samples from individuals heterozygous (ALDH2*1/*2) for the ALDH2 487G/A polymorphism, and individuals with a homozygous genotype (ALDH2*1/*1) for the wildtype allele. Metabolic rates for acetaldehyde, propionaldehyde, and *n*-heptanal were comparable (35.01−59.07 nmol/min/mg protein) in the homozygous wildtype group, providing further support for the metabolic similarity between the target chemical and these analogs. More pronounced differences were reported in subjects heterozygous for the mutant allele (2.72−36.99 nmol/min/mg protein). The study authors concluded that ALDH2 genetic polymorphisms could influence the metabolism and presumably the toxicity of short chain aliphatic aldehydes.

As their metabolism and excretory pathways are similar to those of *n*-heptanal, acetaldehyde, propionaldehyde, and glutaraldehyde are considered potential metabolic surrogates for *n*-heptanal.

Table A-2. Available Metabolism and Excretion Data for *n*-Heptanal (CASRN 111-71-7) and Candidate Analogs

Compound	Metabolism and Excretion	Reference
n-Heptanal	• Oxidation to heptanoic acid. • Heptanoic acid undergoes β-oxidation, yielding acetyl-CoA and propionyl-CoA. • Propionyl-CoA is converted to succinyl-CoA. • Acetyl-CoA and succinyl-CoA are used by Krebs cycle and ultimately exhaled as CO_2.	WHO (1999); RIFM (1979)
Acetaldehyde	• Oxidation to acetic acid. • Acetic acid condenses with CoA to form acetyl-CoA. • Acetyl-CoA is used by the Krebs cycle and ultimately exhaled as CO_2.	U.S. EPA (2008b); WHO (1999)
Propionaldehyde	• Oxidation to propanoic acid. • Propanoic acid condenses with CoA to form propionyl-CoA. • Propionyl-CoA is converted to succinyl-CoA. • Succinyl-CoA is an intermediate in the Krebs cycle and is ultimately exhaled as CO_2.	U.S. EPA (2008b); WHO (1999)
Glutaraldehyde	• Oxidation to glutaric acid. • Glutaric acid reacts with CoA to form glutaconyl-CoA. • Glutaconyl-CoA is decarboxylated to crotonyl-CoA, followed by hydration to β-hydroxybutyrl-CoA. • β-hydroxybutyrl-CoA condenses to form acetyl-CoA, which is used by the Krebs cycle and ultimately exhaled as CO_2.	Beauchamp et al. (1992); NTP (1999)

CoA = coenzyme A; CO_2 = carbon dioxide.

Toxicity-Like Surrogates

Table A-3 summarizes available toxicity data for *n*-heptanal and the structurally similar analogs. *n*-Heptanal lacks repeated-dose toxicity data in experimental animals. Inhalation reference concentrations (RfCs) for acetaldehyde and propionaldehyde are available on IRIS (U.S. EPA, 2008a, b, 1998) and chronic inhalation reference levels (REL) were derived for glutaraldehyde by Cal/EPA (2000). The critical effect for the three structural analogs to *n*-heptanal are based on upper respiratory tract lesions in rodents. Nevertheless, differences in the potency of these analogs with respect to repeated-dose toxicity in the airway are apparent. The points of departure (PODs) for degenerative changes in the nasal cavity of rats treated with acetaldehyde or propionaldehyde are very similar (no-observed-adverse-effect level [NOAEL] human equivalent concentration [HEC] of 8.7 mg/m^3 for acetaldehyde and 10% benchmark concentration lower confidence limit [$BMCL_{10}$] [HEC] of 8 mg/m^3 for propionaldehyde), meanwhile the POD for glutaraldehyde identified for noncancer nasal lesions in mice is three orders of magnitude lower (5% benchmark concentration [BMC_{05}] [HEC] of 0.002 mg/m^3). Indirect systemic effects following inhalation exposure to acetaldehyde, propionaldehyde, and glutaraldehyde were only observed at concentrations considerably higher than those associated with portal-of-entry (airway) toxicity (see Table A-3).

Acute lethality studies in rodents are available for *n*-heptanal and the structural analogs via multiple routes of exposure, providing an opportunity for comparison of acute toxicity

potencies. Study results are presented in Table A-3. Further details on study design and protocol were not found (ChemIDplus, 2017). Oral median lethal doses (LD_{50}s) in rats suggest that *n*-heptanal (LD_{50} = 3,200 mg/kg) is less acutely toxic than propionaldehyde (rat LD_{50} = 1,410 mg/kg), acetaldehyde (rat LD_{50} = 661 mg/kg), and glutaraldehyde (rat LD_{50} = 134 mg/kg). Intraperitoneal (i.p.) LD_{50}s are similar for acetaldehyde, propionaldehyde, and *n*-heptanal in mice (LD_{50} = 200−400 mg/kg), and in rats, acute lethality values for propionaldehyde (LD_{50} = 200 mg/kg) are lower compared to *n*-heptanal (LD_{50} = 1,600 mg/kg). Notably, i.p. LD_{50}s for glutaraldehyde are approximately one to two orders of magnitude lower (13.9 and 17.9 mg/kg in mice and rats, respectively) in relation to the monoaldehyde compounds. Acute inhalation toxicity in rodents is comparable for acetaldehyde, propionaldehyde, and *n*-heptanal (median lethal concentration [LC_{50}] = >18,400 − 24,000 mg/m^3), whereas glutaraldehyde is distinctly more potent (LC_{50} = 480 mg/m^3). Finally, *n*-heptanal, acetaldehyde, and propionaldehyde showed analogous acute target organ effects, including neurological and respiratory tract toxicity.

In general, the acute lethality information described above suggests the rank order of potency to be glutaraldehyde >> acetaldehyde ≈ propionaldehyde > *n*-heptanal. Likewise, median reference irritation dose (RD_{50}) values (concentration producing a 50% respiratory rate decrease), which represent a measure of respiratory irritation potential, are similar for acetaldehyde and propionaldehyde, but remarkably lower for glutaraldehyde (see Table A-3). In summary, data from repeated-dose exposure, acute lethality, and respiratory irritation (RD_{50}) indicate that glutaraldehyde exhibits enhanced chemical reactivity and inhalation toxicity compared to *n*-heptanal and the monoaldehyde analogs; therefore, glutaraldehyde is not considered an appropriate toxicity-like surrogate for *n*-heptanal.

Comparative studies of low molecular-weight aldehydes (C1−C4) note a reduction in potency with increasing carbon chain length based on measurements of in vitro cytotoxicity and acute lethality (Bombick and Doolittle, 1995; Koerker et al., 1976; Skog, 1950), which is consistent with the above findings that indicate *n*-heptanal is slightly less acutely toxic than acetaldehyde and propionaldehyde. Structure-activity relationship analyses of aldehydes reveal that carbon chain length can have a modest effect on respiratory irritating potency; however, major differences are most prominently observed across different aldehyde groups (Alarie et al., 1998; Babiuk et al., 1985; Steinhagen and Barrow, 1984). Indeed, mouse RD_{50} values for C2−C6 saturated aliphatic aldehydes, including acetaldehyde and propionaldehyde, were similar (1,014−5,689 ppm), and approximately three orders of magnitude higher than for unsaturated aliphatic aldehydes (RD_{50} = 1.03−4.88 ppm) and formaldehyde (RD_{50} = 3.2−4.9 ppm). Cyclic aldehydes displayed moderate irritating potency with RD_{50} values in the range of 59−186 ppm. RD_{50} values for *n*-heptanal are not available; nonetheless, acute studies in rodents demonstrate similarly low inhalation potency for *n*-heptanal, acetaldehyde, and propionaldehyde (see Table A-3). The MOA for nasal toxicity relates to the reactivity of the aldehyde moiety (U.S. EPA, 2008b) and is expected to be similar for *n*-heptanal as for the shorter-chain monoaldehydes. Indeed, respiratory irritation was consistently reported in acute inhalation studies with rats exposed to concentrations of *n*-heptanal ≥520 mg/m^3, supporting the relevance of the respiratory tract as a potential target organ of toxicity for this chemical (Bio Dynamics, 1989; Shell Oil Co, 1982; Bio Dynamics, 1981; Dow Chemical Co, 1958). In summary, both

acetaldehyde and propionaldehyde are considered potential toxicity-like surrogates for *n*-heptanal.

Table A-3. Comparison of Available Toxicity Data for *n*-Heptanal (CASRN 111−71−7) and Candidate Analogs

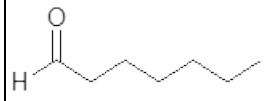
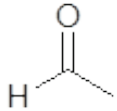
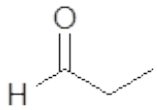
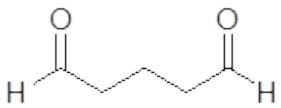
	***n*-Heptanal (heptaldehyde)**	**Acetaldehyde (ethanal)**	**Propionaldehyde (propanal)**	**Glutaraldehyde (pentanedial)**
Structure				
CASRN	111-71-7	75-07-0	123-38-6	111-30-8
Repeated-dose toxicity (inhalation)				
POD (mg/m^3)	NV	8.7	8	0.002
POD type	NV	NOAEL (HEC)	$BMCL_{10}$ (HEC)	BMC_{05} (HEC)
UF_C	NV	1,000	1,000	30
RfC or REL (mg/m^3)	NV	9×10^{-3}	8×10^{-3}	8×10^{-5}
Critical effects	NV	Degeneration of olfactory epithelium at concentrations ≥400 ppm.	Atrophy of the olfactory epithelium in rats at concentrations ≥150 ppm.	Squamous metaplasia of the respiratory epithelium at concentrations ≥62.5 ppb.

Table A-3. Comparison of Available Toxicity Data for *n*-Heptanal (CASRN 111−71−7) and Candidate Analogs

	***n*-Heptanal (heptaldehyde)**	**Acetaldehyde (ethanal)**	**Propionaldehyde (propanal)**	**Glutaraldehyde (pentanedial)**
Other effects in principal study	NV	Effects at higher exposures: severe degenerative hyperplastic and metaplastic changes of the nasal, laryngeal, and tracheal epithelium at ≥1,000 ppm; growth retardation at ≥1,000 ppm and mortality at ≥2,200 ppm; decreased percent of lymphocytes and increased percent of neutrophils in the blood at 5,000 ppm; organ-weight changes at 5,000 ppm.	Additional effects reported include: vacuolization of olfactory epithelium and rhinitis in the respiratory epithelium at ≥150 ppm; squamous metaplasia of the respiratory epithelium in males only at ≥750 ppm. Maternal (decreased body weight and food consumption during GD 0−21) and developmental (reduced pup body-weight gain at birth and PND 4) effects were noted at 1,500 ppm. No effects on reproductive parameters up to 1,500 ppm.	Additional lesions found at concentrations ≥62.5 ppb in female mice only included: increased incidence of nose inflammation and hyaline degeneration of the respiratory epithelium; mean body weight in female mice was lower compared to controls at 250 ppb. In an accompanying rat study, non-neoplastic nasal lesions (hyperplasia and inflammation of the squamous and respiratory epithelia, and squamous metaplasia of the respiratory epithelium) occurred at ≥250 ppb; decreased body weight at ≥250 ppb and increased mortality in females at ≥500 ppb.
Species	NV	Rat (males)	Rats (males)	Mice (females)
Duration	NV	4 wk	7 wk	104 wk
Route	NV	Inhalation	Inhalation	Inhalation

Table A-3. Comparison of Available Toxicity Data for *n*-Heptanal (CASRN 111−71−7) and Candidate Analogs

	***n*-Heptanal (heptaldehyde)**	**Acetaldehyde (ethanal)**	**Propionaldehyde (propanal)**	**Glutaraldehyde (pentanedial)**
Notes		The same types of lesions appear at longer exposure times and higher exposure levels in chronic-duration studies.	Liver cell vacuolation was observed in rats exposed to 1,300 ppm for 6 d. Cardiovascular effects (blood pressure and heart rate) reported in rats with acute inhalation exposures ≥10 µg/mL (~24,000 ppm).	Respiratory tract toxicity was also reported in acute, short-term- and subchronic-duration studies in rats and mice with inhalation exposure. Effects described in humans with occupational exposure include asthma, skin sensitivity, and irritation of the eyes and nose with accompanying rhinitis.
Source	NV	U.S. EPA (1998)	U.S. EPA (2008a); U.S. EPA (2008b)	Cal/EPA (2000)
Acute toxicity				
Rat oral LD_{50} (mg/kg)	3,200	661	1,410	134
Toxicity target	Behavioral	Peripheral nervous system; behavioral; respiratory tract	NS	NS
Mouse oral LD_{50} (mg/kg)	3,200	900	NV	100
Toxicity target	Behavioral	NS	NV	NS
Rat inhalation LC_{50} (mg/m^3)	>18,400	24,000	NV	480
Toxicity target	Respiratory tract; Behavioral; GI tract	Respiratory tract; behavioral	NV	NS
Mouse inhalation LC_{50} (mg/m^3)	NV	23,000	21,800	NV
Toxicity target	NV	NS	NS	NV
Rat i.p. LD_{50} (mg/kg)	1,600	NV	200	17.9

Table A-3. Comparison of Available Toxicity Data for *n*-Heptanal (CASRN 111−71−7) and Candidate Analogs

	***n*-Heptanal (heptaldehyde)**	**Acetaldehyde (ethanal)**	**Propionaldehyde (propanal)**	**Glutaraldehyde (pentanedial)**
Toxicity target	Behavioral; GI tract	NV	Behavioral	NS
Mouse i.p. LD_{50} (mg/kg)	400	500	200	13.9
Toxicity target	Behavioral; skin and appendages	NS	Respiratory tract; behavioral	NS
Source	ChemIDplus (2016)	ChemIDplus (2016)	ChemIDplus (2016)	ChemIDplus (2016)
Respiratory irritation				
Mouse RD_{50} (ppm)	NV	3,900[a]	5,700[a]	NV
Swiss-Webster mouse RD_{50} (ppm)	NV	2,845[b]	2,052[b]	13.9[c]
$B6C3F_1$ mouse RD_{50} (ppm)	NV	2,932[b]	2,073[b]	NV

[a]Alarie et al. (1998).
[b]Steinhagen and Barrow (1984).
[c]Werley et al. (1995).

BMC_{05} = 5% benchmark concentration; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; GD = gestation day; GI = gastrointestinal; HEC = human equivalent concentration; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; NOAEL = no-observed-adverse-effect level; NS = not specified; NV = not available; PND = postnatal day; POD = point of departure; RD_{50} = median reference dose; REL = reference level; RfC = reference concentration; UF_C = composite uncertainty factor.

Weight-of-Evidence Approach

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

Based on a WOE analysis, acetaldehyde and propionaldehyde are considered appropriate chemical surrogates for *n*-heptanal via the inhalation route. No surrogate candidates were identified with available oral toxicity values; therefore, the development of screening provisional reference doses (p-RfDs) is precluded. Acetaldehyde and propionaldehyde are shorter chain analogs of *n*-heptanal that share a key functional group (i.e., aldehyde moiety). Indeed, the reactive mechanism for the aldehyde moiety of acetaldehyde and propionaldehyde has been associated with the critical effect for inhalation exposure, (i.e., nasal toxicity) and is anticipated to be analogous to that of *n*-heptanal. Similarities in metabolism and excretion pathways indicate acetaldehyde and propionaldehyde are also metabolic surrogates for *n*-heptanal. Moreover, acute lethality studies in rodents showed comparable LD_{50} values and target-organ effects (neurological and respiratory tract toxicity) for *n*-heptanal, acetaldehyde, and propionaldehyde. Conversely, glutaraldehyde is not considered an appropriate surrogate based on the presence of an additional aldehyde moiety in the molecule that is anticipated to result in substantially greater airway reactivity and inhalation toxicity for this chemical in relation to *n*-heptanal.

Consistency in functional group properties, metabolism and excretion pathways, critical endpoints, and PODs for repeated-dose toxicity for propionaldehyde and acetaldehyde provide additional support for the use of the surrogate approach and suggest that either compound could be considered a suitable surrogate for *n*-heptanal. However, given the perceived effect of carbon chain length on the physicochemical properties and acute toxicity of these monoaldehyde compounds, propionaldehyde is selected as the final surrogate chemical because it is the closest analog to *n*-heptanal (heptanal is C7, propinaldehyde is C3, and acetaldehyde is C2). Furthermore, the POD value for propionaldehyde is based on a study of slightly longer exposure duration (7 weeks) than that of acetaldehyde (4 weeks), thus, increasing confidence in the principal study as the basis for a screening subchronic and chronic provisional reference concentration.

INHALATION TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Concentration

Based on the overall surrogate approach presented in this PPRTV assessment, propionaldehyde is selected as the surrogate for *n*-heptanal. The study used in deriving the IRIS RfC for propionaldehyde is a 7-week inhalation study in male CD rats [Union Carbide (1993) as cited in U.S. EPA (2008b)]. The IRIS toxicological review for propionaldehyde described the study as follows (U.S. EPA, 2008b):

Young adult male and female CD rats (15/sex/group) were exposed to 0, 150, 750, or 1,500 ppm (0, 357, 1,785, or 3,570 mg/m^3) propionaldehyde for 6 hours/day, 7 days/week via whole-body inhalation, during a 2-week premating period and a 14-day (maximum) mating phase (Union Carbide, 1993). The mated females were exposed daily through Gestation Day (GD 20 only for a minimum of 35 days and a maximum of 48 days depending upon when they mated (average exposure period ~38 days). The females were then allowed to deliver their litters naturally and raise their offspring until postnatal day (PND) 4 both free of exposure to propionaldehyde. The males continued to be exposed for a total of 52 exposures until sacrifice in week 7. Clinical observations were made daily, following exposure, and body weight and food consumption were measured at regular intervals throughout the study. Offspring body weight, viability, and disposition were monitored from birth until PND 4. Following the last exposure, males were fasted and blood samples were obtained for clinical pathology analyses prior to necropsy. On PND 4, necropsies were performed on adult females, and a number of organs and tissues, including at least two sections of the nasal cavity (sectioning details not provided), were examined histologically. The offspring were examined externally and sacrificed without pathologic evaluation.

No exposure-related clinical signs were noted in the adult females. During the first week of exposure to 750 and 1,500 ppm, body weight gains were decreased to approximately 60 and 71% ($p < 0.01$), respectively, of controls, and food consumption was decreased by approximately 7% ($p < 0.05$) of controls at both concentrations. No differences were observed during the second week of exposure. During gestation, body weight (over GDs 0–14) and food consumption (over GDs 0–21) were decreased in the high exposure group compared with controls, but no significant differences in body weight gain were observed. At sacrifice, no gross lesions attributable to propionaldehyde exposure were found. However, microscopic examination of the nasal cavity revealed propionaldehyde-induced vacuolization of the olfactory epithelium in the 150 and 750 ppm exposure groups and atrophy of the olfactory epithelium in the 750 and 1,500 ppm exposure groups. These effects were noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 0/15, 2/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively (see Table 4-1). The severity of this nasal lesion increased with exposure concentration being minimal to mild at 750 ppm and moderate to marked at 1,500 ppm. No evidence of squamous metaplasia was found in olfactory or respiratory epithelium. Low incidences of minimal to mild rhinitis involving the respiratory epithelium were also noted at 150, 750, and 1,500 ppm. No significant effects of exposure on any of the reproductive parameters assessed were found. Litter size and viability were similar among the groups. Pup body weights on the day of birth and PND 4 were not affected by exposure, although at the high concentration only body weight gain for that period was significantly depressed ($p < 0.05$, –0.8 g) compared with controls. The biological significance of this finding is difficult to assess since changes in absolute body weight were not demonstrated and the time period of observation was relatively short.

The adult males did not display any overt signs of toxicity at any time during the study. Body weight, weight gain, clinical observation, and food consumption were similar among all exposure groups and controls. Hematology and clinical chemistry analyses revealed elevated erythrocyte counts, with a corresponding increase in hemoglobin and hematocrit values and an increase in monocytes in the males exposed to 1,500 ppm. These effects were considered to be consistent with and indicative of dehydration. At necropsy (examination performed as per the 10 adult females), no gross lesions were found that could be attributable to propionaldehyde exposure. However, similar to effects in the females, microscopic examination revealed exposure-related effects in the olfactory epithelium of the nasal cavity that consisted of vacuolization and atrophy in the low, intermediate, and high exposure groups. These effects were also noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 2/15, 10/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively (see Table 4-1).

The severity of this nasal lesion increased with exposure concentration being minimal at 150 ppm, minimal to moderate at 750 ppm, and mild to marked at 1,500 ppm. Squamous metaplasia of the respiratory epithelium was reported in one male from the 750 ppm group and two males from the 1,500 ppm group. An increased incidence of minimal to moderate rhinitis involving the respiratory epithelium was also noted at 750 and 1,500 ppm. The results of this study indicate a lowest-observed-adverse-effect level (LOAEL) for portal-of-entry toxicity of 150 ppm as a result of olfactory atrophy graded by Union Carbide (1993) as being of minimal severity by the study authors and supported by the presence of vacuolization.

The critical effect identified for propionaldehyde in the Union Carbide (1993) study was nasal olfactory atrophy (U.S. EPA, 2008b). Benchmark Dose Software (BMDS) was used to model incidence of atrophy in the olfactory epithelium of male rats using a benchmark response (BMR) of 10% extra risk (U.S. EPA, 2008b). A $BMCL_{10}$ of 32 mg/m^3 was derived from BMDS and converted to a HEC by applying a regional gas dose ratio (RGDR) of 0.26 for extrathoracic respiratory effects in accordance to U.S. EPA (1994) guidelines. The resulting $BMCL_{10}$ (HEC) of 8 mg/m^3 was used as a POD in the RfC for propionaldehyde and is, therefore, adopted as the surrogate POD for the derivation of a screening subchronic p-RfC for *n*-heptanal. The $BMCL_{10}$ (HEC) of 8 mg/m^3 was not adjusted for molecular-weight differences in the derivation of the *n*-heptanal provisional toxicity value because the molecular-weight difference between *n*-heptanal and propionaldehyde is less than twofold (Wang et al., 2012).

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

Screening Subchronic p-RfC = Surrogate POD (HEC) ÷ UF_C
= 8 mg/m^3 ÷ 300
= **3×10^{-2} mg/m^3**

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfC for *n*-heptanal.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfC for *n*-Heptanal (CASRN 111−71−7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty, including toxicodynamic differences, between rats and humans following *n*-heptanal inhalation. The toxicokinetic uncertainty has been accounted for by calculation of a HEC through application of a RGDR in extrapolating from animals to humans (U.S. EPA, 2008b) according to the procedures in the RfC methodology (U.S. EPA, 1994).
UF_D	10	A UF_D of 10 is applied due to the absence of repeated-dose toxicity studies for *n*-heptanal and the use of a surrogate approach to derive the screening p-RfC.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *n*-heptanal in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMCL_{10}$.
UF_S	1	A UF_S of 1 is applied because a 7-wk study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; RGDR = regional gas dose ratio; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

The IRIS assessment for propionaldehyde derived a chronic RfC using the critical effect (atrophy of the olfactory epithelium) and POD ($BMCL_{10}$ [HEC] of 8 mg/m^3) identified in the 7-week inhalation study in rats (U.S. EPA, 2008b). The database for propionaldehyde lacks longer duration studies; however, the pattern and progression of the nasal lesions (atrophy accompanied by vacuolization, necrosis, and squamous metaplasia) observed in the 7-week rat study are consistent with those reported from chronic-duration studies with other aldehydes, including acetaldehyde (U.S. EPA, 2008a, b, 1998). Importantly, no adverse systemic effects occurred in chronic-duration studies with acetaldehyde or short-term-duration studies with propionaldehyde at concentrations that caused significant portal-of-entry toxicity (see Table A-3). Therefore, a screening chronic p-RfC for *n*-heptanal is derived using the POD ($BMCL_{10}$ [HEC] of 8 mg/m^3) from the 7-week inhalation study with propionaldehyde and applying an additional uncertainty factors of 10 to account for increased uncertainty associated with longer exposure. A total UF_C of 3,000 was derived, reflecting a 3-fold uncertainty factor value for UF_A, and 10-fold uncertainty factor values for UF_H, subchronic-to-chronic

extrapolation (UF_S), and UF_D. Finally, the screening chronic p-RfC for *n*-heptanal is derived as follows:

Screening Chronic p-RfC = Surrogate POD (HEC) ÷ UF_C
= 8 mg/m^3 ÷ 3,000
= **3×10^{-3} mg/m^3**

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfC for *n*-heptanal.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfC for *n*-Heptanal (CASRN 111−71−7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty, including toxicodynamic differences, between rats and humans following *n*-heptanal inhalation. The toxicokinetic uncertainty has been accounted for by calculation of a HEC through application of a RGDR in extrapolating from animals to humans (U.S. EPA, 2008b) according to the procedures in the RfC methodology (U.S. EPA, 1994).
UF_D	10	A UF_D of 10 is applied due to the absence of repeated-dose toxicity studies for *n*-heptanal and the use of a surrogate approach to derive the screening p-RfC.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *n*-heptanal in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMCL_{10}$.
UF_S	10	A UF_S of 10 is applied due to increased uncertainty associated with extrapolating from a subchronic-duration study (7-wk) to a chronic exposure.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; RGDR = regional gas dose ratio; UF = uncertainty factor; UF_A = interspecies 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. REFERENCES

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